Neutral Citation Number: [2022] EWHC 369 (Ch)

Case Nos: HC-2011-000064
HC-2012-000189
HC-2012-000188

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS
OF ENGLAND AND WALES
COMPETITION LIST (ChD)

Rolls Buildings, Fetter Lane
London, EC4A 1NL

Date: 21/02/2022

Before:

MR JUSTICE ROTH

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Between:

THE SECRETARY OF STATE FOR HEALTH AND ANOTHER — **English Claimants**

- and -

(1) SERVIER LABORATORIES LIMITED
(2) SERVIER RESEARCH AND DEVELOPMENT LIMITED
(3) LES LABORATOIRES SERVIER SAS
(4) SERVIER SAS — **Defendants**

And between

THE SCOTTISH MINISTERS AND OTHERS — **Scottish/NI Claimants**

- and -

(1) SERVIER LABORATORIES LIMITED
(2) SERVIER RESEARCH AND DEVELOPMENT LIMITED
(3) LES LABORATOIRES SERVIER SAS
(4) SERVIER SAS — **Defendants**

And between

THE WELSH MINISTERS AND OTHERS — **Welsh Claimants**

- and –

(1) SERVIER LABORATORIES LIMITED
(2) SERVIER RESEARCH AND DEVELOPMENT LIMITED
(3) LES LABORATOIRES SERVIER SAS
(4) SERVIER SAS **Defendants**

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Jon Turner QC and Josh Holmes QC for the **Claimants collectively**
David Drake and Philip Woolfe (instructed by **Peters & Peters Solicitors LLP**) for the **English Claimants**
Julian Gregory and Alexandra Littlewood (instructed by **RPC LLP**) for the **Scottish / NI Claimants**
Laura Elizabeth John and Ciar McAndrew (instructed by **Geldards LLP**) for the **Welsh Claimants**
Nicholas Saunders QC, Daniel Piccinin and Emma Mockford (instructed by **Sidley Austin LLP**) for the **Defendants**

Hearing dates: 17-18, 21-25, 28-30 June, 1-2, 5-7, 14-15 July 2021

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Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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Mr Justice Roth:

INTRODUCTION

1. These three actions, which are being heard together, are claims for damages brought on behalf of, respectively (i) the English health authorities, (ii) the Welsh health authorities, and (iii) the Scottish and Northern Irish health authorities. It is convenient to refer to them, save where further elaboration is required, as the English Claimants, the Welsh Claimants, the Scottish Claimants and the NI Claimants, and to the respective authorities compendiously as the English NHS, Welsh NHS, Scottish NHS and N Irish NHS. They were referred to together, in a nomenclature I shall adopt, as "the four nations."

2. This judgment follows the trial of preliminary issues. To explain the nature of those issues and how they arise, it is necessary to describe the background and substance of the proceedings in some detail.

3. The proceedings concern a pharmaceutical prescription-only drug, perindopril. It is an angiotensin-converting enzyme ("ACE") inhibitor ("ACEI") used in the treatment of a number of conditions.

4. The First and Second Defendants are English companies and the Third and Fourth Defendants are French companies. The Fourth Defendant is the parent company of the Servier group and the other Defendants are, directly or indirectly, its subsidiaries. I shall refer to the First Defendant as "SLL", to the Third Defendant as "LLS" and to the Defendants compendiously, save where it is necessary to distinguish between them, as "Servier." Perindopril, marketed under the brand name "Coversyl", was a major product of Servier in the period with which these proceedings are concerned, i.e. 2003-2009 ("the Relevant Period").

5. Both during and since that time, there has been significant reorganisation of the health authorities in all the four nations. The present claimants are, as appropriate, the successors to the relevant health authorities responsible for payment or purchasing of prescription medicines in each of the four nations over the Relevant Period.

6. Supply of Coversyl, protected by European patents with a UK designation, began on the UK market in about 1990, after Servier obtained a UK marketing authorisation. The present actions relate to a patent which was granted to LLS for the alpha crystalline form of the perindopril salt: EP No 1 296 947 (the "947 Patent") which had, among others, a UK designation. The application for the 947 Patent was filed at the European Patent Office (the "EPO") on 6 July 2001 and the patent was granted on 4 February 2004. The patent was opposed by ten opponents and following the hearing of the opposition on 27 July 2006, the Opposition Division of the EPO decided to maintain the patent. SLL was the exclusive licensee under the UK designation of the 947 Patent.

7. LLS and SLL obtained interim injunctions in the Patents Court, on the basis of the 947 Patent, against a number of generic companies seeking to enter the UK market with generic perindopril. One of those generic companies was Apotex, but following the

subsequent substantive trial, the Court held on 11 July 2007 that the 947 Patent was invalid: [2007] EWHC 1538 (Pat). Servier's appeal against that decision was dismissed: [2008] EWCA Civ 445. Those decisions of course only applied to the UK designation of the European patent.

8. In the meantime, an appeal was proceeding before the EPO Technical Board of Appeal. By a decision dated 6 May 2009, the Board of Appeal revoked the European 947 Patent.

9. The present proceedings allege a series of infringements of both EU and UK competition law. In particular, it is alleged that Servier entered into a series of agreements with generic manufacturers and suppliers not to enter the market with a generic version of perindopril and/or to withdraw their challenges to Servier's patent; and that those agreements constituted an infringement of Art 101 of the Treaty on the Functioning of the European Union ("TFEU") and/or the equivalent s. 2 of the Competition Act 1998 ("CA"), and also an abuse of a dominant position which Servier held in the UK, and therefore an infringement of Art 102 TFEU and/or the equivalent s. 18 CA. Moreover, the claims allege that LLS obtained the grant of the 947 Patent, and further successfully defended it in opposition proceedings, by misleading or dishonest misrepresentations made to the EPO; and that LLS and SLL further repeated or relied on those misrepresentations in obtaining interim relief in the English courts. That alleged conduct, which is expressly pleaded as constituting deceit, is said to be a separate abuse of Servier's dominant position and thus contrary to Art 102 TFEU and/or s. 18 CA. Further and alternative grounds of abuse are alleged on the basis that the conduct of LLS and/or SLL by which they "obtained, defended and enforced" the rights in relation to the 947 Patent was unreasonable or an abuse of process, and that Servier was "not transparent in its provision of relevant information to the EPO and courts".

10. In the proceedings brought by the English Claimants, there was also a claim for the economic tort of unlawful means, but that has been struck out and is no longer relevant. For the purpose of the preliminary issues, it is unnecessary to distinguish between the three sets of proceedings, and all references to the pleadings will be to the statements of case in the English action.

11. Following the commencement of these proceedings, on 9 July 2014, the European Commission adopted a decision ("the EC Decision") addressed to SLL, LLS and the Fourth Defendant finding that they had contravened Arts 101 and 102 TFEU by reason of various agreements made with generic manufacturers and suppliers involving patent settlements or the acquisition of technology, and imposing very substantial fines: Case AT.39612 *Perindopril (Servier)*. From that point, these proceedings became in part 'follow-on' actions, relying on the EC Decision.

12. On 12 December 2018, the EU General Court largely dismissed Servier's appeal against the Art 101 infringement (save in respect of agreements made with one of the generic companies, Krka) but allowed the appeal against the finding that Servier was dominant on the relevant market and accordingly annulled the EC Decision as regards an infringement of Art 102: Case T-691/14 *Servier v Commission*, EU:T:2018:922 ("the General Court judgment"). Appeals by both the EU Commission and Servier against the General Court judgment are still pending before the Court of Justice of the EU (the "CJEU"): Case C-176/19P (the Commission's appeal) and Case 201/19P (Servier's appeal). Unless the General Court judgment is reversed as regards the finding of dominance, the Claimants accept that they cannot proceed with the Art 102/s. 18 claim.

However, the distinction between the Art 101 and Art 102 claims are not material for present purposes.

13. On the trial of a previous preliminary issue, this court held that the findings of the General Court on market definition are not *res judicata* for the purpose of the present proceedings: [2019] EWHC 1004 (Ch). Servier's appeals against that decision were dismissed by the Court of Appeal [2019] EWCA Civ 1096 and the Supreme Court [2020] UKSC 44.

14. The claims allege that by reason of the anti-competitive agreements and abusive conduct referred to above, Servier obtained and/or maintained the protection of the 947 Patent, until it was finally invalidated in the UK in July 2007 and by the EPO Board of Appeal in May 2009. As a result, the price of perindopril was much higher than it would have been had generic suppliers entered the UK market. The Claimants seek as damages the difference between their expenditure at the price they paid and what they allege it would have been had the price been determined under conditions of generic competition.

15. By the Amended Defence, Servier denies that it infringed Art 101/s. 2 CA, that it held a dominant position for the purpose of Art 102/s. 18 CA and that, even if it was dominant, its conduct amounted to an abuse.

THE PRESCRIBING ARGUMENT

16. By a further amendment to the Defence, Servier introduced into its pleading a separate line of argument entitled "Failure to Mitigate, Causation/Remoteness and/or Contributory Negligence". However, as was stated in the opening skeleton argument for Servier and as is common ground, there is substantial overlap between mitigation, causation and remoteness of damage. As Scott LJ (as he then was) stated in *Schering Agrochemicals Ltd v Resibel* (unreported, transcript of 26 November 1992), at p 16:

> "The argument before us has dealt with the principles of law applicable to causation, to remoteness of damage and to the so-called duty to mitigate. These, however, are not concepts which are independent of one another. Each of them serves a function in placing a limit on the extent of the liability of a wrongdoer, whether for breach of contract or in tort. Each of them may be useful as a tool to enable a decision to be reached as to whether particular loss or damage is recoverable from the wrongdoer. But none, in my opinion, should ever be regarded as anything more than a tool and whether any, and if so which, of these concepts can play a useful role in a particular case must depend on the facts of the case".

17. In the Re-Amended Defence, Servier pleads as follows:

> "<u>Failure to take reasonable steps to encourage switching to cheaper ACE Inhibitors</u>
>
> 83.B. The Claimants were aware or should have been aware that:

(a) Alternative ACE Inhibitors were available in generic form. In particular, generic launch of Enalapril took place in or around December 1999, Lisinopril in or around September 2002 and Ramipril in or around December 2003;

(b) ACE Inhibitors exert a 'class effect' and there was no clinical difference between Perindopril and the other ACE Inhibitors already available in generic form. NHS prescribers could therefore prescribe these ACE Inhibitors as an alternative to Perindopril; and

(c) The reimbursement prices of generic ACE inhibitors were significantly less than the reimbursement price of Perindopril during the relevant period.

83.C. In these circumstances, the Claimants should have taken all reasonable steps to encourage switching from the prescription of Perindopril to the prescription of cheaper alternative ACE Inhibitors in generic form. In particular, but without limitation, the Claimants should have:

(a) Removed Perindopril from the local formularies;

(b) Issued national guidance encouraging a switch from Perindopril to the prescription of cheaper alternative ACE Inhibitors in generic form;

(c) Issued local PCT guidance encouraging a switch from Perindopril to the prescription of cheaper alternative ACE Inhibitors in generic form, including through meetings with GPs, through newsletters and through meetings with individual PCT pharmacists or agents;

(d) Used the national Quality and Outcomes Framework to incentivise a switch from Perindopril to the prescription of cheaper alternative ACE Inhibitors in generic form. For example in 2004, GPs were incentivised to meet with their prescribing advisor and review all patients with repeat prescriptions or multiple therapies. This would have provided the opportunity to encourage switching;

(e) Introduced or encouraged the introduction and use or further use of software such as 'Scriptswitch' which provides a visual prompt for NHS prescribers in order to highlight the availability of an alternative, more cost-effective treatment;

(f) Provided additional support reasonably necessary to facilitate the switching of patients from Perindopril to cheaper alternative ACE Inhibitors, including by providing patient information leaflets and/or template letters for use by GPs when switching patients; and

> (g) Taken all reasonable steps and allocated reasonable resources to ensure that the foregoing measures were complied with, including monitoring compliance and taking further steps in circumstances of non-compliance.
>
> 83.D. Pending full disclosure, the Defendants are presently unable to particularise the extent to which each individual Claimant took or failed to take one or more of the above identified steps. However, each of the Claimants either failed to take the steps identified above and/or alternatively having taken such steps, failed to take any or any sufficient steps to ensure compliance with them."

18. In the Response dated 29 September 2017 to a Request for Further Information, Servier clarified its position on substitution of another ACEI for perindopril, stating:

> "The Defendants do not accept that there are any circumstances in which it would not have been clinically appropriate to prescribe another ACE inhibitor instead of Perindopril, except where the patient was allergic to or intolerant of all alternative ACE inhibitors."

19. By their Amended Reply, the Claimants admitted that generic versions of other ACEIs were introduced as set out in para 83B(a), did not admit the difference in reimbursement prices alleged in para 83B(c), and responded to para 83B(b) as follows:

> "24.2. The Claimants' case as to the facts and matters which affected the choice by NHS prescribers of ACE Inhibitors during the material period is set out at PoC/§§46-57. In the premises it is specifically denied that there was no clinical difference between Perindopril and the other ACE Inhibitors and further denied that such other ACE Inhibitors could in all circumstances be prescribed as "an alternative" to Perindopril."

20. The Claimants responded to the allegation in para 83C that they should have taken all reasonable steps to encourage switching from perindopril to other ACEIs available in generic form as follows:

> "25.1. The relevant criterion is whether it was unreasonable for the Claimants or former Claimants *not* to take particular steps: not whether taking them would have been reasonable. It is denied that the Claimants or former Claimants should (in the sense of the relevant criterion) have taken all or any of the steps alleged in paragraph 83C to encourage switching from the prescription of Perindopril to the prescription of cheaper alternative ACE Inhibitors in generic form, and/or that the Claimants' damages should be reduced on that account.
>
> 25.2. Further, it is denied that the steps set out at paragraphs 83C(a) to (g) or any of them were steps which it was reasonable to expect the Claimants or former Claimants to take…."

And the Claimants set out various facts which they say are relevant to the assessment of reasonableness.

21. The cross reference in para 24.2 of the Amended Reply to paras 46-57 of the Particulars of Claim is in my view significant. That section, entitled "Factors Relevant to the Prescribing of Perindopril", includes the following assertion, at para 49:

> "ACE Inhibitors are typically prescribed on a long-term basis and NHS clinicians will take different considerations into account on the one hand when deciding which ACE Inhibitor to prescribe at the outset of treatment, and on the other hand when deciding whether to continue treatment with the same ACE Inhibitor or to switch the patient to another ACE Inhibitor. Factors which influence NHS clinicians in choosing whether to prescribe a particular ACE Inhibitor at the outset of treatment include the following:
>
> 49.1. NHS clinicians will take into account the extent, quality and specificity of the evidence base for the following:
>
> 49.1.1. the therapeutic benefit of using an ACE Inhibitor to treat the particular indication for which the prescription is being written;
>
> 49.1.2. the presence or absence of relevant side-effects and interactions with drugs used for other conditions;
>
> 49.1.3. reasons why a drug should not be prescribed for particular groups of patients or patients suffering from particular conditions ("contra-indications")."

Paras 49.2-49.5 set out further factors which NHS prescribers take into account, or may take into account, including at para 49.4:

> "the extent to which NICE and/or other NHS bodies recommend the use of particular drugs for the treatment of particular indications…"

And as regards specifically the treatment of hypertension, a condition for which perindopril was frequently prescribed, the Claimants state at para 56.5:

> "… at all material times the evidence base and available guidance for the use of Perindopril in the treatment of hypertension was superior to the evidence base and guidance for the use of any other ACE Inhibitor. Further or alternatively Coversyl was marketed by Servier on that basis."

22. In its Defence, Servier alleges, in a passage at para 17(c) which remained unchanged through the various stages of amendment:

> "… the choice of NHS prescribers is in practice often heavily constrained by prescribing guidelines and policies issued by their

> relevant PCTs and acute trusts. These include policies requiring prescriptions to refer, where possible, to the generic name of a product rather than a particular brand name (the effect of which is to favour dispensing of generic medicines by pharmacists), and policies requiring NHS prescribers to prescribe products available in generic form rather than therapeutically equivalent products that are not available in generic form."

23. Servier's response to the Claimants' assertions as regards prescribing practice is, first, at para 35 of the Defence:

> "The first sentence of paragraph 49 is admitted. As to the second sentence of paragraph 49, it is admitted that the factors listed in that paragraph are relevant to the consideration of which ACE Inhibitors (or indeed other pharmaceutical products) are most appropriate for a particular patient. It is denied (if so alleged) that the factors set out in paragraphs 49.1-49.3 and/or 49.5 are decisive considerations in prescribing practice. On the contrary, it is averred that in practice prescribers almost always comply with the recommendations referred to by the Claimants in paragraph 49.4, and paragraph 17(c) above is repeated in this regard."

And specifically, as regards para 56.5, Servier contends, at para 42(e) of its Defence:

> "… the first sentence of paragraph 56.5 is denied insofar as it relates to the available guidance for the use of Perindopril in the treatment of hypertension. In relation to the evidence base for the use of Perindopril, and the second sentence of paragraph 56.5, it is admitted that the totality of the evidence base for the use of Perindopril was in general terms superior to that for the use of other ACE Inhibitors, and that D1 marketed Coversyl® on that basis. For the avoidance of doubt, however, Coversyl® was not marketed, during the relevant period, on the basis of direct claims to superiority over other ACE Inhibitors as regards clinical outcomes."

THE PRELIMINARY ISSUES

24. It is common ground that a full trial in these proceedings cannot take place until the pending appeals to the CJEU have been determined. However, given the extensive duration of the European proceedings, the Court decided that it is appropriate to make progress with these cases in the meantime, including by way of disclosure.

25. The application by Servier to re-amend its Defence and introduce the prescribing argument was opposed by the English Claimants. In granting permission to amend, Henderson J (as he then was) observed, [2016] EWHC 2381 (Ch) at [3]:

> "A prime motivation of the English claimants in opposing Servier's application to make the amendments based on the

> prescribing argument is that giving disclosure of all documents formerly held by the English Primary Care Trusts in relation to the prescribing argument, as well as addressing it comprehensively in witness evidence and at trial, would be extremely burdensome and expensive…. If the disputed amendments are allowed, careful consideration will need to be given to the resulting disclosure by the English claimants, and the need to keep it within reasonable bounds, for example by confining it to a representative cross-section of Primary Care Trusts and Strategic Health Authorities."

26. That observation proved prophetic. In England, from the start of the Relevant Period to 2006, there were 28 Strategic Health Authorities ("SHAs") and 303 Primary Care Trusts ("PCTs"). In 2006, under an NHS reorganisation, the numbers of both SHAs and PCTs were significantly reduced and in 2013, under a further reorganisation, both the SHAs and PCTs were abolished and Clinical Commissioning Groups ("CCGs") were established.[1] There has also been reorganisation within the NHS in the other three nations.

27. Since NHS prescribing initiatives are frequently initiated or conducted at the local level, Servier sought extensive disclosure relevant to the prescribing argument of documents produced by, in the English action, the SHAs and PCTs. In view of not only the number of bodies concerned but the fact that those bodies no longer exist so that relevant documents would have had to be retrieved from storage by various successor bodies, this would have been a hugely burdensome and expensive exercise. Efforts were therefore made to select a representative sample, as envisaged by Henderson J's judgment. However, it became clear through case management hearings and preliminary experts' reports that this course was not practicable: there was substantial variety between the various entities which precluded a proportionate and cost-effective method for selecting a sample in the particular circumstances of this case: see e.g. the judgment of Sir Geoffrey Vos C. of 13 December 2016, [2016] EWHC 3357 (Ch) and my own judgment of 19 July 2017, [2017] EWHC 1914 (Ch).

28. Therefore, it appeared that a more sensible route in case management terms was to select preliminary issues which, depending on how they were determined, might preclude the need for very extensive disclosure related to the prescribing argument. The wording of the issues was subsequently revised by consent, so that the issues for trial were as follows:

> "(a) Would it have been reasonable or appropriate in the period between 2003 and 2009 for a clinician to prescribe another ACE inhibitor instead of perindopril in all circumstances, except where the patient was allergic to or intolerant of all alternative ACE inhibitors?
>
> (b) If not, in what circumstances would that have been unreasonable or inappropriate?

[1] Under the Health and Care Bill now going through Parliament, the CCGs will in turn be abolished and replaced with a new system of Integrated Care Boards.

> (c) Was it unreasonable for either of the present three sets of claimants or the various relevant predecessor organisations (including PCTs and SHAs) to fail to take any (and, if so, which) of the steps set out in paragraphs 83C to 83D of the Defendants' Re-Re-Amended Defence to the English Claimants' claim or identified in the Defendants' Further Information dated 29 September 2017?"

29. The reference in issue (c) to Servier's Further Information response of 29 September 2017 ("Servier's FI Response") is to its allegations of the respects in which four particular PCT guidance documents, which it had identified in an "illustrative" list in a previous response, were alleged to be unreasonable or inadequate.

30. At the outset, it is appropriate to make five preliminary observations:

    i) These issues fall to be determined in the context of this litigation and to assist in deciding whether or not to accept Servier's prescribing argument. This is not a public inquiry into the prescribing practice of doctors within the NHS in the four nations or into the organisation of medicines management across the health services.

    ii) Further, the prescribing argument only arises in the event that there is loss for which Servier would otherwise be liable. Therefore it proceeds on the assumption that Servier was in breach of (at least) Art 101 TFEU/s. 2 CA through entering into anti-competitive agreements with generic companies which led to the maintenance of a high price for perindopril.

    iii) In the context of this case, issues (a)-(b) are relevant as the threshold for issue (c). Prescribing doctors in the NHS are independent of the Claimants and Servier accepts that, if its prescribing argument is to succeed, it must prevail, at least to some extent, on issue (c).

    iv) The Relevant Period in respect of which the questions are to be addressed (i.e. the period of the damages claims, January 2003 – February 2009) is a relatively long period and some material circumstances changed during that time. Moreover, in terms of the subject-matter, it is also a relatively long time ago. There is a danger of hindsight, so care must be taken to avoid addressing the questions in the light of the understanding of the relevant medicines and the approach to prescribing that exists today.

    v) The four nations are different. Although it is common to speak of "the NHS", and I shall often use that term for convenience in this judgment, the provision of health services is separately organised, structured and financed in each of the four nations. Moreover, in the Relevant Period there was already an emphasis on maintaining a considerable degree of autonomy within each nation.

31. There was a dispute as to what factors are relevant to issues (a)-(b). Servier correctly emphasised that the question is not whether a prescribing decision to choose perindopril was reasonable but whether the doctor could instead reasonably or appropriately have chosen to prescribe another ACEI. Some of the Claimants' submissions appeared to blur this distinction. However, for its part, Servier at times seemed to argue that this

depended purely on clinical equivalence and thus was solely a question of expert evidence on that issue. However, the question is not whether ACEIs (including perindopril) have a so-called 'class effect'[2], and deliberately so. Moreover, although expressed in the alternative, I think that "reasonable" and "appropriate" effectively go together. If it was not appropriate to prescribe another ACEI instead of perindopril then it would not have been reasonable to do so, and vice versa. That is to be assessed not on the basis of a doctor's preference for perindopril through ignorance, misunderstanding or bias, but on whether there was an objectively rational basis for the prescriber to decide that perindopril was more appropriate than another ACEI. For example, since switching a patient from perindopril to another ACEI would need the patient's consent, it would not be appropriate to make this switch if the patient refused to consent despite the doctor's assurance that the alternative was just as good. Mr Saunders QC, appearing for Servier, accepted this. But the point goes rather wider. Hence the Claimants assert, at para 49A of the Particulars of Claim:

> "When deciding whether to continue treatment with the same ACE Inhibitor or to switch the patient to another ACE Inhibitor (or another anti-hypertensive drug), an NHS clinician will consider the matters set out [at para 49 of the Particulars of Claim (see para 21 above)], but in addition will take into account (i) the experience of the patient with the existing ACE Inhibitor; and/or the risk that switching the patient to a different ACE Inhibitor will cause undesirable side-effects; and/or (ii) the risk that switching the patient to a different ACE Inhibitor will cause a loss of adequate control of blood-pressure, whether temporary or permanent. For long-term patients, ACE Inhibitors are therefore an 'experience good', i.e. products for which exact information concerning the qualities of the product is acquired through consumption and in respect of which consumers are typically inclined to continue using the product for which the valuation (here efficacy and side-effects) is known rather than switching to another product for which the respective valuation is uncertain."

And the Claimants also relied strongly on various pharmacokinetic factors: see paras 179-182 below.

32. Much of the evidence and submission at the trial was directed at the basis on which doctors could (or could not) reasonably choose to prefer perindopril as more appropriate than other ACEIs. That evidence, in my judgment, is clearly relevant to issues (a)-(b).

THE HEALTH SERVICES

33. As mentioned above, in all the four nations, the public health services went through significant reorganisation over the Relevant Period. But within each nation, the provision of health service was divided into primary care (GPs, nurses, pharmacists and dentists), secondary care (hospitals) and tertiary care (specialist treatment centres).

[22] See further para 174 below.

England

34. Throughout the Relevant Period, the Secretary of State for Health had the statutory duty of securing the provision of services for the purpose of providing a comprehensive health service in England. The Department of Health ("DoH"), now the Department of Health and Social Care, was accordingly the relevant Government department.

35. At the regional level, in April 2002, 28 SHAs were established following the abolition of the previous Health Authorities. In July 2006, these were reorganised into 10 SHAs. The SHAs were not directly involved in service planning and commissioning but had a strategic and supervisory role in respect of both primary and secondary care in their areas. SHAs were dissolved on 1 April 2013 when the CCGs were created.

36. At the local level, by 2002 when the SHAs were set up, there were, as noted above, 303 PCTs across the country. In October 2006, the PCTs were reconfigured to match local authority boundaries, reducing the number from 303 to 152 and giving them additional responsibilities. Broadly, the PCTs had responsibility for securing the provision of health services in the local community, including the management of GP services. This included responsibility for management of budgets for GP prescribing and for seeking to influence prescribing decisions. The PCTs were also dissolved when the CCGs were created.

Wales

37. The provision of healthcare was devolved to Wales in 1999. The Minister for Health (called, during the Relevant Period, the Cabinet Secretary for Health and Social Services) has responsibility for the provision of health services at national level.

38. In 2003, 22 Local Health Boards ("Health Boards") were established, which were responsible for planning, securing and delivering health services within their respective areas. The Health Boards held and managed contracts for primary care with local GPs and commissioned secondary care from NHS trusts. There were 7 NHS Trusts during the Relevant Period responsible for secondary care. In October 2009, the structure was reorganised: the Health Boards were combined with the NHS Trusts and given responsibility for delivering secondary care directly, and they were reduced to 7 in number. There remained 3 specialist all-Wales NHS Trusts.

39. There were no equivalent bodies to the English SHAs in the Welsh system.

Scotland

40. At national level, the Scottish government is responsible for NHS policy in Scotland.

41. The policy is implemented at regional/local level by 14 Health Boards, each responsible for providing services in its designated area. The Health Boards were responsible for managing GP contracts and setting budgets for GPs. However, it appears there were also some PCTs within at least some of these Health Boards. During the Relevant Period there was also reorganisation concerning at least some of the Health Boards. For example, in 2006 the Argyll & Clyde Health Board was dissolved, with part of its area going to the Highland Health Board and the remainder moving to become part of the new Greater Glasgow and Clyde Health Board.

42. There were no equivalent bodies to the English SHAs in Scotland.

Northern Ireland

43. Since 1999, the Department of Health, Social Services and Public Safety in Northern Ireland ("DHSSPS"), subsequently renamed the Department of Health (Northern Ireland), has had overall responsibility for health policy in Northern Ireland. Prior to 2010, the DHSSPS allocated indicative prescribing budgets to individual GP practices and each practice provided a monthly report of their prescribing costs shown against budget.

44. Until 1 April 2009, health and social care services were implemented at the local level by four area Health and Social Services Boards: the Northern, Southern, Eastern and Western Boards. Those Boards commissioned health and social services and reported directly to the DHSSPS. Each was autonomous and held its own budget.

45. In April 2009, the area regional Health and Social Services Boards were merged to form the Regional Health and Social Care Board ("RHSCB"), and five new local regions were created. Sub-committees of the RHSCB, called Local Commissioning Groups, oversee the delivery of health and social care now, but the RHSCB is not equivalent to the English SHAs. The transition process was completed in 2010.

46. The DHSSPS and the RHSCB are the two Northern Irish Claimants in the Scottish/NI proceedings.

47. There were some other relevant bodies at national level in the different nations which will be referred to below.

48. Prescriptions in primary care are predominantly written by GPs and dispensed by community pharmacists. In all the four nations, the overwhelming majority of GPs are independent contractors who generally provided their services through General Medical Services ("GMS") contracts.[3] With effect from 1 April 2004, a new GMS contract was introduced which had been negotiated between the British Medical Association ("BMA") and representatives of the DoH and the equivalent bodies from the other three devolved administrations. The new contract was therefore implemented throughout the UK.

49. The new contract included the Qualities and Outcomes Framework (the "QOF") which sought to resource and reward GPs on the basis of how well they cared for patients rather than simply paying them for the number of patients that they treated. The QOF brought a very significant change in the relationship between GPs and their contracting partners: it incorporated a series of key indicators related to different aspects of performance, grouped under four domains: (i) clinical, (ii) organisational, (iii) additional services and (iv) patient experience. The GP practice received points according to its compliance with the indicators and each point had a financial value, so that according to the number of indicators that were met, a GP could substantially increase the income of their practice. Various revisions to the QOF were subsequently agreed and introduced, adjusting the number of points and varying the indicators or introducing new ones. Two of the organisational indicators relevant to these

[3] In the Relevant Period, less than 5% of GPs were salaried employees of individual GP practices or locums.

proceedings gave points (a) if the practice met with the primary care organisation prescribing advisor at least annually and agreed up to three actions relating to prescribing; and (b) if they subsequently provided evidence of change in those respects.

50. It is a feature of both primary and secondary care that the prescribing clinician selecting the ACEI for a patient was not responsible for paying for the drug. That was done at a more centralised level.

51. As Servier accepts, it has been fundamental throughout that clinicians, whether in primary or secondary care, exercise their independent clinical judgment when deciding what drug to prescribe, and cannot be ordered or directed by any of the Claimants to prescribe a particular drug. At the same time, there are various bodies which offer guidance and advice on prescribing and play a significant role in influencing prescribing choices. There are also constraints on prescribing as a result of local and hospital formularies. Moreover, and as further discussed below, the prescribing advisers employed by PCTs and Health Boards were engaged in seeking to influence the prescribing practice of GPs. These aspects are reflected in the prescribing argument in para 83C of Servier's Defence: para 17 above.

THE TRIAL

52. The trial was conducted as a hybrid hearing due to the restrictions of the Covid pandemic. Some members of the various legal teams attended remotely but all counsel were in court. All the witnesses save one gave evidence in person.

53. The exception was Mr Eric Falcand, now the Vice-President, Head of Business Development & Licensing for the Servier group. The Claimants had been concerned that he should attend in person, but because of the Covid travel restrictions I directed that he could give his evidence by videolink from Paris. In the event, the arrangements worked well and I consider that the Claimants were able to cross-examine him as effectively as if he had been present in court in London.

The factual witnesses

54. Mr Falcand was the only witness of fact called by Servier. Between January 2002 and May 2007, he was the CEO of SLL, Servier's UK operating subsidiary, and therefore effectively the head of Servier's UK operation.

55. Mr Falcand is, as one would expect from his position, highly intelligent. I found him to be an honest witness and he made clear that he was not involved in Servier's strategy in this litigation, of which he indeed appeared to be unaware. However, I found that he was somewhat evasive when facing questions as to why, in various contemporary documents, Servier had asserted that ACEIs had no class effect whereas his view is that there was a class effect. He was reluctant to acknowledge what seems to me obvious, namely that Servier's "medical representatives" in their repeated contacts with GPs were stressing not only the advantage of ACEIs generically over alternative medications but also the particular benefits of perindopril, and therefore Servier's Coversyl, which distinguished it from other ACEIs. Moreover, by 'class effect', Mr Falcand said that he meant that in terms of clinical efficacy there was no difference between the various ACEIs. Mr Falcand stood by Servier's assertions in its promotional material in the Relevant Period that for prescribing doctors there may be

good reason to prefer perindopril based on the ease of titration and, when it came to switching a patient already on perindopril, that the burden of the checks involved in switching had to be carefully considered as against any possible benefit.

56. The Claimants between them called 11 witnesses of fact, as follows:

English Claimants

Ms Claire Potter: Head of the Prescribing Policy and Legislation Team within the Medicines and Pharmacy Directorate at the Department of Health and Social Care. Between May 2004 and February 2008, Ms Potter lead a team within the Clinical and Cost Effectiveness Branch of that Directorate working to extend prescribing responsibilities to non-medical health service professionals.

Prof Neal Maskrey: formerly a GP and currently Visiting Professor of Evidence-informed decision making at Keele University. From 2001 and throughout the Relevant Period, Prof Maskrey served as Medical Director of the National Prescribing Centre ("NPC").

Dr Laurence Buckman: for many years until his retirement in March 2019, a GP in London and between 2007 and 2013 the chairman of the General Practitioners' Committee of the BMA which led the negotiation over the 2004 GMS contract.

Dr Graeme Smithard: currently a consultant geriatrician at Queen Elizabeth Hospital, Woolwich; during the Relevant Period a consultant in Stroke and Elderly Medicine at William Harvey Hospital in Kent. During that time, Dr Smithard was also appointed the Director of Research and Development for East Kent Hospitals NHS Trust and he is a founder member of the British Association of Stroke Physicians.

Mrs Joanne Watson: a qualified pharmacist who is currently Head of Medicines Optimisation for New Devon and South Devon and Torbay CCG. During the Relevant Period, Mrs Watson was the Head of Medicines Management for Plymouth PCT.

Welsh Claimants

Mr Jamie Hayes: a qualified pharmacist who since 2003 has been Director of the Welsh Medicines Resources Centre ("WeMeReC"), the Welsh equivalent of the NPC. Mr Hayes has also been a member of the All Wales Medical Strategy Group ("AWMSG") and a director of the All Wales Therapeutics and Toxicology Centre (previously the Welsh Medicines Partnership).

Dr Brian Hawkins: currently the Chief Pharmacist (Primary Care) for Cwm Taf Health Board and during the Relevant Period the Head of Medicines Management at Rhondda Cynon Taff Local Health Board.

Scottish Claimants

Dr Simon Hurding: a practising GP, who is currently also GP Adviser in the Medicines Management Team at the Lothian Health Board and further works for the Scottish Government as clinical lead for their Effective Prescribing and Therapeutics Branch and Clinical Lead for National Therapeutics Indicators. During the Relevant Period,

from 2004 Dr Hurding combined his GP practice with one day a week as Clinical Prescribing Lead for the Highland Health Board.

Ms Margaret Ryan: a qualified pharmacist who prior to her retirement in 2018 was Lead Clinician Prescribing Services for the Glasgow & Clyde Health Board ("NHS GGC") and also a member of the Therapeutics Branch Pharmacy and Medicines Division at the Scottish Government. During the Relevant Period, Ms Ryan was Senior Prescribing Adviser for Lomond and Argyll PCT until 2004, then Head of Prescribing Management for the Argyll and Clyde Health Board, and from 2006 the Lead for Prescribing Governance and Development at NHS GGC. She also served as chair of the Scottish Prescribing Advisers Association until 2017.

Prof. Angela Timoney: a qualified pharmacist, currently Director of Pharmacy at Lothian Health Board and also Visiting Professor at the University of Strathclyde Institute of Pharmacy and Biomedical Sciences and chair of the Scottish Intercollegiate Guidelines Network ("SIGN"). During the Relevant Period, Professor Timoney worked for Tayside Health Board, first as a consultant in Pharmaceutical Public Health and from 2007 as Director of Pharmacy. She also served as chair of the Scottish Executive of the Royal Pharmaceutical Society of Great Britain between 2004 and 2006.

NI Claimants

Mr Joseph Brogan: a qualified pharmacist who since June 2009 has been Head of Pharmacy and Medicines Management and Assistant Director of Integrated Care for the RHSCB. At the start of the Relevant Period, Mr Brogan was working at the DHSSPS as Senior Principal Pharmaceutical Officer for policy and practice, and from April 2004 he became Director of Pharmaceutical Services for the Western Health and Social Services Board.

57. Although they were challenged in cross-examination and criticised by Servier in terms of emphasis and approach, and as to what would be reasonable, it is not suggested that any witness was dishonest or unreliable. Indeed, since all the Claimants' witnesses were healthcare professionals (either clinicians or pharmacists), there was inevitably some overlap between the factual and expert evidence. This is not a case where the credibility of the witnesses is in question but some of the Claimants' witnesses were rather defensive under cross-examination and reluctant to accept obvious propositions that were put to them. I do not consider it necessary to lengthen this judgment by setting out observations on each of the Claimants' factual witnesses but will refer to their evidence as appropriate in the relevant part of the judgment.

The expert witnesses

58. The parties were given permission to put in expert evidence on three topics: (i) the clinical qualities and differences as between perindopril and other ACEIs; (ii) the prescribing practices of NHS clinicians, as regards perindopril and other ACEIs; and (iii) prescribing guidance and policies issued by national and local health authorities.

59. There were five expert witnesses, three called by the Claimants and two by Servier. On topic (i), the Claimants' expert was Dr James Coulson and Servier's expert was Prof Morris Brown. On topic (ii), the Claimants' expert was Dr Martin Duerden and

Servier's expert was again Prof. Brown. On topic (iii), the Claimants' expert was Prof Stephen Chapman and Servier's expert was Ms Sarah Kerr. All the experts served lengthy reports and reply reports, and there were joint meetings resulting in joint statements by the respective experts addressing each of the three topics.

The Claimants' experts

Dr James Coulson is Clinical Reader in Clinical Pharmacology, Therapeutics and Toxicology at Cardiff University and Visiting Professor of Clinical Pharmacology at the University of South Wales. He also holds an honorary contract and practises as a Consultant Physician, Clinical Pharmacologist and Toxicologist at Cardiff and Vale University Health Board.

Dr Martin Duerden qualified as a GP and from 1997 to 2001 was medical director of the NPC. Since then, he has held a number of senior positions in Heath Boards in Wales and various university posts involving teaching on prescribing and therapeutics. He was clinical advisor on prescribing to the Royal College of GPs from 2009 to 2019 and continues to be an Honorary Research Fellow at the Centre for Health Economics and Medicines Evaluation at Bangor University.

Prof. Stephen Chapman is Professor of Prescribing Studies at the Keele Centre for Medicines Optimisation, Keele University. Established as the Department for Medicines Management, of which Prof Chapman was one of the founders, the Centre for Medicines Optimisation delivers advisory services to health authorities at various levels in England, including PCTs and, now, CCGs and hospital trusts. He is the co-editor of *Medicines Management* published by BMJ Press.

Servier's experts

Prof Morris Brown is currently Professor of Endocrine Hypertension at Queen Mary University, London. Between 1985 and 2016 he was Professor of Clinical Pharmacology at the University of Cambridge and an Honorary Consultant Physician at Addenbrookes Hospital, where for many years he chaired the Drug and Therapeutics (Formulary) Committee. In 2005-2007, Prof Brown was President of the British Hypertension Society and was a member of the committee of the National Institute for Health and Care Excellence ("NICE") which published the NICE guideline for hypertension in 2006. He has received a Lifetime Achievement Award from the International Society of Hypertension.

Ms Sarah Kerr is a very experienced pharmacist. In 1996-2003, she worked in the private sector for Ciba Pharmaceuticals, which became Novartis Pharmaceuticals ("Novartis"), latterly as a Healthcare Programmes Manager focused on developing programmes and marketing initiatives for market access of Novartis products to the NHS. During the Relevant Period, Ms Kerr worked as a pharmaceutical adviser first at Totton and Waterside Primary Care Group, which became New Forest PCT, and from October 2005 at Southampton City PCT/CCG. In 2012 she became Commissioning Lead Pharmacist at West Hampshire CCG, now the Hampshire, Southampton and Isle of Wight CCG.

60. Dr Coulson, Dr Duerden and Prof Brown were cross-examined on their written reports in the traditional way. I heard the evidence of Prof Chapman and Ms Kerr concurrently in a so-called 'hot-tub', followed by supplementary cross-examination from counsel.

61. I consider that all the experts expressed their honest opinions, as one would expect. I found Dr Coulson to be a very independent witness and he expressed his views carefully, without regard to the position adopted by the two sides in the case. Indeed, although Dr Coulson was called by the Claimants, it is significant that Servier relies strongly on his evidence. Prof Brown is clearly a very eminent specialist in the field of hypertension but I found him somewhat reluctant to accept that any opinion on clinical matters which did not match his own could also be worthy of respect, dismissing contrary opinions as confused or not properly based on the evidence. I also consider that on topic (ii) concerning prescribing practice, although Prof Brown offered some valuable insights his evidence at some points strayed beyond his area of expertise. Prof Brown explained that he has worked closely with general practice and held many discussions about hypertension with GPs, but he has not worked in primary care and his experience of primary care was largely derived in the rather elevated atmosphere of a Cambridge teaching hospital. I found he was rather one-sided or selective in some of the evidence he put forward on issues relevant to general prescribing practice, as in his presentation of comparative price data for ACEIs. By contrast, Dr Duerden has specialised in the subject of prescribing and therapeutics and was well qualified to address this topic. His reports were very comprehensive and provided a great deal of helpful information. However, when scrutinised under effective cross-examination it became clear that some of his evidence lacked empirical foundation and reflected his personal estimate or assumption, although he had not made that clear in his written report, for example on the question of the proportion of patients with hypertension who had significant cardio-vascular or stroke-related co-morbidities. Therefore, on topic (ii) I found that both Prof Brown and Dr Duerden's evidence required careful scrutiny.

62. Ms Kerr's evidence was largely drawn from her own experience as a pharmaceutical adviser and in the medicines management team of particular PCTs, and then comprised comments on documents shown to her by Servier's solicitors. On the whole, I found the opinions she expressed were very reasonable and she provided some valuable insights. However, she lacked the overview brought by Prof Chapman who had the benefit of having considered the question of effective medicines management more widely. I found that Prof Chapman brought a realistic perspective, often agreeing with Ms Kerr as to what ideally should be done but pointing out that what reasonably could be done would depend on a variety of factors, including local resources, the experience of the particular medicines management team, and the extent of support given by the local consultants.

63. There was one very curious feature of this trial. Servier's branded perindopril (Coversyl) was a very important product for Servier over the Relevant Period. Mr Falcand said that during that time Coversyl accounted for the majority of Servier's turnover in the UK, and in 2005-6 it accounted for over 85% of that turnover. As he put it, Coversyl was "a very critical part of the business" on which SLL was relying "in order to be sustainable". Understandably, and as discussed further below, Servier therefore devoted extensive efforts to market perindopril to clinicians, including by detailed efforts to differentiate perindopril from other ACEIs. The Claimants are suing Servier for the allegedly excessive price which they paid for perindopril which

clinicians decided to prescribe, caused by what the European Commission and the General Court held were anti-competitive agreements whereby Servier paid large sums to generic suppliers to stay out of the market and thereby prevented a fall in price. The prescribing argument, in essence, amounts to the contention by Servier that the Claimants should have avoided that loss by encouraging clinicians not to prescribe Servier's own product which Servier was actively seeking to promote to those clinicians at the time. The causation/remoteness argument goes even further and contends that the failure by the Claimants to take the various alleged steps to discourage clinicians to prescribe perindopril was the sole effective cause of the Claimants' loss. A disinterested observer might find it surprising that such arguments would, or could, be advanced by a defendant found to have committed a very serious infringement of competition law.

64. The curiosity does not end there. By reason of this argument, Servier was in the position of having to disavow in these proceedings some of the claims which it made to doctors at the time for perindopril, and where its own expert variously described some of those claims as "not remotely justified", "fake science" and "misleading". Moreover, Servier subjected Dr Smithard, a senior consultant who firmly believed in the advantage of perindopril over other ACEIs for stroke patients, to strong cross-examination suggesting that his views were mistaken. Indeed, Servier's closing submissions accused him of having "quite extraordinary ignorance". However, Servier's contemporaneous internal documents showed that at the time Dr Smithard had been valued by Servier as a "Key local opinion leader" who would assist Servier's efforts to keep perindopril on local formularies; and in the early 2000s Servier had demonstrated its support for Dr Smithard by contributing to the cost of employment of a specialist stroke nurse assigned to his clinic.

ACEIs

65. The account below is derived from the helpful expert reports of Prof Brown and Dr Coulson.

66. The body's renin-angiotensin system controls constriction of the arteries. ACE is an enzyme, present in the membrane lining the blood vessel walls, which converts the inactive angiotensin I into angiotensin II which has the effect of narrowing arteries (i.e. vasoconstriction), thereby increasing blood pressure. ACE also has the effect of inactivating bradykinin, a chemical which relaxes blood vessels (i.e. vasodilation).

67. In the 1970s/80s, ACEIs were the first drugs to be developed as a means of preventing the formation of angiotensin II by inhibiting the action of ACE. Hypertension is the technical term for high blood pressure ("BP"), i.e. the pressure exerted on the walls of the arteries as blood flows through them. Since ACEIs reduced vasoconstriction they could accordingly be used in the treatment of hypertension.

68. The first orally administered ACEI to be identified was captopril in 1977. However, there were found to be a number of problems associated with captopril. It has a relatively short duration of action and therefore the patient requires dosing three times daily. It is associated with a significant first-dose fall in blood pressure, which could leave the patient unable to stand without fainting or feeling faint. This required patients, particularly the elderly or dehydrated, to have their first dose administered as an in-patient. And it gives rise to a high incidence of skin rashes and loss of taste. The last

two features were attributed to the presence of a sulfhydryl group in the drug and consequently further types of ACEIs were developed which contained a carboxylic acid group instead of the sulfhydryl group present in captopril. These included enalapril, lisinopril, ramipril and perindopril. Fosinopril, developed in 1988, is a different chemical form of ACEI, containing a phosphonic acid group instead of the sulfhydryl group.

69. In the 1990s, a further class of drugs called angiotensin receptor blockers ("ARBs")[4] was introduced which also target the renin-angiotensin system and could be used as an alternative for treatment of hypertension. ARBs and ACEIs both have the same ultimate effect of preventing angiotensin II from constricting arteries: whereas ACEIs block the formation of angiotensin II, ARBs block the action of angiotensin II (once formed) on the arteries.

70. There are other classes of drugs used to treat hypertension. They include beta blockers, calcium channel blockers and diuretics. Diuretics are the oldest class still in common usage. Calcium channel blockers and diuretics affect blood pressure in a fundamentally different way from ACEIs and ARBs in that they principally reduce salt which increases the volume of fluid flowing through the arteries. Research, to which Prof Brown materially contributed, demonstrated that combining drugs with opposite effects on the renin-angiotensin system (e.g. an ACEI with a diuretic) would be complementary and that such combinations have the most additive effects.

71. All the various ACEIs available in the Relevant Period were licensed for use in treatment of hypertension. However, ACEIs are also used in treatment of other conditions for which high blood pressure is a known risk factor. The conditions for which they are used has developed and expanded over the years as a result of various drug trials, and the conditions for which the different ACEIs are licensed in the UK are not the same. The licensed uses are set out in the British National Formulary, which is periodically revised. The licensed uses for the principal ACEIs is summarised in the following table (derived from the tables and schedules produced by Prof Brown and Dr Coulson):

[4] Also known as Angiotensin-II receptor antagonists ("AIIRAs", "A2RAs" or "ARAs").

Licensed indications for ACEIs

ACE Inhibitor	Hypertension	Heart Failure	Acute Myocardial infarction (i.e heart attack)	Prophylaxis of symptomatic heart failure in patients with asystomatic left ventricular dysfunction	Diabetic nephropathy (i.e diabetic kidney disease)	Prophylaxis of cardiac events following myocardial infarction or revasculari-sation in stable coronary artery disease	Susceptible patients over 55 - prevention of cardiovascular events (myocardial infarction, stroke, cardiovascular death or need of revasculari-sation procedures)
Captopril	X	X	X	X	X		
Enalapril	X	X		X			
Lisinopril	X	X	X		X		
Perindopril	X	X				X[5]	
Ramipril	X	X	X		X		X

Heart failure refers to a condition in which the pumping of the heart is reduced, either all the time or temporarily (e.g. on exercise), of which a primary symptom is breathlessness. The two right hand columns concerning prevention of cardiac or cardiovascular ("CV") events in high risk patients are similar and these indications are often referred to by the acronym "MACE" (major adverse cardiac events). Although MACE as a broad category includes stroke, treatment after a stroke or transient ischaemic attack (a 'mini-stroke' or "TIA") to prevent recurrence was seen clinically as distinct, and a matter for stroke specialists. Therefore, in practical terms, it is relevant to consider the use of perindopril and other ACEIs for the treatment of hypertension, heart failure, MACE and post-stroke/TIA. Since perindopril was not used for treatment of acute myocardial infarction ("MI") it is unnecessary to address that aspect. However, the variation in uses of the different ACEIs beyond hypertension illustrates that for many purposes they were not all interchangeable.

72. Some of the other indications in the table above are often, but not necessarily, found in patients together with hypertension and they are often indications for which high blood pressure is a known risk factor. The simultaneous presence of two or more conditions in a patient is referred to as a co-morbidity.

73. ACEIs are prescribed in both primary and secondary care. But it is important to distinguish between the various conditions for which they are prescribed and therefore the circumstances in which prescribing would occur. For straightforward hypertension, most prescribing would originate in primary care, i.e. by a GP. By contrast, for MACE, and post-stroke, the initial prescription is generally by a consultant and only after discharge into primary care would the GP take over the prescribing. For heart failure, the initiation of medication usually (in the Relevant Period) was undertaken on specialist referral but sometimes was done by the patient's GP.

[5] Since November 2005, following the EUROPA study: see para 84 below.

74. However, clinicians are not restricted to prescribing only for the licensed indications. In certain specialisms, such as paediatrics, much of the prescribing is 'off-licence'. In general, consultants treating patients in secondary care are more ready, given their specialist expertise, to prescribe outside a licensed indication: for example, it is clear that perindopril was not infrequently prescribed for stroke patients, and equally there was no suggestion that consultants refrained from prescribing ramipril for a stroke patient under 55. GPs are much more reluctant to prescribe outside the licensed indications, save when they were continuing treatment for a patient originated in secondary care, in which they case they would generally continue to prescribe the medication started by the consultant.

75. Once an ACEI had been prescribed, then unless the patient had an adverse reaction or the drug was unsuccessful in controlling blood pressure, the patient is likely to remain on that medication for a long time. A very significant proportion of prescriptions for ACEIs are accordingly repeat prescriptions.

76. Of the other classes of drugs used in treatment of high blood pressure, ARBs are significantly more expensive than ACEIs. However, a recognised side-effect of ACEIs in a minority of patients is a severe cough. The general approach where a patient displayed that adverse reaction to an ACEI was to switch him or her to an ARB.

Clinical drug trials

77. The properties and efficacy of drugs for treatment of relevant indications are determined and tested by clinical trials. There have been a number of major control trials involving different ACEIs. However, a significant feature of these trials that is of obvious relevance when assessing the substitutability of the various ACEIs, is that (before the end of the Relevant Period) there were no 'head-to-head' trials of ACEIs, i.e. trials testing one ACEI as against another. Trials testing long-term morbidity and mortality, often called 'outcome' trials, require a large population and have to occur over a long period since not every patient will experience a relevant event. Accordingly, such a head-to-head trial between ACEIs would be very expensive. Moreover, most clinical trials are subsidised by a drug company and drug manufacturers do not generally wish to fund a trial that compares their product with a close competitor's since there is a risk that it may prove to be inferior in one or more respects.

78. Therefore much of the discussion concerning perindopril as compared to other ACEIs was based on comparison of different outcome trials each involving a different ACEI. As Dr Coulson observed in his first report:

> "Interpreting the significance of indirect comparisons is complicated by the different doses of individual ACE inhibitors used in the studies; the different methodologies used to measure blood pressure in the studies; the study population; differences in drug combinations; and the outcomes measured."

Sometimes that comparison is undertaken by meta-analyses, i.e. rigorous overviews of multiple outcome trials, pooling the data involved. However, as Prof Brown pointed out, there have been no meta-analyses comparing drugs within the ACEI class, although there have been several comparing one class with another.

79. The major control trials referred to by the experts and in the contemporary guidance were as follows.

HOPE

80. The Heart Outcomes Prevention Evaluation Study Investigators ("HOPE") was published in *The New England Journal of Medicine* in January 2000. It was a trial involving ramipril in 9,297 high-risk patients over 55. Each had evidence of vascular disease (including stroke) or diabetes and a cardiovascular risk factor, but not heart disease. Each patient was randomly assigned either 10 mg ramipril daily or a placebo over a 5-year period. The study found that treatment with ramipril in that cohort reduced the rate of death from cardiovascular causes by 26%, the rate of heart attack (MI) by 20% and the rate of stroke by 32%. The authors of the study concluded:

> "Our findings clearly demonstrate that ramipril, a long-acting angiotensin-converting-enzyme inhibitor, reduces the rates of death, myocardial infarction, stroke, revascularization, cardiac arrest, heart failure, complications related to diabetes, and new cases of diabetes in a broad spectrum of high-risk patients."

PROGRESS

81. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was published in September 2001 in *The Lancet*. The study comprised 6,105 patients with a history of stroke or TIA. Some were treated with either perindopril 4mg daily alone or perindopril in combination with a diuretic, indapamide (at the treating physician's discretion and thus not randomly), whereas others received a placebo. The primary outcome (i.e. focus of the study) was stroke and over a 4 year period the study found that the combination therapy reduced the risk of stroke by 43% whereas treatment with perindopril alone produced no discernible reduction in stroke-risk. The summary interpretation in the study concludes:

> "This blood-pressure-lowering regimen reduced the risk of stroke among both hypertensive and non-hypertensive individuals with a history of stroke or transient ischaemic attack. Combination therapy with perindopril and indapamide produced larger blood pressure reductions and larger risk reductions than did single drug therapy with perindopril alone. Treatment with these two agents should now be considered routinely for patients with a history of stroke or transient ischaemic attack, irrespective of their blood pressure."

82. Professor Brown and Dr Coulson agreed that PROGRESS was not evidence for use of perindopril to treat hypertension since less than 50% of the patients in the study had hypertension and the study did not establish any benefit from single therapy with perindopril.

ALLHAT

83. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was published in the *Journal of the American Medical Association* in

December 2002. It was a large-scale trial sponsored by the US National Heart, Lung and Blood Institute, involving 33,357 patients aged 55 or older who had hypertension and at least one other risk factor for coronary heart disease. The objective was to determine whether treatment with a calcium channel blocker or an ACEI lowered the incidence of coronary heart disease or other cardiovascular disease events compared to treatment with a diuretic. The patients were randomly assigned either (i) the calcium channel blocker, amlodipine; or (ii) lisinopril (10-40 mg); or (iii) the thiazide-like diuretic, chlorthalidone. The study concluded that thiazide type diuretics are superior in preventing one or more major forms of coronary vascular disease, and that they should therefore be preferred as they were less expensive.

EUROPA

84. The European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease investigators (EUROPA) was published in September 2003 in *The Lancet*. The study aimed at examining whether treatment with perindopril also reduced cardiovascular risk in a low risk population (i.e. a population with stable coronary heart disease and no apparent heart failure). It involved 13,655 patients, who received perindopril for a run-in period of 4 weeks. After that, patients were randomly assigned either perindopril 8 mg daily or a placebo, with a mean follow-up period of 4.2 years. The primary endpoint was cardiovascular death, MI or cardiac arrest. The study found a 20% relative risk reduction across all subgroups. The authors note that their findings extend the observations of HOPE in which cardiovascular events were reduced with ACE inhibition in high-risk patients with coronary heart disease:

> "The risk level in our patients was lower than that in HOPE, which selected patients aged 55 years or older who had cardiovascular disease or diabetes plus at least one additional cardiovascular risk factor. In our study, almost a third were younger than 55 years, fewer had diabetes and hypertension, and more used aspirin, beta-blockers, and lipid-lowering drugs."

85. The EUROPA study led to perindopril's licence indications being extended in November 2005 to cover MACE as set out in the table above.

ASCOT-BPLA

86. The Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm (ASCOT-BPLA) was published in September 2005 in *The Lancet*. This was a randomised control trial including 19,257 patients with hypertension aged 40 to 79 who had had at least three other cardiovascular risk factors. Patients either received (i) a calcium blocker called amlodipine, along with perindopril as required, or (ii) a beta-blocker called atenolol, along with a thiazide-like diuretic, bendroflumethiazide, and potassium as required. The study found that fewer patients on regime (i) had a major cardiovascular event, but the results were not statistically significant. The trial was stopped prematurely because of the highly significant benefits of the amlodipine-based treatment regimen in relation to stroke and the onset of diabetes.

87. According to Professor Brown, ASCOT was initially a morbidity-mortality study comparing the beta blocker with the calcium blocker, and the secondary agent was given to achieve adequate blood pressure reduction. As the study was designed such

that perindopril was used as a second-line drug in a variable number of patients, he did not think that any conclusions can be drawn from ASCOT about perindopril with respect to treating hypertension. NICE considered ASCOT as part of the basis for its updated guidance in 2006 that beta-blockers should not be a preferred initial treatment for hypertension.

PATENTS

88. It is not in dispute that as high volume, prescription-only drugs, ACEIs are drugs with which generic manufacturers will seek to enter the market when the opportunity arises.

89. Generic enalapril became available around December 1999; generic lisinopril in about December 2002; and generic ramipril was introduced in the UK in about January 2004. In each case, this generic entry followed very swiftly on the drug coming off patent.

90. Although there can be a delay following generic entry before the NHS reimbursement price to pharmacists declines, a downward spiral in the drug's price is the inevitable consequence of the generic product coming onto the market. Servier indeed relied on this as a basis for obtaining interim injunctions in the Patents Court to prevent supply of generic perindopril by Apotex and Krka. In his evidence in support of the interim application against Krka, Mr Falcand explained that within two months of the entry of generic lisinopril, the branded producer had lost 90% of the market, and that in the case of ramipril, within two months 80% of the market had been lost: *Servier v Krka Polska SP.Zo.o* [2006] EWHC 2453 (Pat) at [83].

91. For perindopril, Servier obtained the first and basic patent for perindopril and its tert-butylamine salt with a priority date of 2 October 1980. The supplementary protection certificate which effectively extended that patent expired, as regards the UK, on 22 June 2003. Servier obtained additional protection by way of several process patents in respect of a process of industrial synthesis of perindopril, including EP No 0 308 341 ("the 341 Patent"). Those process patents were filed with the EPO on 16 September 1988 and accordingly were due to expire on 16 September 2008. It is well-recognised that a process patent may give less secure protection than a product patent since a generic manufacturer may be able to design around it: i.e. to use a different process to produce the drug.

92. As noted at the outset, the patent with which the present proceedings are concerned is a further patent, the 947 Patent, which Servier applied for on 6 July 2000. It is for a particular crystalline form of the tert-butylamine salt of perindopril and the process for making it.

93. In June 2004, Servier brought infringement proceedings against Niche for infringement of the 341 Patent (and two other associated process patents) after Niche applied for a marketing authorisation for generic perindopril in the UK. On 8 February 2005, after half a day of argument before the Patents Court, those proceedings were settled. The settlement agreement with Niche, whereby Servier made a transfer of value of some £11.8 million to Niche, is one of the agreements found to infringe Art 101 TFEU: see para 11 above.

94. In late July 2006, Apotex entered the UK market with a generic version of perindopril, but it was then restrained from further marketing by an interim injunction obtained by

Servier on 8 August 2006: [2006] EWHC 2137 (Pat).[6] A speedy trial was ordered of the claim.

95. On 3 October 2006, on the basis of the 947 Patent, Servier obtained an interim injunction against Krka, which had obtained marketing authorisations for generic perindopril in the UK: para 90 above. On 27 October 2006, Servier and Krka entered into a settlement agreement whereby Krka agreed to renounce any claim in relation to the patents and not to challenge them in future.

96. Meanwhile, on 18 October 2006, another generic manufacturer, Lupin, commenced an action in the Patents Court seeking a declaration of invalidity of Patent 947 or alternatively of non-infringement of that patent by the generic version of perindopril which it intended to market in the UK: see the General Court judgment, para 24. On 30 January 2007, Servier entered into a settlement agreement with Lupin whereby Lupin undertook similar obligations to those of Krka, and at the same time Servier agreed to pay Lupin €40 million for the transfer of the rights to three patent applications: ibid, paras 52-58. This was another of the agreements found to infringe Art 101.

97. The trial of the Apotex action took place in March 2007. By a judgment dated 11 July 2007, Pumfrey J held that the 947 Patent was invalid since it lacked novelty, or alternatively was obvious over the 341 Patent: [2007] EWHC 1538 (Pat). The judge refused to give relief pending an appeal and in July 2007 Apotex successfully entered the UK market. In dismissing Servier's appeal, the Court of Appeal delivered what must be one of the most excoriating judgments ever given in a patents case. Jacob LJ (with whose judgment Phillips LCJ and Lloyd LJ agreed) described Servier's 947 Patent as "plainly" invalid and a "try-on". He said: "It is the sort of patent which can give the patent system a bad name" [2008] EWCA Civ 445 at [9]-[10]. Lord Phillips LCJ deprecated the fact that permission to appeal had been given at all: at [41].

DRUG AND PRESCRIBING GUIDANCE AND INFORMATION

98. During the Relevant Period, a significant number of guidelines and authoritative reference documents were produced that covered various indications for which ACEIs were prescribed. Prof Brown considered that such guidance influences practice more than any other factor, either directly by doctors reading or consulting them, or indirectly through the opinions expressed by leading specialists who themselves read the guidelines and speak at educational meetings with GPs. Given the care, deliberation and effort devoted to the production of these guidelines, I consider that it was entirely appropriate for clinicians to follow them, and no one in the trial suggested otherwise.

99. I summarise below the main national guidelines and sources of information relevant to the issues. There were also more local guidelines in some fields, to which reference will be made when addressing the preliminary issues.

NICE Guidelines

[6] Servier had obtained urgent interim relief a few days earlier, on 3 August 2006, restraining further supplies by Apotex other than in fulfilment of existing, binding orders.

100. Dr Duerden said (and it was not disputed) that national guidelines from bodies such as the National Institute for Clinical Excellence ("NICE") and also the Scottish Intercollegiate Guideline Network ("SIGN") and the All Wales Medical Strategy Group ("AWMSG") were some of the most influential guidelines. Ms Kerr pointed out that sometimes the influence was indirect as not all GPs read the NICE guidelines themselves.

101. NICE was established in 1999 by statutory instrument as a special health authority and has a remit to provide evidence-based guidance to the English NHS on the use of selected and new drugs and technologies. It also publishes clinical guidelines for clinicians in some important treatment areas. In April 2005, NICE was renamed the National Centre for Health and Clinical Excellence after merging with the Health Development Agency.

102. NICE published its first clinical guideline in 2002 (on schizophrenia). Guidelines were gradually produced addressing other indications, and each guideline goes through an extensive and robust process of review before publication.

103. NICE Clinical Guideline No. 5 ("CG5") on Chronic Heart Failure – diagnosis and management in primary and secondary care, was issued in 2003. The full guideline[7] is a long (157 pages) and very detailed document, and one section concerns ACEIs. The Guideline there notes the effectiveness of ACEIs in treating patients with heart failure due to left ventricular systolic dysfunction. The Guideline states:

> "Treatment of heart failure with ACE inhibitors is cost effective, largely due to the costs saved from the reduced risk of hospitalisation. Treatment can be cost saving and has very favourable cost effectiveness ratios even when conservative assumptions are employed."

104. The Guideline includes a table of relevant dosages:

Table 5 Practical recommendations on the use of ACE inhibitors*

Which ACE inhibitor and what dose?

Licensed ACEI	*Starting dose (mg)*	*Target dose (mg)*
Captopril	6.25 three times daily	50–100 three times daily
Cilazapril*	0.5 once daily	1–2.5 once daily
Enalapril	2.5 twice daily	10–20 twice daily
Fosinopril*	10 once daily	40 once daily
Lisinopril	2.5–5.0 once daily	30–35 once daily
Perindopril*	2.0 once daily	4 once daily
Quinapril*	2.5–5.0 once daily	10–20 once daily
Ramipril	2.5 once daily	5 twice daily or 10 once daily

*Target dose based on manufacturer's recommendation rather than large outcome study

[7] An abbreviated version was also produced.

105. The specific recommendations in the Guideline include the following:

> "R22 All patients with heart failure due to left ventricular systolic dysfunction should be considered for treatment with an ACE inhibitor.
>
> …
>
> R24 ACE inhibitor therapy should be initiated at the appropriate dose [referring to the dosage table], and titrated upwards at short intervals (eg every two weeks) until the optimal tolerated or target dose is achieved.
>
> R25 Blood biochemistry (urea, creatinine and electrolytes) should be measured after initiation *and at each dose increment.*" [my emphasis]

106. NICE Clinical Guideline No 18 ("CG18") on "Essential hypertension: managing adult patients in primary care" was published in August 2004.[8] Essential hypertension is hypertension that has no known secondary cause, such as kidney disease. CG18 is a lengthy (261 pages) and detailed document which covers such matters as cardiovascular risk assessment, prognostic information, lifestyle advice and pharmacological intervention. Among the recommendations on pharmacological interventions are the following:

- "Offer drug therapy to (i) patients with persistent high blood pressure of 160/100 mmHg or more and (ii) patients at raised cardiovascular risk (ten-year risk of CHD15% or CVD20°/0 or existing cardiovascular disease or target organ damage) with persistent blood pressure of more than 140/90 mmHg.

- Offer drug therapy, adding different drugs if necessary, to achieve a target of 140/90 mmHg or until further treatment is inappropriate or declined. Titrate drug doses as described in the British National Formulary noting any cautions and contraindications.

- Drug therapy should normally begin with a low dose thiazide-type diuretic. If necessary, second line add a beta-blocker unless a patient is at raised risk of new-onset diabetes, in which case add an ACE-inhibitor. Third line, add a dihydropyridine calcium-channel blocker.

- Where possible recommend treatment with drugs taken only once a day.

[8] It was developed for NICE by the Newcastle Guideline Development and Research Unit.

- Prescribe non-proprietary drugs where these are appropriate and minimise cost."

107. CG18 provides a brief summary of drugs used for essential hypertension in a table, stating that further information can be found in the British National Formulary. The section of the table covering ACEIs lists captopril, enalapril, lisinopril, perindopril, ramipril and trandolapril. Under the heading, "Duration of action", it states: "Vary by drug from once to several times a day". And the column headed "Usage notes" states:

> "Dose titration and monitoring is necessary. Contraindicated in pregnancy and some kidney diseases. Caution when initiating while on a diuretic or with renal failure. Adverse effects include a persistent dry cough, rash and loss of taste."

The guideline then summarises and discusses the various randomised controlled trials on the various different drug therapies as at that date. It distinguishes between placebo-controlled trials and head-to-head trials where drugs of different types are compared (e.g., ALLHAT, comparing an ACEI with a thiazide-like diuretic). In the former category, for ACEIs CG18 identifies PROGRESS as the only relevant trial and explains that HOPE is not included since that study randomised patients with two or more cardiovascular risk factors and was designed similarly to trials of secondary cardiovascular prevention rather than treatment of hypertension and the trial population was not hypertensive.

108. In 2006, NICE issued (in collaboration with the British Hypertension Society) an update to the pharmacological part of CG18 to take account of the various subsequent large clinical outcome trials. This guideline (CG34) adopted, as Prof Brown put it, a 'bottom up' approach, analysing the evidence of those studies in order to revise the recommendations on pharmacological interventions. It was in this guideline that NICE recommended that beta-blockers should no longer be a preferred initial treatment for hypertension. The Guideline's 11 new recommendations included the following:

> "1. In hypertensive patients aged 55 or over, or black patients of any age, the first choice for initial therapy should be either a calcium-channel blocker or a thiazide-type diuretic.
>
> 2. In hypertensive patients younger than 55, the first choice for initial therapy should be an ACE inhibitor [or an ARB if an ACEI is not tolerated].
>
> 3. If initial therapy was with a calcium-channel blocker or a thiazide-type diuretic and a second drug is required, add an ACE inhibitor. If initial therapy was with an ACE inhibitor, add a calcium-channel blocker or a thiazide-type diuretic."

At the same time, the Update expressly did not change various recommendations from CG18, including the advice about titration and once daily medication quoted above.

109. The NICE Hypertension Guidelines do not express a preference for any individual ACEIs. CG34 states:

> "In formulating their recommendations, the GDG have assumed a 'drug class effect' when assessing results of studies using any particular pharmacological agent, unless there was clear evidence to the contrary."

British Hypertension Society Guidelines

110. The British Hypertension Society ("BHS") published guidelines for management of hypertension in 2004, updating guidance previously issued. It is clear that they were widely influential. Unlike the NICE Guideline, they are not confined to the treatment of "essential hypertension" but cover also various sub-groups such as people with diabetes or patients post-stroke. The BHS Guidelines are also very detailed. They emphasise the importance of blood pressure as a risk factor for CV disease. The guidelines refer to the new data on the safety and effectiveness of different classes of BP-lowering drugs, including ACEIs, calcium channel blockers and ARBs. The guidelines were produced by a working party, of which Prof Brown was a member. They stress the evidence from clinical studies showing that the majority of patients require two or more drugs to achieve BP goals and advise on the preferable drug combinations.

111. The BHS Guidelines describe each of the various classes of antihypertensive drug, and state:

> "For each major class of antihypertensive drug, there are compelling indications for use in specific patient groups, and also compelling contraindications. There are also indications, contraindications and cautions that are less clear-cut, and which are given different weight by different doctors."

Those indications, contraindications and cautions are set out for each drug class in a table.

112. The BHS Guidelines refer to the HOPE, PROGRESS and EUROPA trials on patients with high CVD risk, as showing that patients allocated to an ACEI demonstrated a substantial reduction in CVD events, accompanied by a reduction in blood pressure. The Guidelines state:

> "... these cardiovascular benefits were most likely explained by better BP control in those allocated to the ACE inhibitor, but it is not possible to rule out other additional benefits."

113. There is no reference in the BHS Guidelines to individual ACEIs or indeed individual drugs within the other drug classes (ARBs, beta-blockers, etc).

Joint British Societies' Guidelines

114. The Joint British Societies' ("JBS") Guidelines on prevention of cardiovascular disease in clinical practice ("JBS 2") were published in December 2005 and prepared on behalf of five relevant British professional societies, including the BHS, the British Cardiac Society and the Stroke Association. Their stated aim was:

> "to promote a consistent multi-disciplinary approach to the management of people with established atherosclerotic cardio-vascular disease (CVD) and those at high risk of developing symptomatic atherosclerotic disease.
>
> We recommend that CVD prevention in clinical practice should focus ***equally*** on (i) people with established atherosclerotic CVD, (ii) people with diabetes, and (iii) apparently healthy individuals at high risk (CVD risk of 20% over 10 years) of developing symptomatic atherosclerotic disease. This is because they are all people at high risk of CVD."

115. JBS 2, which comprises 56 pages plus appendices, is divided into sections and designed to present advice and recommendations in an approachable manner that would be of most assistance to clinicians. The Guidelines explain the advantages of a multifactorial approach to identification and treatment of high-risk individuals, including the following:

> - "The concept of total CVD risk replaces the traditional dichotomous classification of risk factors in most people. The physician asks the question "What is this person's CVD risk?" rather than does this person have "hypertension" or "hypercholesterolaemia". In other words, the physician considers the person's blood pressure and lipid values in the context of overall CVD risk. Even in people with very high single risk factors, the levels of other factors will still influence their total CVD risk.
>
> …
>
> - It is consonant with clinical practice whereby physicians deal with the whole person rather than just one aspect of cardiovascular risk."

116. Addressing the selection of drug therapy, JBS 2 endorses the combined treatment approach in the BHS Guidelines, referring to the different antihypertensive drugs classified as (A) ACEIs or ARBs, (B) Beta-blockers, (C) calcium channel blockers and (D) thiazide/thiazide-like diuretics. That approach sets out four potential steps:

> "Step 1 is a single drug: A or B or C or D, depending on age and ethnic group, titrated up to the highest recommended dose if tolerated. When the first drug is well tolerated but the response is small and insufficient, substitution of an alternative drug is appropriate if hypertension is mild (that is, grade 1) and uncomplicated. In more severe or complicated hypertension it is safer to add drugs stepwise until blood pressure is controlled."

117. Step 2 is combination therapy combining A or B with C or D. Step 3 is triple therapy combining A with C and D; and Step 4 involves the addition of an alpha blocker or additional diuretic. JBS 2 reproduces the table from the BHS Guidelines showing the indications, contraindications and cautions for each of the four classes.

118. There is no reference at all in the Guidelines to particular ACEIs or guidance as to selection between them.

NHS Prodigy Guidance – Hypertension

119. This guidance was aimed at GPs and others in the primary care sector. The November 2005 edition stated that among its goals was:

> "To treat hypertension adequately to reduce the risk of cardiovascular morbidity and mortality."

In the overview of hypertension management, the Prodigy Guidance advises:

- "Drug treatment should normally begin with a low dose thiazide diuretic.
- Consider initiating with a beta-blocker in people <55 years old, with moderately raised BP.
- Consider adding in drugs in a stepwise approach to achieve a target of =<140/90 mmHg Titrate drug doses as according to the manufacturer's instructions noting any cautions and contraindications.

…

- If further BP lowering is warranted, consider an ACE inhibitor or beta-blocker (if not yet used), another antihypertensive drug, or referring to a specialist."

Then under the heading: "What drug should I start treatment with?", the guidance goes into considerably more detail. Three bullet points are initially set out:

- "In general, the main determinant of benefit from BP-lowering drugs is the achieved BP, rather than the choice of treatment - this has been confirmed by head to head studies that indicate similar benefits irrespective of which major antihypertensive drug class is used to begin treatment [Blood Pressure Lowering Treatment Trialists Collaboration, 2000; Staessenetal, 2001].

- However, the blood pressure lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), a large trial (19,000 people) comparing BP lowering treatments, has recently been halted. Significant cardiovascular benefits were seen using a calcium channel blocker (amlodipine) and/or an angiotensin enzyme inhibitor (perindopril) compared to a beta-blocker (atenolol) and/or a thiazide diuretic (bendroflumethiazide[bendrofluazide]). The results of this trial are expected to be published in the second half of 2005 [ASCOT 2004].

- Co-morbidity will often influence the choice of antihypertensive treatment selection."

120. After summarising the NICE and BHS recommendations, the guidance provides a table of "Compelling indications for antihypertensive drug groups and evidence from trial data". For ACEIs, the table states the indications and recommendations as being:

> "first choice in heart failure, left ventricular dysfunction, and Type 1 diabetic nephropathy. Also used in post Ml or established coronary heart disease and secondary stroke prevention."

For these recommendations, the "key trial data" is expressed by reference to the ALLHAT and PROGRESS trials.

121. In the section headed "Medicines management" the Prodigy guidance sets out general principles, of which the first is:

> "Where possible recommend treatment with drugs taken only once a day."

122. Finally, the guidance notes that all ACEIs "seem to have comparable BP-lowering efficacy" and states:

> "• PRODIGY recommends enalapril, lisinopril, perindopril, ramipril, or trandolapril as first-choice ACE inhibitors. These are established ACE inhibitors with trial data for improving cardiovascular outcomes in hypertensive populations and can all be taken once a day.
>
> • Captopril is no longer recommended as a first-choice ACE inhibitor - it has a shorter half-life than other ACE inhibitors and needs to be taken in divided doses."

123. The Prodigy guidance then poses the question, "What dose of ACE inhibitor should I use?", which it answers with a table that I reproduce below (excluding trandolapril which was scarcely mentioned in the expert evidence and was much less significant at the time):

PRODIGY: Initiation, maintenance and maximum doses for ACE inhibitors

Dose of drug	Enalapril	Lisinopril	Perindopril	Ramipril
Elderly initiation*	5mg/day*	2.5 mg/day*	2 mg/day*	1.25 mg/day*
Standard initiation*	5mg/day*	2.5 mg/day*	4 mg/day*	1.25 mg/day*
Usual maintenance	20mg/day	20 mg/day	4 mg/day	2.5-5 mg/day
Max/day	40mg/day	Caraca® 40 mg/day, Zestril® 80 mg/day	8 mg/day	10 mg/day

*Initiation doses may differ if used in addition to a diuretic or in renal impairment

European Stroke guidelines

124. These guidelines were produced by the European Stroke Initiative and would come to the attention of specialist stroke clinicians. The 2003 Update to these guidelines, in the section headed "Antihypertensive Treatment" summarises the result of a meta-analysis from nine randomised controlled trials and refers specifically to the results of the HOPE and PROGRESS trials. The discussion concludes with the following Recommendations:

> "1 After stroke or TIA, blood pressure should be lowered, irrespective of its level, with a diuretic and/or an ACE inhibitor, subject to toleration of the treatment (level I).
>
> 2 The effectiveness of other classes of blood pressure-lowering drugs has not yet been established by controlled trials."

That was not changed in the updated guidelines published in May 2008. Dr Smithard agreed that these guidelines did not suggest that perindopril had a superior evidence base to any other ACEI.

RCP National Clinical Guideline for Stroke

125. The Royal College of Physicians ("RCP") issued a second edition of its Stroke guidelines in June 2004, prepared by the Intercollegiate Stroke Working Party, which comprised a large number of stroke specialists, and the guidelines were further subject to peer review. The guidelines run to 82 pages, plus appendices, and Prof Brown agreed that they are very respected. They cover the management of stroke and TIA. In the section on Clinical Care, under the heading of "Secondary prevention" the guidelines note that patients who have suffered a stroke remain at an increased risk of a further stroke and also of MI and other vascular events. The guidelines state:

> "These guidelines apply to all patients with TIA and stroke, even those not admitted to hospital."

126. Under the sub-heading, "Blood pressure", the guidelines make the following recommendations:

> "a. All patients should have their blood pressure checked, and high blood pressure persisting for over two weeks should be treated. …
>
> b. Further reduction of blood pressure should be undertaken using a thiazide diuretic (eg indapamide or bendrolluazide) or an ACE inhibitor (eg perindopril or ramipril) or preferably a combination of both, unless there are contraindications (A)."

The British National Formulary

127. The British National Formulary ("BNF"), published jointly by the British Medical Association and the Royal Pharmaceutical Society of Great Britain is very widely

consulted by GPs and clinicians generally as an authoritative source of information on specific prescription drugs and recommended dosage. At the time, it was published biannually. Both sides referred to the September 2004 edition and it was not suggested that the BNF changed in relevant respects over the Relevant Period.

128. The format of the BNF is, for each category of drugs, first to describe generally the indications and contraindications for prescribing, and then for each drug within the class to set these out specifically, with details of any side effects, specify the dosage to be administered.

129. Hence section 2.5.5 of the BNF concerns drugs affecting the renin-angiotensin system, i.e. ACEIs and ARBs. The general introduction to that section is headed "Heart failure" and states:

> "The treatment of chronic heart failure aims to relieve symptoms, improve exercise tolerance, reduce the incidence of acute exacerbations and reduce mortality. An ACE inhibitor given at an adequate dose[1] generally achieves these aims; a diuretic is also necessary in most patients to reduce symptoms of fluid overload.
>
> ---
>
> [1]For heart failure the dose of the ACE inhibitor is titrated to a 'target' dose (or to the maximum tolerated dose if lower). Target doses for some ACE inhibitors may exceed licensed ones, e.g. captopril (target dose 50 mg three times daily), enalapril (10-20 mg twice daily), lisinopril (30-35 mg daily), ramipril (5 mg twice daily), trandolapril (4 mg daily [unlicensed indication])"

130. In subsection 2.5.5.1 discussing specifically ACEIs, there is a summary account of the main indications for which they are used (heart failure, hypertension, prophylaxis of CV events, etc.), the contraindications and side-effects. Under "Heart Failure", the BNF states:

> "An ACE inhibitor can be initiated in the community in patients who are receiving a low dose of a diuretic or who are not otherwise at risk of serious hypotension; nevertheless, care is required and a very low dose of the ACE inhibitor is given initially."

131. Under "Hypertension", the BNF states that ACEIs should be considered when thiazides and beta-blockers are contra-indicated, not tolerated or fail to control blood pressure. However, there is a warning that ACEIs may cause very rapid falls of blood pressure in some patients, especially in patients receiving diuretics for whom the ACEI needs to be initiated with care.

132. The dosages set out in the entries for each individual ACEI, as modified by the target doses for heart failure set out above, can be summarised as follows:

BNF: Daily Dosages (mg)

	Hypertension			Heart Failure		
	Initial	*Maintenance/ Target*	*Maximum*	*Initial*	*Maintenance*	*Maximum*
Captopril	12.5* twice daily	25 twice daily	50 twice daily	6.25-12.5	25: 2-3 times daily	150
Enalapril	5*	20	40	2.5	10-20 in 2 doses	40
Lisinopril	10*	20	80	2.5	30-35	-
Ramipril	1.25	2.5-5	10	1.25	5 twice daily	10
Perindopril	4*	4	8	2	4	-

*But if used in addition to a diuretic: captopril 6.25 (also in elderly); enalapril 2.5; lisinopril 2.5-5; perindopril 2 (also in elderly).

The National Prescribing Centre

133. The National Prescribing Centre ("NPC") was established in April 1996 by the DoH. By the start of the Relevant Period, it was funded by the DoH and by NICE. In 2011, after the end of the Relevant Period, the NPC was merged with NICE and became its Medicines and Prescribing Centre.

134. As explained by Prof Maskrey, who served for many years as Medical Director of the NPC, the aim of the NPC was to facilitate the promotion of high quality, cost-effective prescribing, through providing information to pharmaceutical advisers and GPs, delivering a programme of training and education, dissemination of good practice, assisting in the development of IT systems relating to prescribing, and informing health authorities, pharmaceutical advisers and other relevant NHS staff about research and initiatives emerging from bodies such as NICE. The Medicine Resources Centre ("MeReC"), which had previously been an independent body, was part of the NPC and produced a number of publications.

135. Prof Maskrey said many GPs did not subscribe to such journals as *The Lancet* and the *New England Journal of Medicine*, and that even if the results of research and control trials were published in the *British Medical Journal* ("BMJ"), many GPs struggled to understand the more technical aspects of published research. Therefore:

> "… the NPC's publications and training performed what was in my view a useful function in distilling the implications of key research into guidance calculated to be more coherent, authoritative, readily digestible and practical for GPs and their prescribing advisers, in a way that was designed to complement their reading of journals and other publications."

136. In his oral evidence, Prof Maskrey explained that while some MeReC publications were sent directly to GPs, given the volume of information that busy GPs receive, the NPC recognised that realistically the effective way to get its information across to GPs was through the pharmaceutical advisers working for the PCTs. On that basis, the NPC saw the pharmaceutical advisers as its primary audience. Dr Duerden noted that while GPs did not always read them at first, the fact that GPs received the publications independently was of assistance to pharmaceutical advisers in their meetings with GPs when they could refer to those publications as appropriate.

137. The NPC produced a range of publications and sources of information, in particular: Reference Sheets, MeReC Bulletins, MeRec Extra and the NPCi.

Reference Sheets

138. These were bulletins that gave a brief precis of all the significant research papers and studies in respect of particular conditions, and the NPC produced periodical updates. With respect of some of the referenced publications, the NPC education team added a comment on the particular implications that might arise from the particular paper. Thus the December 2006 update to the Hypertension Reference Sheet included summaries of the ASCOT-BPLA, EUROPA and PROGRESS studies. Following the summary of EUROPA, the Reference Sheet drew the reader's attention to the debate around EUROPA:

> "Our comment: this study is similar in design to HOPE, but the population of patients were at lower risk as they were younger and fewer had diabetes or hypertension (although more had previous MI). As with HOPE, the authors claim the benefits seen with perindopril were greater than could be expected by its antihypertensive effects (the placebo group had an average BP 5/2mmHg higher than the perindopril group), but again, letters have questioned this (*Lancet* 2003; 362: 1935-1936)."

The account of PROGRESS summarises the findings in these terms, with the NPC's added comment:

> "Combination therapy with perindopril and indapamide produced larger blood pressure reductions and larger risk reductions than did single drug therapy with perindopril alone. Suggests that treatment with these two agents should now be considered routinely for patients with a history of stroke or transient ischaemic attack, irrespective of their blood pressure. Our comment: BP reduction in people with stroke is important. We are still waiting for the optimal BP target."

MeReC Bulletins

139. These were sent free of charge to GPs and pharmacists in England and Wales on a quarterly basis, and after 2006/07 in electronic form. For example, in September 2006, there was a MeReC Bulletin on the management of hypertension in primary care, dealing with the updated NICE guideline CG34 (see para 108 above). As Prof Maskrey explained, the bulletin provides a summary which "replicates hundreds of pages of a NICE guideline into a more digestible format." Under the heading, "Which drug to use", that bulletin refers to the various groups of drugs and continues:

> "In general, there is no compelling evidence of any clinically significant, drug-specific effects to distinguish between drugs in terms of efficacy (within or between classes) when their BP lowering effect is taken into

> account. However, there may be some benefits for particular drug classes in specific patient groups. Choice should be made on individual patient factors, side-effect profiles, and costs."

MeRec Extra:

140. These were shorter briefing papers, produced more rapidly and on an ad hoc basis, to address current issues, questions and controversies by providing updates on key clinical papers and guidelines. For example, in September 2002 the NPC issued a MeReC Extra paper on the randomised control trials of various cardiovascular drugs, including the HOPE trial. Commenting on HOPE, the paper states:

> "It is unclear whether the benefits are due to a specific effect of ramipril, to ACE inhibitors as a class or to an antihypertensive action, especially as PROGRESS showed that lowering blood pressure in people with a history of stroke reduces the risk of further strokes. Since hypertension is the most important risk factor for stroke, blood pressure control is important in all high-risk patients. A technology appraisal of ramipril and other ACE inhibitors is included in the NICE work programme."

141. In September 2003, the NPC published an issue of *MeReC Extra* summarising the recommendations of the NICE CG5, and in December 2004 it produced a *MeReC Extra* making practitioners aware of the key points in NICE CG18. When NICE produced its update to CG18, the NPC sought to publicise that in its *MeReC Bulletins* and therapeutic workshops and also through the NPCi.

NPCi

142. The NPCi was an e-learning platform developed by the NPC in 2006. It hosted the more text based outputs, such as the *MeRec Bulletins* and *MeRec Extra* but also exploited newer technology in producing data-focused commentaries, voice-over Power Point presentations and patient decision aids, generally focused on key therapeutic areas.

143. Hence in 2007, the NPC produced on the platform a data-focused commentary on Hypertension. Prof Maskrey explained that this was primarily targeted at pharmaceutical advisers who might then discuss it with GP prescribing leads and their PCT committee. The commentary looked at the use of each of the five categories of anti-hypertension drugs, including for each category charts showing the numbers of prescriptions and value of spend over each of the five years to March 2006. For each category there was also a map of England and Wales showing each PCT colour-highlighted to show the relative spend on that category of drug. Under ACEIs, the commentary observed:

> "The proportion of items which were for ramipril has increased significantly. Ramipril has a very strong evidence base, including the HOPE study. There has been some increase in the use of perindopril, perhaps

> associated with marketing of trials such as EUROPA and PROGRESS, although there are still fewer prescriptions for perindopril than Ramipril. The number of prescriptions for other products has remained more or less static. There is no reason to believe that perindopril has any superiority over ramipril or indeed other ACE-inhibitors. By contrast, the NHS spends much more on perindopril than any other ACE-inhibitor …."

The last observation was a reference to the position after March 2005, when generic ramipril was available. Prior to that date, the chart shows that since early 2003 ramipril had accounted for the highest NHS spend among ACEIs.

144. Under each category, the commentary posed three "Questions for reflection". The questions were similar in each case, and for ACEIs they were:

> "a. What is the pattern of ACE-inhibitor use in my practice/locality/PCT? Could it be more cost-effective?
>
> b. What barriers prevent it being more cost-effective?
>
> c. How can I go about improving the cost-effectiveness? Who do I need to work with?"

The UKMi and Prescribing Outlook

145. The UK Medicines Information ("UKMi") was described by Prof Maskrey as a loose collaboration of specialist pharmacist units, historically located in large teaching hospitals. Its website at the time, to which he referred, described it as a "network" of local and regional medicines information centres. Those were centres or departments which at that time usually existed in the main or teaching hospital in each region, and among their responsibilities was to disseminate information about drugs to the hospitals and PCTs in the area. The members of the centre were accordingly employed by the hospital. UKMi was set up as a means of cooperation between those centres.

146. The UKMi, in collaboration with the NPC, produced a publication called *Prescribing Outlook* to assist NHS budget holders and those involved in prescribing planning by providing information on medicines anticipated to come on the market and the potential impact of national guidance on the local health economy. The role of the NPC in the production of *Prescribing Outlook* concerned the checking of initial drafts against the information the NPC had itself gathered on forthcoming medicines. Prof Maskrey agreed that *Prescribing Outlook* was an important source of information for those involved in medicines management, but he observed that:

> "the very nature of the "commercial in confidence" information held by pharmaceutical companies meant very little about forthcoming medicines was certain."

147. *Prescribing Outlook* included information on drugs with forthcoming patent expiry. In the August 2003 edition, perindopril was listed in a table showing its patent expiry date as June 2003. The October 2003 edition said that "generic versions of perindopril and

ramipril should become available over the next 12 months". The October 2004 edition stated as regards treatment for heart failure that:

> "The patents for perindopril and ramipril have expired and generic versions of ramipril are available."

And when it came to hypertension, the same edition stated that there were generic products in the ACEI class, expressly referring to captopril, enalapril, lisinopril, ramipril and perindopril. As regards perindopril, this was of course incorrect.

148. The UKMi periodically also produced other advice and information sheets in support of medicines management within the various NHS organisations.

SERVIER'S CLAIMS FOR AND PROMOTION OF PERINDOPRIL

149. Servier had a sustained and sophisticated marketing operation in the UK. Its activity in that regard was governed by the Code of Practice of the Association of the British Pharmaceutical Industry ("ABPI"). The ABPI Code of Practice was first established in the early 1990s. The 2003 edition[9] included the following provisions:

> "7.2 Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication.
>
> 7.3 A comparison is only permitted in promotional material if:
>
> • it is not misleading
>
> …
>
> 7.10 Exaggerated or all-embracing claims must not be made, and superlatives must not be used except for those limited circumstances where they relate to a clear fact about a medicine. Claims should not imply that a medicine or an active ingredient has some special merit, quality or property unless this can be substantiated."

150. Mr Falcand emphasised that Servier took care in the promotional materials which it used in the UK, and for which he took responsibility, not to put forward inaccurate or misleading claims and to adhere to the ABPI Code of Practice. He accepted that occasionally mistakes had been made but said that when detected they were quickly corrected. Indeed, he stated: "SLL's scientific credibility has always been sacrosanct."

151. SLL's Coversyl promotional budget peaked at £17.4 million in 2003/2004, on the back of the EUROPA study, which it expected would give perindopril a significant boost, and then steadily decreased to £4.3 million in 2007/2008. The majority of that budget

[9] The 2006 edition of the Code of Practice amended the last sentence of cl 7.2 to read: "They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis" and added: "Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine."

went on its medical representatives ("reps") but it also spent money on sponsorship of national and regional meetings and speaker events, and occasional grants and sponsorship to a number of organisations.

152. SLL had, in about October 2004, 160 medical reps whose task it was to visit GPs and provide them with information, and the sales force also targeted hospital consultants and the PCTs or Health Boards. The number of Servier medical reps was broadly similar to Aventis, the manufacturer of ramipril. The medical reps were given targets as to the frequency with which they should visit each GP. Some doctors refused to meet medical reps from drug companies but others met them regularly. For those GPs who were prepared to meet medical reps, Servier assigned one rep for each 200 GPs, with an expectation that they would meet 'their' GPs every two months. In those meetings, the rep would, unsurprisingly, focus on the major drug being marketed by Servier at the time, which between 2003 and 2007 was Coversyl. SLL had a separate group of 64 medical reps assigned to target those hospital consultants who worked in the areas where ACEIs were prescribed. And SLL in addition had a number of specialist regional clinical liaison executives to liaise with PCTs and pharmaceutical advisers, with the aim of ensuring that perindopril was included in local formularies and remained there. In its marketing plan for Coversyl for 2004/05, this was expressed as follows:

> "The aim is to use EUROPA and sub-study results to differentiate Coversyl from other ACEI and ARBs in order to gain support for formulary listings to aid maximum freedom to prescribe and sell-out in primary care. In order to achieve this it will also be necessary to show economic analyses of EUROPA to show the benefits and costs of treatment with Coversyl."

153. The nature of Servier's promotional activity was no different from its competitors. Mr Falcand explained that the companies' promotion of a particular product tailed off after that product lost its patent protection. Given the effect on price once the product was off patent, that is hardly surprising. As a result, from 2004 onwards, perindopril was the only leading ACEI being actively marketed, until that marketing was halted in 2007.

154. There was a dispute between the parties as to what effect this activity had and whether it is relevant to the issues before the Court. I shall return to the question of relevance below. But as regards effect, the National Audit Office ("NAO") Report, *Prescribing costs in primary care* (May, 2007), noted that GPs receive relatively little formal training in clinical pharmacology and prescribing (para 3.3). The NAO Report stated:

> "3.4 GPs receive a large amount of prescribing information, and have to reconcile different, sometimes conflicting, sources of advice. …
>
> 3.5 GPs have limited time to process all the material they receive related to prescribing. Seventy-five per cent of the GPs we surveyed estimated that they read less than half of the prescribing information they received over the past year; and 40 per cent said they read less than a quarter. Most GPs in the focus groups conducted for us by RAND Europe felt that due to limited time

> and resources, their practice was only able to focus on two or three issues in prescribing at any one time.
>
> 3.6 It can be difficult for GPs, who are not generally experts in pharmacology or statistics, to appraise technical and statistical information about the effects and efficacy of drugs. Only five per cent of respondents to our GP survey said they always felt confident in appraising prescribing information. Research in 1996 found that different statistical presentations of the same research results led to different prescribing decisions by GPs, and that the majority of GPs studied admitted to having problems understanding statistics commonly found in medical journals."

155. Then, under the heading, "GPs are influenced by the pharmaceutical industry's marketing", the NAO Report states:

> "3.11 The pharmaceutical industry spends more than £850 million annually on marketing and promotional efforts, and there are 8,000 pharmaceutical industry representatives (about one representative for every four GPs) visiting doctors and marketing their drugs across the country….
>
> 3.12 The Health Select Committee's 2005 inquiry into the influence of the pharmaceutical industry concluded that the industry promotes medicines aggressively after launch. It found that industry promotional efforts were 'relentless', and targets included not only prescribers but also the general public…."

156. The NAO's survey of GPs found that, nationwide, 21% of GPs reported that they saw industry reps at least once a week, and the majority saw a rep between once a week and once every three months.

157. Discussing the important role which pharmaceutical prescribing advisers employed by PCTs have in advising GPs and helping them assimilate prescribing information, the NAO reported the results of its commissioned survey:

> "3.19 Prescribing advisers are effective at influencing GPs' behaviour, but the pharmaceutical industry also has a significant influence. Two thirds of the GPs we surveyed said that prescribing advisers have more influence on their prescribing behaviour than pharmaceutical companies, with 43 per cent indicating that prescribing advisers have much more influence than the industry. Prescribing advisers themselves also felt that they had more influence than industry, but they did not rate their own influence on GPs as highly as GPs themselves did. Fifty nine per cent of prescribing advisers felt they have more influence on GPs than big pharmaceutical companies, and 29 per cent rated themselves as having much more influence than the industry. However 21 per cent of GP respondents indicated that they felt that pharmaceutical companies have much more or slightly more influence than prescribing advisers."

158. Prof Chapman and Dr Duerden also relied on an article by Prosser, Almond and Walley, "Influences on GPs' decision to prescribe new drugs – the importance of who says what" (2003) *Fam Practice*, 20, 61-68.[10] That involved a survey of 107 GPs in the north west of England, through semi-structured interviews, and found that pharmaceutical reps were more important in influencing GPs than biomedical influences like the failure or adverse effects of current treatment or hospital consultants.

159. Servier criticised reliance on this paper as the survey involved was of limited size and restricted to GPs' decisions regarding only new drugs (launched no less than 20 months previously). I acknowledge that extrapolation from those results must be made cautiously, but Servier's expert, Ms Kerr, said that perindopril was viewed at the time as a 'new' drug in that it was available only on-patent as a branded medicine. And Dr Duerden said that perindopril (and also ramipril) was somewhat unusual in being heavily marketed like a new drug on the back of recent drug trials late in its patent life.

160. Servier also drew attention to the NAO's commissioned survey of GPs, which was a background document to its report, where pharmaceutical company reps were ranked low down the list of useful information sources.

161. In my view, it is not necessary to determine the hierarchy of influences on GPs, still less to seek to estimate the degree of weight that various influences might have had. Clearly, there were a variety of influences and GPs are not naïve but appreciate that pharmaceutical reps are there to promote their company's products whereas guidance from independent public bodies is more objective. But GPs are unquestionably busy people and, as outlined below, the promotional materials are sophisticated documents which present in an accessible form the results of drug trials and scientific studies where GPs will not have the time or, often, the understanding to evaluate those primary sources. Prof Chapman stated, in the course of the 'hot tub':

> "The industry is very organised and very effective in its approach to influencing. It will have a marketing platform which will be agreed by the business, it will have a sales force who have uniform messages, and they will be trained in delivering those uniform messages, and those messages will go out in a pulsed manner, campaigns will change over time, emphasis will shift according to the lifetime of the drug, and a lot of training and a lot of money goes into making sure those messages are as optimised as they can be."

Ms Kerr, who herself had previously worked for a large pharmaceutical company, did not disagree with this summary.

162. I consider that the Prosser, Almond and Walley study, which I was told is one of the few surveys of its kind, can legitimately be looked at as part of the overall picture, and I note that it was relied on in shaping the findings in the NAO Report, which was not

[10] They referred also to Prosser and Walley's follow-up study of 30 of those 107 GPs who were 'outliers' in their approach: (2003) *Fam Practice* 20, 583-591.

restricted to new drugs.[11] That, as I understood it, was the approach of Dr Duerden and I think it was entirely legitimate.

163. At the end of the day, as both Prof Chapman and Dr Duerden pointed out, sophisticated pharmaceutical companies like Servier would not spend such a large budget on medical reps and drug promotion to GPs if it was not effective. The fact that Servier did so with regard to Coversyl over this period is, in my judgment, very significant and more powerful evidence than any individual survey that, inevitably, is looking more generally and where the methodology can always be criticised. Professor Brown indeed gave a telling example of how a pharmaceutical company can influence prescribing behaviour as regards ACEIs. Referring to the period from January 2003 to the autumn of 2004 when lisinopril was considerably more expensive than enalapril, he said that the decision among many clinicians nonetheless to prescribe lisinopril "was undoubtedly driven by a very successful sales campaign at the time by the manufacturer of lisinopril". And he added that there was no denying that such sales campaigns can be effective. Prof Brown was asked about the effect on specialists of Servier's messages about perindopril based on the EUROPA study:

> "Q. At this time, 2003, do you consider that that messaging about the special qualities of perindopril was capable of producing an impact on the specialists?
>
> A. My Lord, the simple answer is yes."

Moreover, Prof Maskrey said in his evidence that the NPC was hearing from pharmaceutical advisers that the marketing of perindopril was having an effect.

164. I also find that the way Servier described internally the result of its promotional campaigns is instructive, even allowing for some self-serving exaggeration. The executive summary of its very detailed 2005/2006 Orientation Plan for Coversyl stated:

> "The campaigns have been focussed over the last 12 months on highlighting the efficacy of Coversyl as the key point. EUROPA has successfully been used as the main proof of efficacy, while the campaigns also differentiated Coversyl from other ACE inhibitors and ARB's. The successful implementation of strategy to focus on a EUROPA sell-in to secondary care, and cardiology in particular, has led to a massive increase in market share at a hospital level (especially cardiology), which has helped drive increased use in primary care. The targeting strategy that we pursued has successfully increased the depth of Coversyl prescriptions.
>
> Many pharmacy advisors are still sceptical to [sic] implementing EUROPA because of a perceived class effect among ACEI. There has also been an increase in skill levels of the reps, which has aided the rapid implementation of the EUROPA results in everyday practice. The main reasons why doctors prescribe Coversyl are efficacy and tolerability. The reps have most

[11] NAO Report at para 3.39.

> success in sourcing hypertensive patients, where the biggest opportunity is as an add-in when patients are uncontrolled."

And the detailed discussion in the Orientation Plan includes the following:

> "In a survey, representatives believe their doctors prescribe Coversyl for the following reasons, ranked in order: 1) Efficacy, 2) Tolerability, 3) New Data, 4) Hospital Usage, 5) Cost and 6) Habit. These are consistent with the results of GP focus groups that were held earlier in the year that listed 24-hour control (which meant absolute [Blood Pressure] reductions), beyond BP effects (by which they mean risk reductions) and tolerability as the main reasons to prescribe an anti-hypertensive agent, and efficacy, ease of use and strong data as the key advantages of Coversyl.
>
> …
>
> In secondary care the strategy was well implemented and contributed to a high level of awareness of EUROPA — a survey among cardiologists in June showed 60% where [sic] spontaneously aware of EUROPA with 96% aware when prompted — and have resulted in changes in perceptions towards Coversyl. This focus in hospitals meant our key messages were successfully relayed as soon as the trial results were announced and numerous new hospital and PCT listings were gained. There has been a huge increase in usage of Coversyl at a secondary care level, resulting in 15 consecutive monthly increases in hospital market share …, at the expense of ramipril."

165. Specifically, as regards cardiologists, the Plan reported:

> "Coversyl was often perceived as having a poor evidence base compared to the other leading ACE inhibitors. For this reason, a specific project was initiated to raise the awareness of Servier and Coversyl within cardiology, both from a corporate perspective and from a Coversyl perspective using the EUROPA data (specific activities are outlined in the Cardiovascular awareness Orientation Plan). The result has been a tremendous uplift in cardiologist's perception of Coversyl as a highly effective and evidence-based ACE inhibitor, which has resulted in huge increases in sales. Many, previously negative cardiologists believe EUROPA is now the definitive study of ACE inhibition in CHD and have changed their prescribing as a result. Over the last 12 months, Coversyl usage in cardiology has grown by over 140%, usage in cardiothoracic surgery by 105% and usage in coronary care units by 108% …. These data reflect the newfound confidence and belief that cardiologists now have in Coversyl, as a result of EUROPA."

166. The training slides which Servier used for its medical reps and the promotional materials with which they were supplied to give to doctors emphasised various strengths of Coversyl and comparisons of certain features of perindopril with other ACEIs, referenced to scientific papers and presented in the form of tables, graphs and headline features. Among the points made were that:

i) Coversyl "has one of the highest [trough-to-peak] ratios of any ACEI. This ensures that patients treated with Coversyl receive full 24-hour inhibition." That serves to avoid the danger of a fall in blood pressure in the early morning hours before the patient takes their medication at breakfast.

ii) Coversyl enables a single step titration from 2mg to the usual maintenance dose of 4mg compared to three steps for ramipril (from 1.25 mg to 10 mg) and lisinopril;

iii) The simplicity for patients of taking just one tablet a day.

iv) Coversyl is highly lipophilic. Mr Falcand explained that this was a particular characteristic of perindopril and ramipril, compared to other ACEIs.

v) Coversyl is well tolerated by patients with cardiovascular disease, with lower withdrawal in clinical studies due to cough in the EUROPA and PROGRESS trials than ramipril in the HOPE trial.

And in a document prepared for doctors in April 2005, Servier stated:

> "COVERSYL even works in patients who were unresponsive to other ACEIs & ARBs"

The footnote to that statement gives references to two academic papers, and below the statement is a bar chart showing the extent of systolic and diastolic blood pressure reduction achieved by treatment with Coversyl following failures of treatment with ramipril, lisinopril, enalapril and an ARB.

167. There is a further aspect of Servier's promotional activities. Servier identified what it described internally as "key opinion leaders" (or "KOLs") who were consultants or academics known to favour the use of perindopril. The sophistication of Servier's efforts is evident from its internal differentiation of these KOLs as between key national, regional and local opinion leaders ("KNOLs", "KROLs" and "KLOLs", respectively). Servier provided sponsorship of the expenses for KOLs to attend conferences and in some instances for their research and publications. Servier also sponsored a number of national and regional medical meetings in relevant subject areas. It referred to certain doctors as "product advocates" for Coversyl and sponsored what it called round table meetings for them to discuss the product with GPs. As Mr Falcand explained:

> "A product advocate is a doctor who is convinced by the data and would be keen either to prescribe it in primary care or in secondary care, or to be able to speak about it. …

> A round table is one cardiologist, for instance, in one particular hospital with the ten GPs around him, and usually they were meeting for two hours in the evening and they are talking about papers, they are talking about the science, and the GPs believe that this is a good way for them to get to know the science.
>
> So classically, a product advocate would be one of those cardiologists, for instance, who is able to present the paper in a fair way to a round [table] of GPs around him."

168. I should make clear that there is no suggestion that activity of this nature was unique to Servier. Further, there is no suggestion that the KOLs and other consultants were not expressing their own, genuinely held opinions. However, as discussed further below, where consultants who were highly regarded in their field by their peers had views about the particular benefits of perindopril, this was a way in which Servier ensured that those views gained wide circulation and acceptance in the medical community.

ISSUES (A)-(B)

169. The first two preliminary issues are inter-related and I therefore consider them together. For convenience, I repeat them:

> "(a) Would it have been reasonable or appropriate in the period between 2003 and 2009 for a clinician to prescribe another ACE inhibitor instead of perindopril in all circumstances, except where the patient was allergic to or intolerant of all alternative ACE inhibitors?
>
> (b) If not, in what circumstances would that have been unreasonable or inappropriate?"

170. There was a dispute between the Claimants and Servier as to what these two issues mean. Servier submitted that these are questions of objective, clinical fact, as understood in the Relevant Period. On that basis, as Mr Saunders QC put it in his opening:

> "all ACEIs were clinically substitutable and believing that they were not was necessarily unreasonable."

And he submitted that:

> "the relevant guidelines that were issued all proceeded on the basis of the class effect."

171. Those submissions were in line with Servier's pleaded case, which was the foundation for the order for these preliminary issues. The pleaded prescribing argument starts with the contention at para 83B(b) of the Defence that:

> "ACE Inhibitors exert a 'class effect' and there was no clinical difference between Perindopril and other ACE Inhibitors already available in generic form."

See further para 17 above.

172. The Claimants approached the questions rather differently. They did not suggest that there was any indication for which perindopril was the only appropriate ACEI, but their submission was that:

> "during the relevant period, there was serious debate about whether the different ACE inhibitors had or might have different clinical qualities, and there were important and widely-publicised evidence studies endorsing the clinical advantages of perindopril (alone, or in combination with other medicines); and prescribers could reasonably conclude that the best interests of their patients were served by prescribing perindopril."

And the Claimants submitted that the first two issues are not capable of a binary answer for all patients:

> "in the individual circumstances presented by a given patient, it may not have been reasonable or appropriate for the clinician to prescribe an ACE inhibitor other than perindopril. Specifically, in a situation where the clinician (reasonably) concluded that the patient's overall best interests were served by prescribing perindopril, or by continuing to prescribe perindopril rather than switching to an alternative, then it would not have been appropriate for the clinician to prescribe another ACE inhibitor instead."

173. In my view, it is clear that the first two issues are not limited to questions of clinical equivalence, and advisedly so. They are addressed to clinicians' prescribing decisions in practice. Although clinical equivalence or substitutability may be necessary for any decision to prescribe another ACEI instead of perindopril, that does not mean it was a sufficient condition. There are other considerations which the prescriber may appropriately take into account, as discussed further below. Indeed, Mr Saunders realistically accepted, when I put it to him, that if the evidence showed that putting the patient on an ACEI other than perindopril would require them to make an additional visit to the surgery and the patient is very old, then a GP could reasonably decide that they should not prescribe a different ACEI. He suggested, however, that that situation was limited to switching a patient already on perindopril to another ACEI. It is indeed the case that switching patients gives rise to distinct considerations, as I shall explain. But it is necessary to consider whether such factors may arise also when it came to initiating patients onto an ACEI. This all goes to the question of what would have been in the patient's overall best interests which, as the Claimants submitted and I accept, as indeed I believe did Servier, is the touchstone in addressing the questions.

174. A more difficult question is how the issues are to be answered if there was a genuine division of opinion among respected experts and specialists at the time as to whether perindopril might be clinically more appropriate for particular indications. I should emphasise that the issues are not asking whether it would have been unreasonable for a clinician to prescribe perindopril. Self-evidently, many clinicians did select this drug. Moreover, and notwithstanding Servier's case as set out above, I consider that a positive answer to issue (a) does not require a finding that *all* ACEIs were substitutable, i.e. that

there was a true 'class effect': it would be sufficient if one other ACEI could reasonably have been selected, although, as will be apparent, determination of which ACEI that was has significant implications.

175. In my judgment, if in certain circumstances a prescriber could reasonably consider, in the light of the knowledge and understanding at the time, that perindopril offered a real advantage for her or his patients compared to other ACEIs, then it would not have been reasonable or appropriate for them to prescribe another ACEI. By 'advantage' I include the possibility that the clinical benefit of perindopril was better established than for the alternatives such that the prescriber could, objectively viewed, be more confident of its likely effectiveness; and I also include non-clinical benefits such as convenience. Moreover, aside from potentially relevant circumstances of the particular patient, I think that to the extent that there was a lack of consensus among acknowledged specialists, that could preclude giving a uniform answer to the questions which the two issues pose. Clinicians who had to decide at the time which ACEI to prescribe will not have had the benefit of hearing the views tested, having the underlying scientific papers analysed, and observing experts subject to cross-examination, as occurred during this trial.

176. However, in the overall context of the decision this Court has to reach, I do not think that this distinction between the rival interpretations of issues (a)-(b) is critical. As I have emphasised, those issues are relevant only as the foundation for issue (c). If and to the extent that there was at the time a respectable body of opinion that regarded perindopril as the most appropriate ACEI to use, in my view that is very significant when asking what the Claimants should reasonably have done to seek to persuade doctors to prescribe another ACEI instead.

177. Self-evidently, the various ACEIs are not chemically identical: if they were, they would be the same drug. The problem in assessing clinical substitutability is that there are no head-to-head studies between different ACEIs, for reasons explained above. Assessment of substitutability or differences therefore depend on inferences and assumptions from the various trials and comparisons based on related meta-analyses, combined with clinical experience.

178. I think it is clear that there was not complete interchangeability within the class in pharmacological terms. Captopril, the oldest ACEI, was falling out of favour by the start of the Relevant Period. That was because of its significantly shorter 'half-life', i.e. the time it takes for the concentration of the drug in the bloodstream to fall by half. Prof Brown and Dr Coulson agreed that this made it reasonable <u>not</u> to select captopril, and the PRODIGY guidance to GPs in November 2005 advised that captopril was no longer recommended. From the approved licensed uses, as set out in the table at para 71 above, it is also evident that not all ACEIs were licensed for all indications.

179. In his first report, Prof Brown conveniently set out, following his article in *Heart* (2003), the parameters that might be considered when addressing the question of which drug to prescribe within a class:

> "These include pharmacodynamic factors (efficacy and potency), pharmacokinetic factors (route of administration, frequency of dosing and drug interactions), tolerability (safety and side effects) and cost. Of these, long-term efficacy in

> morbidity-mortality studies (i.e. reduced risk of death and serious illness) and long-term safety trump other parameters."

180. Frequency of dosing was highlighted also by the other witnesses. Dr Hurding, who has worked as a GP in Scotland for over 20 years and is also a prescribing adviser, referred to a "widely quoted statistic that up to 50% of medicines are not taken as prescribed". And his unchallenged evidence was that:

> "Patient compliance is likely to be lower where a drug is more complicated to take, e.g. if it has to be taken more than once a day, or if several tablets need to be taken at the same time. The simplest case is where a patient only needs to take a single tablet once per day."

181. This is reflected in various Guidelines. The BHS Guidelines state:

> "The drug formulation used should ideally be effective when taken as a single daily dose."

Similarly, the PRODIGY Guidelines give general advice on medicines management:

> "Where possible recommend treatment with drugs taken only once a day."

182. Prof Brown agreed that some ACEIs are more convenient in terms of administration than others, and that once daily dosing is relevant to the clinical decision of which drug to prescribe. In his written report, he noted that all the ACEIs, except for captopril and enalapril, have a sufficient duration of action that they can be used once-a-day.[12] The BNF advice for enalapril was that for heart failure it should be administered in two doses. Although the BNF and PRODIGY guidance both indicated that for hypertension enalapril was a once daily drug, Prof Brown explained that this was "borderline" and that as at March 2003 enalapril was dropping out of use as a once daily drug.[13] It was notable that little emphasis was placed by the experts on enalapril as an alternative that should potentially have been used instead of perindopril. Their focus was heavily on lisinopril and ramipril.

183. In his summary of the factors that are properly relevant to prescribing decisions, Prof Brown refers to cost. There is a question of how to deal with cost considerations in the context of the preliminary issues. If all other relevant factors mean that perindopril offers no advantage or benefit, then if the alternative is notably cheaper, it is clear (subject only to patient consent, where applicable) that it would be reasonable and appropriate for the clinician to select that alternative. But what if, for a significant period, there was no real difference in cost? On one approach, that should not affect the answer to preliminary issues (a)-(b), on the basis that it is still reasonable and appropriate to prescribe another ACEI because it would not be unreasonable or inappropriate to do so. However, the fact that there is no cost advantage will then

[12] This was somewhat more qualified in Prof Brown and Dr Coulson's joint statement, where they said that the minimum half-life was achieved by all ACEIs except for captopril and "possibly, enalapril."
[13] Prof Brown considered this was why the *Guidelines for the Management of Hypertension* produced by the Department of Clinical Pharmacology at Cambridge University in March 2003 (and revised in January 2006) did not include enalapril as a recommended ACEI.

feature prominently in discussion of issue (c) since in that event it is much more difficult to argue that the Claimants should reasonably have taken steps to encourage or persuade clinicians to prescribe a different ACEI (and in terms of mitigation, taking such steps would not have reduced the Claimants' loss). An alternative approach is to say that if all other factors are equal and there is no cost advantage in selection of a different ACEI, it would not be reasonable or appropriate to prescribe that alternative *instead of* perindopril. At the end of the day, I do not think it matters whether the question of relative cost is taken into account under issues (a)-(b) or only under issue (c). It is self-evidently a relevant factor and neither side advanced submissions as to whether it could be considered in the context of the first two preliminary issues or only in the context of the third preliminary issue. Although a literal reading of the preliminary issues supports the first of these two approaches, I have found it convenient to take the second approach since the prescribing practices of doctors is discussed in the context of issues (a) and (b) and cost is a factor relevant to prescribing practice. In my view, that also fits better with the rationale for issue (c), which considers what the Claimants should reasonably have done in the light of the answers to issues (a)-(b). But in adopting this approach, I shall make clear how the cost factor affects my conclusions on the first two preliminary issues.

184. It was manifest on the evidence, as both sides recognised, that there is an important distinction between initiation of a patient onto an ACEI and switching a patient who is already taking a particular ACEI. Different considerations apply, both clinically and practically. Furthermore, I consider that it is necessary to distinguish the various conditions or indications for which the patient is being treated.

Initiation

185. A patient may be initiated on an ACEI in primary care or in secondary care.

Primary care

186. In primary care, initiation of patients with an ACEI was generally following diagnosis of "simple" or uncomplicated hypertension: i.e. hypertension with no other symptoms requiring treatment. For that indication, I consider that in terms of efficacy and once daily dosage, there was no reason to prefer perindopril over ramipril or lisinopril. That was agreed between Prof Brown and Dr Coulson, and they indicated that their favoured ACEI was lisinopril because of the evidence base found in the ALLHAT study. Dr Duerden also agreed that there were no pharmacological properties that favoured perindopril.

187. As noted above, some patients diagnosed with mild heart failure may also have been initiated on an ACEI by their GP: see the BNF guidance at para 130 above. NICE CG 5 recommends that the question of referral for specialist advice should be guided by the level of expertise of the professional involved, and that a referral should always be made in certain clinical situations. But even if treatment was initiated in primary care, I consider that the prescribing decision of the GP would be influenced by the view of CV consultants; and that not only was this reasonable but it would have been unreasonable if a GP did not have regard to the specialists' views. As Prof Brown stated in his second report:

> "In my experience hospitals and opinion leaders are, *and should, be* influential on GP prescribing practices." [my emphasis]

I accordingly discuss the substitutability of ACEIs for heart failure under the heading of secondary care, below.

188. However, in addition to clinical substitutability, it is necessary to take account of a pharmacokinetic factor concerning titration. The prevailing guidance at the time was that a patient should be started on a low dose and gradually titrated up to the maintenance or target dose: see NICE CG5 (heart failure), para 105 above; CG18 and CG34 (hypertension), paras 107-108 above; BNF (re heart failure) para 129 above. Both the PRODIGY guidance and the BNF in their dosage tables distinguish between the recommended starting dose and the maintenance dose: paras 123 and 132 above. Prof Brown explained the practical implications of titration in his oral evidence:

> "… according to the licence rules, etc, you should bring the patient back, check them and re-prescribe. When a drug has been around a long time and if a doctor is very familiar they might well give a prescription for two doses and especially – probably not so much in the relevant period but now, with home blood pressure monitoring, we would commonly do that."

189. I think that having to get the patient to attend the GP surgery several times, even if seen only by a practice nurse not the GP, would reasonably be seen by GPs as an inconvenience and cost. Where a patient was frail or elderly, this could be a burden on the patient which I consider the GP could legitimately take into account. Although Prof Brown expressed the view that many GPs went straight to the target dose, it was not apparent that he had any empirical evidence for that and, indeed, such an approach would have been directly contrary to the established Guidelines. In any event, as I understood it, Prof Brown's view was more directed at the situation where a patient established on one ACEI was switched to another, and even then he said he was less confident of the ability to dispense with re-titration if the patient was being treated for heart failure. Servier strongly emphasised in its promotional materials to GPs the advantage of perindopril as needing limited titration steps, and I consider that it would not have done so if GPs had not perceived this as a benefit.

190. As shown in the tables above, the dosages differ as between hypertension and heart failure. I concentrate here on hypertension in view of my finding above on clinical substitutability. For enalapril, titration to target dose would appear to involve several steps. For lisinopril, the number of titration steps would depend on whether a patient's target dose was 20 mg or the higher dose of 40 mg, and whether the patient could be started at 10 mg (as per the BNF) or was elderly or the ACEI was combined with a diuretic, in which case the starting dose would be much lower: see the PRODIGY Guideline. I therefore think that for patients where a dosage regime with lisinopril would involve more than one titration step, this practical consideration meant that a GP could reasonably or appropriately prefer perindopril or ramipril. Even ramipril involves one titration step whereas many patients could be initiated on perindopril 4 mg and thus achieve the target dose without any titration.

191. Then there is the question of cost. Comparison of price between ACEIs is fundamentally affected by the assumed treatment dosage. Prof Brown produced with

his supplementary report a graph prepared for him by Servier's solicitors showing lisinopril and enalapril as significantly cheaper than perindopril throughout, and ramipril much cheaper from March/April 2005 when its price fell dramatically (it seems as a result of its reclassification into Category M under the NHS Drug Tariff). However, I think that presented a somewhat misleading picture as it plotted the price of the *maintenance* dose of 20 mg lisinopril against the *maximum* doses of 8 mg perindopril and 10 mg ramipril. Prof Brown accepted under cross-examination that a significant proportion of patients on lisinopril would be taking 40 mg (as in the ALLHAT trial). The Claimants produced a revised graph substituting the price of lisinopril 40 mg, which showed that treatment at that dose was more expensive than 8 mg perindopril or 10 mg ramipril until about August 2004 and became cheaper only in March/April 2005. Moreover, I consider that the relevant comparison for the treatment of hypertension is between 20 mg lisinopril and the maintenance dose of 4 mg perindopril, as set out in the BNF.[14]

192. Taking all these matters into account, I find that for initiation of a patient with uncomplicated hypertension, if the appropriate maintenance dosage of lisinopril was 20 mg, then it would have been reasonable and appropriate to prescribe that drug instead of perindopril, and from March 2005 ramipril was another alternative that could reasonably and appropriately have been used. If the appropriate dosage of lisinopril was 40 mg, then there was only a cost advantage after the end of March 2005, and from that point it was reasonable and appropriate to prescribe either lisinopril or ramipril instead of perindopril, but only if the GP considered that the need for titration would not be a burden on either their practice or the patient.

193. In reaching this conclusion, I recognise that "uncomplicated hypertension" is something of a misnomer since, as Prof Brown pointed out, this is often not a binary question. Prof Maskrey similarly considered that a patient presenting only with hypertension may well have underlying complications that would become apparent on an MRI scan or echocardiogram. Although the Claimants sought to stress this point, I find that it is nonetheless the case that a large number of patients were prescribed ACEIs on the basis simply of having hypertension and nothing else, and the various guidelines and dosage recommendations reflect that.

Secondary care

194. For patients first prescribed an ACEI in secondary care, the choice of drug would be affected by the condition for which it was being prescribed. It is therefore necessary to consider separately the various indications.

Heart failure

195. In an article entitled "Are All Angiotensin-Converting Inhibitors Interchangeable" by Furberg and Pitt, published in the *Journal of the American College of Cardiology* in

[14] I note that Prof Brown and Dr Coulson in their joint statement gave a more nuanced assessment, saying that for 4mg perindopril "we might change to 10 mg lisinopril if blood pressure was well controlled, and the patient was smaller than average; otherwise we would prescribe 20 mg lisinopril." But that (a) is in the context of switching, not the maintenance dose for a patient initiated on the drug; and (b) the 10 mg refers to a sub-category of patients. On dosages generally, I consider it preferable to refer to the published information as set out above, which is what clinicians at the time would consult.

2001, the authors cautioned strongly against the assumption of a class effect for ACEIs. Their article stated:

> "A thorough review of the literature revealed that there is no accepted definition of the term "class effect". It is a convenience term used for multiple purposes. There are good reasons for grouping drugs. However, this term has facilitated incompletely tested "me-too" drugs to be marketed as interchangeable alternatives to the proven, often original, members of a drug group. The lack of a clear scientific definition of the class effect term has had unfavorable consequences for the practice of medicine.
>
> … The grouping of drugs is typically based on one common mechanism of action. The common action of the ACE inhibitors is their ability to inhibit the conversion of the relatively inactive angiotensin I to the active angiotensin II. The definition is qualitative rather than quantitative. The potency or degree of inhibition is not part of the definition…. Moreover, since all drugs have multiple mechanisms of action determined by their unique chemical structure, each ACE inhibitor probably has some "not-in-common" actions. When one considers the marked differences in chemical structure among the available ACE inhibitors, it is not surprising that they might have different clinical actions. While the effects of the "not-in-common" actions may be unimportant, they could also enhance or diminish the overall health effects."

And their discussion of ACEIs concludes:

> "There are many pressures on the clinician to use or substitute a cheaper or formulary-available ACE inhibitor or to use a lower dose than was shown to be effective in the major randomized trials. It would, indeed, be unfortunate if those pressures assuaged our conscience and allowed us to feel as if we were doing something good for our patients. Substituting an unproven alternative for a proven treatment may deny benefit, subject the patient to unnecessary adverse effects and, despite a lower unit cost, may not be cost-effective."

196. Prof Brown disagreed with these views, which he said lacked evidential foundation, and considered that they were confused in using the term 'class effect'. However, Prof Brown acknowledged that both the authors are internationally recognised as specialists (and Prof Furberg was chair of the steering committee for the ALLHAT trial) and are regarded as having made important contributions to cardiovascular medicine. The *Journal of the American College of Cardiology*, in which their article was published, is not only peer-reviewed, which means that the articles are considered more reliable, but a journal with a high "impact factor", which Prof Brown explained is a measure of the degree to which its published articles are cited.

197. I consider that this shows that there was not a consensus among experts at the time as to the extent to which ACEIs were to be regarded as equivalent in treatment of indications other than uncomplicated hypertension. Prof Brown accepted that there was a genuine academic debate around the issue of a class effect although he said that the majority of specialists agreed with him that a class effect should be assumed unless the contrary was demonstrated. But Dr Duerden put it rather differently. As he explained in his second report:

> "Professor Brown's opinion that the benefits of ACEIs flow exclusively from blood pressure lowering was less accepted at the time, and many eminent hypertension specialists and clinical pharmacologists disagreed with his view over the Relevant Period."

And Dr Duerden stated more generally:

> "Over the Relevant Period, there was a big debate between those who (like Professor Brown) were content to assume that drugs in the same class were more or less equivalent therapeutically, in the absence of direct evidence to the contrary, and clinicians who considered that individual drugs should be prescribed only where there was a significant evidence base supporting their use."

198. Although Dr Coulson's own opinion agreed with Prof Brown that there is a class effect as regards treatment for heart failure, and Servier of course placed emphasis on the experts' joint view, Dr Coulson also pointed out that there was uncertainty at the time, in particular as regards perindopril compared to enalapril and captopril.

199. Altogether, I think that the evidence showed that, considered in terms of drug efficacy alone, there were reasonable grounds for clinicians in the Relevant Period to prefer perindopril, lisinopril or ramipril to the other ACEIs for treatment of heart failure.

200. Moreover, according to NICE CG5, along with perindopril only lisinopril and (depending on the dosage regime) ramipril involved once daily doses. The dosage regime for ramipril would be affected by the particular indication for which it was prescribed. Prof Brown and Dr Coulson agreed that although a once daily maintenance dose of 10 mg was generally appropriate, in their view for left ventricular failure they might split the dose to 5 mg twice daily.[15] For that particular indication, which CG5 explains is a common form of heart failure, perindopril therefore had a distinct convenience benefit.

201. Although the target dose of lisinopril is stated in the NICE Guideline as 30-35 mg, Prof Brown explained that few patients would be likely to be prescribed 35 mg as that was not available in one or two tablets; therefore they would have been prescribed either 30 or 40 mg. Either way, as the graph of comparative prices per dose produced by the Claimants showed, lisinopril and also ramipril 10 mg were more expensive than 4 mg perindopril until September 2004 (and two doses of ramipril 5 mg were considerably more expensive). Neither of these alternatives became significantly cheaper until March/April 2005. Servier sought to avoid this conclusion by instead comparing the

[15] This view was based on the AIRE study published in *The Lancet* in 1993.

prices of the alternatives with 8 mg perindopril. However, neither NICE CG5 nor the BNF (which Dr Coulson described as "the two go-to areas for advice" on prescribing) advised perindopril doses for heart failure above 4 mg: see the tables at paras 104 and 132 above. Accordingly, before March/April 2005, although those prescribers who preferred lisinopril or ramipril are not to be criticised, if cost is taken into account I do not consider that it would have been reasonable or appropriate to prescribe those drugs instead of perindopril. Indeed, to the extent that cost is an important consideration, perindopril had a cost advantage until September 2004.

202. That has the significant consequence that for patients prescribed perindopril in 2003-2004, the question of whether to prescribe them a different ACEI in subsequent years raises the issue of switching, which I discuss below. For patients initiated on an ACEI after March 2005, even assuming equivalent efficacy as between perindopril, lisinopril and ramipril, perindopril offered the convenience benefit of one-step titration (2 mg to 4 mg). I referred to the titration issue above in the context of treatment for hypertension, but the issue is more prominent in the case of heart failure because of the additional titration steps to the higher target dosages of alternative ACEIs.

203. Whether the burden involved in the extra titration step or steps could be regarded as offsetting the higher cost of perindopril is, in my judgment, not capable of a universal answer: it would depend on the circumstances of the hospital or GP practice concerned (where the titration and associated testing could be carried out in a GP surgery) and potentially an assessment of how the patient would respond to the requirement for repeated attendance. It appears that in many cases this was not a significant consideration since clinicians did select lisinopril or ramipril; but the factual evidence shows that for some GPs it certainly was an issue. Mrs Ryan, who has extensive experience as a pharmaceutical adviser in Scotland, stated:

> "A message that we heard from GPs was that perindopril was easier to titrate than other ACEIs such as ramipril, particularly given that some patients would not turn up to appointments. With some heart failure patients who were prescribed ramipril (which required more extensive titration) you would find that they were never titrated up to the optimum dosage."

Mr Brogan, who has worked in medicines management in the NHS N Ireland since 1996, stated that as regards ACEIs:

> "… the need to titrate to a particular target in order to achieve a patient's optimum dosage was a key consideration for prescribers."

204. Accordingly, I do not have the evidence to conclude that in *most* cases where perindopril was prescribed for heart failure the issue of titration was irrelevant or so insignificant that those prescribers could reasonably or appropriately have chosen lisinopril or ramipril instead. Indeed, when it was proposed to remove perindopril from the hospital formulary of the North Bristol Trust, one of the consultants strongly resisting that proposal commented:

> "… with a simple 2 step dose titration it is the easiest ACEI for our patients to use."

MACE

205. Only ramipril and, post November 2005, perindopril had licences for MACE reduction in high risk patients. For this, the EUROPA trial was seen as giving a strong evidence base for effective use of perindopril and Servier unsurprisingly emphasised this strongly in its promotions and discussions with clinicians. Unlike HOPE, which selected only patients aged 55 or over, in EUROPA almost a third of the patients were under 55 (although in some other respects HOPE had broader inclusion criteria). It seems clear that as a result of EUROPA many clinicians chose to prescribe perindopril for MACE even before it was formally licensed for this indication.

206. Prof Brown published an article in the peer-reviewed journal *Heart* in 2003 entitled "A Rational Basis for Selection Among Drugs of the Same Class" in which he highlighted as "key points" regarding ACEIs:

> - "For newer indications [i.e. not hypertension and heart failure], in which only one drug has been tested, efficacy is probably a class effect but equal safety cannot be assumed.
>
> - For these newer indications, the trial drugs, ramipril and perindopril, should be used unless greater cost reduces the number of patients who can be treated by more than the possible increase in safety"

207. In my view, whether Prof Brown was there correct as regards the probability of a class effect is irrelevant for present purposes, in view of his comment on drug safety. The practical issue, therefore, is whether ramipril could reasonably or appropriately be prescribed for MACE instead of perindopril. The EUROPA study was published in September 2003, after Prof Brown's article. As already discussed, until late March 2005 there was no cost justification for choosing ramipril instead, as Prof Brown accepted. But aside from cost, it is notable that there were prominent and respected cardiologists who considered that there were objective grounds to prefer perindopril.

208. One was Prof Kim Fox, who was Professor of Clinical Cardiology at the National Heart and Lung Institute, Imperial College London, and held the chair in cardiovascular medicine and science and was consultant cardiologist at the Royal Brompton Hospital. Prof Fox was president of the European Society of Cardiology ("ESC") 2006-2008 and chaired the task force which produced the European Angina Guidelines. In a chapter in a book on perindopril that he co-wrote with Prof Ferrari (also a past president of the ESC) published in 2008, Prof Fox expressed the following view:

> "The evidence base for the clinical use of perindopril is extremely large. As we shall see in the other chapters of this book, it has confirmed efficacy at every stage of the cardiovascular continuum from hypertension, through CAD, cerebrovascular disease and myocardial infarction to heart failure. Perindopril has been tested in more than 50 000 patients in international morbidity/mortality trials. As we have seen in this chapter, this clinical trial evidence lies on the foundations of a solid file of scientific investigations into the mode of action and mechanism of both ACE inhibitors per se and perindopril

> itself. The effects go beyond simple blood pressure reduction to positive effects on the endothelium and other target organs, restoring normal function and structure. Many of these studies place perindopril apart, showing that its effect cannot be generalized to the ACE inhibitor class as a whole, but are unique to perindopril."

209. When this was put to Prof Brown, he said that he disagreed and, indeed, asserted that it was unreasonable of Profs Fox and Ferrari to hold that view. Prof Brown also pointed out that this book, which was sponsored by Servier, was not peer reviewed and was unlikely to have been read by many clinicians at the time. I accept that few doctors may have read, or perhaps even have been aware of, the book, but in my view that is beside the point. It was not suggested that these statements were other than Prof Fox and Prof Ferrari's genuinely held opinions (and the other contributors to the book, who were all cardiology specialists from Europe and North America, took a similar view). Moreover, Prof Ferrari expressed similar views favourable to perindopril in an academic article of which he was the lead author published in the *American Journal of Hypertension* in 2005: "Specific Properties and Effect of Perindopril in Controlling the Renin-Angiotensin System", AJH 2005: 18(Pt 2), 1428-1548. Prof Brown said that he disagreed with the conclusions in that article which he considered went beyond the evidence. Servier's closing submission sought to belittle these as "puff pieces published by various academics who described themselves as, or were asserted by the Claimants to be, famous or eminent." Having looked through Profs Fox and Ferrari's chapter, and briefly at the other contents of the book and at Prof Ferrari's article published in a peer-reviewed journal, I unreservedly reject that derogatory characterisation.

210. Again, there may have been a mixture of views as to whether perindopril was likely to offer significant clinical advantage over ramipril. If the relevant question is whether on the evidence presented to the Court ramipril could reasonably and appropriately have been prescribed instead of perindopril, I think the answer is yes. But if the question[16] is whether between 2003 and 2009 those concerned with prescribing decisions could reasonably and appropriately have preferred perindopril to ramipril, then I would answer that also in the affirmative, given the opinion of some prominent and respected specialists and the presentation of the EUROPA study. Indeed, I note that Servier admits in its pleaded defence at para 42(e) that (other than as regards hypertension):

> "…the totality of the evidence base for the use of perindopril was in general terms superior to that for the use of other ACE Inhibitors"

And the guidance to doctors from the General Medical Council ("GMC") on *Good Medical Practice* (2006), on which Servier also placed reliance, states in its section on good clinical care at para 3(c) that the doctor should: "provide effective treatments based on the best available evidence."

Stroke

211. In his article in *Heart*, Prof Brown indicated that when prescribing an ACEI for patients post-stroke, the only two drugs that should be considered were ramipril and perindopril.

[16] For discussion of which is the appropriate question, see paras 174-176 above.

That was based on analysis of the HOPE and PROGRESS trials: perindopril and ramipril were at that stage the only two ACEIs that had been tested in a non-hypertensive population, and where their observed benefits might be due not to reducing angiotensin but to increasing bradykinin. I think that for post-stroke use, as for MACE, it is relatively clear that the other ACEIs were not regarded as appropriate alternatives.

212. As pointed out above, there was no cost advantage from preferring ramipril before the end of March 2005. But in any event, on the evidence it appears that many stroke specialists regarded PROGRESS as providing a sounder basis for use of perindopril for such patients than HOPE did for ramipril. Dr Smithard, who has been a stroke consultant for over 20 years, gave evidence that for stroke patients he used perindopril because he considered that PROGRESS provided a superior evidence base for its use for that condition. He said that his conversations with other stroke consultants supported that view and that he never heard a stroke consultant suggesting that ramipril was equally effective. The HOPE trial was focused on cardiovascular patients and included only 1000 patients with a previous history of stroke/TIA whereas in PROGRESS the focus was specifically on recurrent stroke risk and all 6000 patients in the study came into this category. And Dr Smithard explained that although there are many kinds of stroke, the two most common are ischaemic stroke and haemorrhagic stroke. The PROGRESS trial included both kinds of patients whereas HOPE did not. While the actual results of the two studies were similar in terms of stroke reduction, Dr Smithard considered that the different size and patient populations made them hard to compare directly. In his view, therefore, PROGRESS provided firmer evidence for use of perindopril (combined with a thiazide-type diuretic) for these conditions although he agreed that HOPE could be relied on for use of ramipril for prevention of heart failure.

213. Further, it is clear that Dr Smithard was not an outlier in his view. The *Greater Manchester Stroke Guidelines*, of which a second edition was published in 2003, produced by a large group of multi-disciplinary specialists, were designed "to provide standards of stroke care for patients throughout Greater Manchester" and circulated accordingly to all hospital trusts, Health Authorities and PCTs in that area. One of the recommendations, as summarised, states:

> "A blood pressure reducing regimen should be considered in all patients at two weeks following stroke (due to infarction or haemorrhage) and TIA, even if not hypertensive though benefits then are small. At present the best evidence is for Perindopril plus a thiazide."

And the more detailed discussion refers to the PROGRESS study and continues:

> "The best evidence is for the use of perindopril plus indapamide post-stroke. The HOPE study showed some evidence for Ramipril, particularly in diabetics"

214. Furthermore, when the Bristol North PCT suggested (it seems in 2005) that perindopril should be removed from the North Bristol Trust formulary, two of the stroke consultants in that region responded as follows:

> Dr Neil Baldwin: " ... From the point of view of stroke secondary prevention Perindopril is the only ACE inhibitor for which there is any evidence. We do not know whether the benefit is a class effect and therefore to be evidence based we will need to continue to prescribe Perindopril…."
>
> Dr Nigel Jones: "I would have serious concerns if the removal of Perindopril was based on our past costings alone. The Europa study would indicate that more people with coronary disease should be on 8mg of Perindopril, which would mean a future saving on a large client population from a change in practice that cannot be calculated from previous levels of drug usage. For Stroke medicine, as you are aware, the PROGRESS study is a powerful argument for Perindopril and indapamide in the secondary prevention of Stroke (28% RRR). It is solid evidence that one cannot say is just an ACEI class effect. There is little enough quality evidence available to ignore the results of a well-conducted study. It would be difficult to validate such a change to clinical practice when this is not just an issue of local policy or of funding, but one of what is currently accepted nationally in the field of stroke medicine to be 'best practice'."

215. Prof Brown's reaction to the *Manchester Guidelines* was to say that they were wrong, although he accepted in cross-examination that if a clinician in Manchester followed them he or she would be acting reasonably. And he doubted that there were many around the country who shared the view of Dr Nigel Jones. However, on the evidence before the Court, I consider that this appears to have been a widespread and considered view, on well-supported grounds, among stroke specialists over the Relevant Period. And I note that Prof Brown accepted in cross-examination that:

> "there was enormous debate as to whether PROGRESS actually was evidence for perindopril itself."

216. I therefore unhesitatingly reject the striking contention in Servier's closing submissions that the views expressed by the North Bristol based consultants "were views which no rational person could have formed if they had read the EUROPA and PROGRESS studies competently." Further, I consider that it would not have been reasonable or appropriate for the many stroke specialists taking this view to prescribe ramipril instead of perindopril. Again, I make clear that by this finding I am not seeking to criticise those stroke physicians who prescribed ramipril.

Switching

217. Switching of a patient taking perindopril to another ACEI would largely be carried out by GPs. The Claimants' unchallenged evidence was that any such switch would need the patient's consent.

218. I consider that there is again a distinction to be drawn between a patient who had been initiated on perindopril by a consultant in hospital and a patient who had first been prescribed perindopril by their GP. In the former category I include also the case where the prescription is not actually written by the consultant but where, as was explained in

evidence, the patient is discharged from hospital and the consultant writes to the GP asking that the patient be prescribed a particular drug. The more usual case is for the hospital pharmacy to dispense, prior to the patient's discharge, about two weeks supply of the drug, and for the GP to prescribe the continuing treatment thereafter.

219. For those patients initiated in secondary care, there was a lot of evidence that most GPs would consider that they should follow the consultant's decision. The GP naturally regards the consultant as the expert in the particular field and, as Dr Buckman, a GP with long experience, said, a GP would therefore be reluctant to vary a consultant's prescribing decision. Moreover, if they sought to do so, they might encounter patient resistance, particularly if when seeking the patient's consent, the patient was told that the reason was cost (and the GP is supposed to explain the rationale for the change when seeking consent).

220. Furthermore, if a patient had been prescribed perindopril in secondary care, that suggests that it was for one of the more serious conditions. Any change by the GP would therefore involve careful monitoring which itself imposes a burden and, accordingly, comes at a cost. As Dr Buckman said in cross-examination:

> " Q. … if a consultant in relation to heart failure had prescribed something, as a GP you would be very loath to change that?
>
> A. Not without extreme care.
>
> Q. You might want to double-check with the consultant or have some careful guidance --
>
> A. I might not, but I would certainly -- I would probably want to refer back to the medical record from the hospital to find out why they had chosen perindopril.… And I would certainly, for someone with heart failure, be very, very careful about monitoring them much more closely than I normally would do so that I didn't make them ill."

221. Dr Duerden's report set out his opinion on the risks of harm which switching could involve to patients with more serious conditions:

> "…, in patients with complicated or more serious conditions, most clinicians would regard switching ACEIs as inappropriate at it would create unnecessary risks. In patients with heart failure, coronary heart disease or who had a stroke/TIA, switching ACEIs risks destabilising the patient's condition.
>
> a) In patients with heart failure the risks include causing postural hypotension/hypovolaemia, with risk of collapse, falls and associated injury. The condition might decompensate requiring admission to hospital. Renal function may be impaired.
>
> b) In patients with ischaemic heart disease, altering treatment might affect the pumping of the damaged heart (left ventricular dysfunction), causing breathlessness and heart failure, or

> aggravate symptoms such as angina. This may also result in the need for admission to hospital.
>
> c) In patients who have had a stroke, altering treatment might affect blood flow to the brain and cause confusion and potentially further stroke. People who have had a stroke often have problems with other parts of their circulation, including ischaemic heart disease, and these may also be affected"

222. Further, Prof Maskrey said in his evidence:

> "A patient with heart failure often has a worse prognosis than if they were diagnosed with one of the more common cancers …. given that level of risk, GPs would be fairly reluctant to alter a prescription for an ACE inhibitor. If a doctor has a cohort of high-risk patients, all in danger of something bad happening to them in quite short order, the last thing that the doctor would want to be doing is switching their prescriptions due to cost. The potential consequences are just too severe."

223. Significantly, although Dr Smithard clearly considered that perindopril was the preferable ACEI for administration to stroke patients, he said that he would not switch a patient who was well controlled on another ACEI to perindopril, because that might cause problems.

224. For patients initiated in primary care, the question of switching is to be addressed for patients who were stable on perindopril. If they were not stable, then the likelihood is that the GP would consider a switch on clinical grounds, but that would probably be away from an ACEI to, for example, an ARB. The reason to switch stable patients who were taking perindopril for hypertension would be cost.

225. However, the evidence was that GPs would be very cautious about seeking to switch frail, vulnerable or elderly patients. Such patients are often on other medication (polypharmacy) and switching one of their drugs can be confusing. In his oral evidence, Prof Brown said in answer to a question from me:

> "In a vulnerable patient you would think twice before any change unless it is likely to cause a measurable increase in the patient's well-being. Obviously, the reason for the discussion about changing within a class is that it is not primarily being driven by a change in the patient's well-being, it is being driven by a need to save costs and spend that money on something else."

226. For other patients on perindopril for uncomplicated hypertension, switching was easier. There was some dispute as to whether titration was appropriate when switching to another ACEI. Guidance on switching ACEIs produced by UKMi in 2008 suggested that titration was advisable. However, Prof Brown and Dr Coulson agreed that there was no pharmacological reason for re-titration when moving from the stable dose of one ACEI to another.

227. I find that the correct position regarding titration was that set out by Dr Duerden in his first report:

> "The need to avoid undesirable effects could *in certain patients* require a process of titrating down the existing ACEI, and often required the new ACEI to be titrated-up to the optimal level. This would be particularly so in older frail patients, those with heart failure, some people with diabetes, and in the context of coronary heart disease or stroke. This titration would require repeat appointments to check the patient's blood pressure and adjust the dose. Several blood tests for renal function would also be necessary." [my emphasis]

Dr Duerden also said that for all patients it would be important to check their blood pressure and renal function within a few weeks after switching, which therefore would be a burden on patients if they had to make multiple appointments.

228. Some PCTs did encourage GPs to introduce switching programmes for hypertensive patients over the Relevant Period, as discussed further below. The Hampshire PCT's medicines management team produced *Guidelines for switching from Perindopril tablets to Ramipril Capsules/Lisinopril Tablets in patients with a diagnosis of Essential Hypertension* in October 2006. In advocating a switching programme, those Guidelines stated:

> "Manually exclude:
>
> • Those Read coded[17] for renal failure or initiation of treatment post MI.
>
> • Any patients previously treated with ramipril with a current issue for perindopril that were changed for clinically justifiable reasons
>
> • Allergy to ramipril
>
> • Hypotensive
>
> • History of falls
>
> • No record of BP in the last year.
>
> • Patients on REPEAT DISPENSING should also be excluded from the switch at this time. In these cases, add a screen message to switch patient at their next review i.e. when the next batch of repeat dispensing scripts are generated.
>
> Considerations should be given to the following:
>
> • Those aged over 75 years: you may wish to exclude these as it is recommended that people over 75 years should be treated on

[17] The Read code gives the reason for the patient's prescription.

> an individual basis taking into account other risk factors such as compliance issues and polypharmacy.
>
> …
>
> It is the GP's responsibility to ensure the BP and U&Es (where necessary) etc. is followed up within 8 weeks. Some practices may decide to delegate this responsibility to a single GP or practice nurse."

229. When asked about these Guidelines, Ms Kerr, the expert on prescribing policies called by Servier, agreed that this approach was reasonable and, by implication, appropriate.

Conclusions on Issues (A)-(B)

230. The result of the discussion and findings above is that there is no simple or binary answer to the questions posed by preliminary issues (a) and (b). The answer varies according to the condition for which the ACEI is being prescribed, the time period concerned and whether the question relates to a prescription initiating a patient for treatment with an ACEI or switching a patient already stable in treatment with perindopril, in which case the circumstances of the patient are also relevant. In my judgment, these preliminary issues are to be answered as follows: -

i) For "straight" or uncomplicated hypertension:

   a) for patients initiated on an ACEI prior to late March 2005, it would have been reasonable or appropriate to prescribe lisinopril instead of perindopril if the appropriate daily dosage of lisinopril was 20 mg; however, if 40 mg lisinopril was the appropriate dose, it was not reasonable or appropriate to prefer lisinopril as against perindopril (or any other ACEI) since there was no cost advantage.

   b) for patients initiated on an AECI from April 2005 onwards, it was reasonable or appropriate to prescribe lisinopril or ramipril instead of perindopril, except where the appropriate target dose was 40 mg lisinopril or 10 mg ramipril and the GP considered that the need for titration would be a burden on the patient or their practice.

ii) Subject to the qualifications as to timing in (i), it would have been reasonable or appropriate at the patient's next review at the GP surgery to switch a patient being treated with perindopril for uncomplicated hypertension to lisinopril or ramipril except where the patient was elderly or frail or vulnerable because of co-morbidities being treated with other drugs or had previously been switched to perindopril because of an adverse experience with either of those alternative ACEIs.

iii) For patients being initiated on an ACEI for heart failure or MACE, there was no reason to choose another suitable ACEI instead of perindopril prior to late March 2005 as this brought no cost advantage for the equivalent dosage. For patients initiated from April 2005 onwards, if the clinician followed the respectable body of opinion that one could have greater confidence in the benefit

of perindopril for these conditions since it was better supported by evidence, then, to adopt the formulation in Servier's skeleton argument, it would not "have been reasonable [or appropriate] for that doctor to prescribe an ACEI other than perindopril." For those clinicians who took a different view, it would have been reasonable or appropriate to prescribe lisinopril or ramipril for heart failure instead of perindopril (unless the patient suffered left ventricular heart failure and administration of ramipril would involve twice daily doses) and to prescribe ramipril for MACE, unless the clinician was concerned about the burden on the patient or the GP practice of more frequent attendance for titration.

iv) For patients being initiated on an ACEI post-stroke or a TIA, a clinician could reasonably regard the evidence supporting treatment with perindopril as significantly stronger than the evidence for ramipril. For those who took that view, it would have been unreasonable or inappropriate to prescribe ramipril instead of perindopril, and no other ACEI would have been appropriate. In any event, there was no reason to prefer ramipril to perindopril prior to April 2005 since there was no cost advantage.

v) For patients initiated on perindopril by a consultant in secondary care for heart failure, MACE or post-stroke, it was unreasonable or inappropriate for the GP to switch the patient to another ACEI prior to March 2005 as that brought no cost advantage; after March 2005, it would have been unreasonable or inappropriate for the GP to make that switch if the GP considered that the consultant had selected perindopril based on his or her more specialised experience and expertise.

231. I observe that this shows, in my view, that in many cases the prescribing decision to choose among the class of ACEIs was not a formulaic exercise but a more evaluative judgment involving varied considerations.

232. For completeness, I should add that I have not ignored the succinct statement agreed to by Prof Brown and Dr Duerden that it would have been reasonable for clinicians to prescribe an alternative ACEI to perindopril for "new patients" during the Relevant Period. However, having regard to the extensive evidence presented at trial, I consider that this requires significant qualification for all the reasons set out above.

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233. Again, for convenience I repeat the issue to be determined:

> "Was it unreasonable for either of the present three sets of claimants or the various relevant predecessor organisations (including PCTs and SHAs) to fail to take any (and, if so, which) of the steps set out in paragraphs 83C to 83D of the Defendants' Re-Re-Amended Defence to the English Claimants' claim or identified in the Defendants' Further Information dated 29 September 2017?"

234. This is effectively the mitigation issue. As such, the question of unreasonableness is to be applied not as an abstract concept but in terms of the established principles governing mitigation of loss.

The law

235. "The fundamental object of an award of damages", said Lord Nicholls in *Kuwait Airways Corpn v Iraqi Airways Co (Nos 4 and 5)* [2002] UKHL 19 at [67], "is to award just compensation for loss suffered." And he continued, in a speech with which Lords Steyn, Hoffmann and Hope agreed, at [69]-[71]:

> "How, then, does one identify a plaintiff's 'true loss' in cases of tort? This question has generated a vast amount of legal literature. I take as my starting point the commonly accepted approach that the extent of a defendant's liability for the plaintiff's loss calls for a twofold inquiry: whether the wrongful conduct causally contributed to the loss and, if it did, what is the extent of the loss for which the defendant ought to be held liable. The first of these enquiries, widely undertaken as a simple 'but for' test, is predominantly a factual inquiry….
>
> 70. The second inquiry, although this is not always openly acknowledged by the courts, involves a value judgment ('.. *ought* to be held liable..'). Written large, the second inquiry concerns the extent of the loss for which the defendant ought fairly or reasonably or justly to be held liable (the epithets are interchangeable). To adapt the language of Jane Stapleton in her article 'Unpacking "Causation"' in Cane and Gardner (ed) *Relating to Responsibility* (2001), page 168, the inquiry is whether the plaintiff's harm or loss should be within the scope of the defendant's liability, given the reasons why the law has recognised the cause of action in question. The law has to set a limit to the causally connected losses for which a defendant is to be held responsible. In the ordinary language of lawyers, losses outside the limit may bear one of several labels. They may be described as too remote because the wrongful conduct was not a substantial or proximate cause, or because the loss was the product of an intervening cause. The defendant's responsibility may be excluded because the plaintiff failed to mitigate his loss. Familiar principles, such as foreseeability, assist in promoting some consistency of general approach. These are guidelines, some more helpful than others, but they are never more than this.
>
> 71. In most cases, how far the responsibility of the defendant ought fairly to extend evokes an immediate intuitive response. This is informed common sense by another name. Usually, there is no difficulty in selecting, from the sequence of events leading to the plaintiff's loss, the happening which should be regarded as the cause of the loss for the purpose of allocating responsibility. In other cases, when the outcome of the second inquiry is not obvious, it is of crucial importance to identify the purpose of the relevant cause of action and the nature and scope of the defendant's obligation in the particular circumstances. What was the ambit of the defendant's duty? In respect of what risks or

> damage does the law seek to afford protection by means of the particular tort?.... ”

236. The locus classicus for the principle of mitigation is the speech of Viscount Haldane LC in *British Westinghouse Co v Underground Ry* [1912] A.C. 673 at 689:

> “The fundamental basis is thus compensation for pecuniary loss naturally flowing from the breach; but this first principle is qualified by a second, which imposes on a plaintiff the duty of taking all reasonable steps to mitigate the loss consequent on the breach, and debars him from claiming any part of the damage which is due to his neglect to take such steps”.

237. The concept of a “duty” to mitigate has subsequently been qualified and explained. In *Banco de Portugal v Waterlow & Sons Ltd* [1932] AC 452, Lord Macmillan said at 506:

> “the measures which [the claimant] may be driven to adopt in order to extricate himself ought not to be weighed in nice scales at the instance of the party whose breach of contract has occasioned the difficulty.”

And in *Lombard North Central plc v Automobile World (UK) Ltd* [2010] EWCA Civ 20, Rix LJ (with whom Rimer and Patten LJJ agreed) stated at [72]:

> “it is well recognised that the duty to mitigate is not a demanding one. Ex hypothesi, it is the party in breach which has placed the other party in a difficult situation. The burden of proof is therefore on the party in breach to demonstrate a failure to mitigate.”

238. More recently, in *Thai Airways International PCL v KI Holdings Co Ltd* [2015] EWHC 1250 (Comm), Leggatt J (as he then was), referring to the *Banco de Portugal* case among other authorities, said at [38]:

> “The standard of "reasonableness" is, however, applied with some tenderness towards the claimant having regard to the fact that the claimant's predicament has been caused by the defendant's wrongdoing …. As stated by Potter LJ in *Wilding v British Telecommunications Plc* [2002] EWCA Civ 349 at para 55:
>
> > "If there is more than one reasonable response open to the wronged party, the wrongdoer has no right to determine his choice. It is where, and only where, the wrongdoer can show affirmatively that the other party has acted unreasonably in relation to his duty to mitigate that the defence will succeed.""

239. In *Borealis AB v Geogas Trading SA* [2010] EWHC 2789 (Comm), the claimant sought damages for the supply of contaminated butane, which the defendant admitted constituted a breach of contract. The claimant alleged that use of the butane caused extensive damage to its plant and equipment, with consequential interruption of its

business. In response to the claim for loss of use of an underground cavern where some of the contaminated butane was stored, the defendant argued that the claimant had failed to mitigate its loss since it unreasonably delayed in replenishing the cavern. Rejecting that argument, Gross LJ stated, at [137]:

> "It would not be right to be unduly precise in assessing every step taken by [the claimant] in dealing with the contaminated cavern and bringing it back into use. I keep in mind – in addition to the authority cited earlier - the trenchant observations of Lord Loreburn LC in *Lodge Holes Colliery Company v Wednesbury Corporation* [1908] AC 323 at p.325:
>
> > "Now I think a Court of Justice ought to be very slow in countenancing any attempt by a wrong-doer to make captious objections to the methods by which those whom he has injured have sought to repair the injury. When a road is let down or land let down, those entitled to have it repaired find themselves saddled with a business which they did not seek, and for which they are not to blame. Errors of judgment may be committed in this as in other affairs of life. It would be intolerable if persons so situated could be called to account by the wrong-doer in a minute scrutiny of the expense, as though they were his agents, for any mistake or miscalculation, provided they act honestly and reasonably. In judging whether they have acted reasonably, I think a Court should be very indulgent and always bear in mind who was to blame.""

As stated by Prof Michael Jones, in summarising the jurisprudence on mitigation in *Clerk & Lindsell on Torts* (23rd edn, 2020) at para 27-09: "Judges are reluctant to impose excessive demands on claimants."

240. It is common ground that Servier as the defendant bears the burden of proof that the Claimants failed to mitigate their loss.

241. The Claimants submitted that a higher standard of unreasonableness is required where the wrong committed by the defendant was a breach of statutory duty, so as not to undermine the statutory protection given to victims. I do not accept that as a general principle, and the authority relied on was in the very different context of a defence of contributory negligence to health and safety requirements imposed on employers: *Cooper v Carillion Plc* [2003] EWCA Civ 1811. But I do accept that reasonableness for the purpose of mitigation has to be assessed in the context of the statutory purpose in creating the duty which has been breached. That seems to me to come squarely within the scope of Lord Nicholls' second stage of inquiry as set out in the *Kuwait Airways* case: para 235 above. And it is encompassed in the formulation articulated by Mr Saunders in his closing submissions by way of reply: "what is the appropriate extent of loss to lay at Servier's door in this claim?"

242. This claim, or more precisely, these claims, are claims in competition law. The purpose of competition law is to protect consumers and the economy generally from the consequences of anti-competitive conduct, of which the most notable example is the artificial maintenance of higher prices than would occur under competitive conditions.

Private actions for damages play an important role in competition law, alongside public enforcement, in strengthening the working of the competition rules and discouraging anti-competitive agreements and practices: see the observations of the CJEU in Case C-453/99 *Courage Ltd v Crehan*, EU:C:2001:465, at para 27. See also the very recent observations of the Grand Chamber of the CJEU, pointing out the contribution of private claims to deterrence, in Case C-882/19 *Sumal SL v Mercedes Benz Trucks España SL*, EU:C:2021:800*,* paras 35-36.

243. Here, the infringement of the competition rules involved arrangements whereby Servier made substantial payments and other transfers of value to generic companies in return for their agreement not to challenge Servier's perindopril patents, thereby avoiding the risk of generic entry into the market and a substantial fall in price. The purpose of the applicable competition rules is to prevent such agreements which sought to ensure that prices for perindopril remained high. That is therefore the context in which it is necessary to consider whether the public health authorities who paid those high prices for perindopril acted unreasonably in not making greater efforts to persuade prescribers to select an alternative drug.

244. However, I do not accept the Claimants' further argument that the question of failure to mitigate should be applied differently when a claimant's loss corresponds to the defendant's gain. As Mr Saunders pointed out, such a contention is contrary to authority: see *The "Solholt"* [1983] 1 Lloyd's Rep 605 at 608. Dismissing the appeal, the Court of Appeal said that the fact that the loss claimed by the buyers of a vessel equalled the profit made by the sellers was wholly irrelevant to the question of mitigation, which was to be assessed on the standard *British Westinghouse* principle. Further and in any event, there is no direct equivalence of the Claimants' alleged losses and Servier's profits since sales of perindopril in the UK were made largely through intermediaries, and for the later years of the Relevant Period (July 2007-March 2009) a significant proportion of the Claimants' losses resulted from payment for generic perindopril before the NHS Tariff price was reduced.

245. For its part, Servier sought to rely on the references to mitigation in the context of competition law damages in the recent Supreme Court judgment in *Sainsbury's Supermarkets Ltd v Mastercard Inc* [2020] UKSC 24 at [194]-[197]. However, *Sainsbury's* was concerned with the approach to establishing whether the claimant had in fact reduced its loss. That is very different from the present case, where the question is whether the Claimants had unreasonably failed to take steps which might have reduced their loss. I therefore do not gain any assistance from the *Sainsbury's* judgment in the present case.

246. I noted above that Servier further relies, in the alternative, on the prescribing argument as the basis for defences of causation and contributory negligence. As regards causation, Servier contends that the alleged failures by the Claimants broke the chain of causation from Servier's anti-competitive conduct. The relevant principle, as set out in Servier's skeleton argument, was summarised by Hamblen LJ (as he then was) in *Clay v TUI UK Ltd* [2018] EWCA Civ at [27]:

> "Determining whether there has been a *novus actus interveniens* requires a judgment to be made as to whether, on the particular facts, the sole effective cause of the loss, damage or injury suffered is the *novus actus interveniens* rather than the prior

> wrongdoing, and that the wrongdoing, whilst it might still be a "but for" cause and therefore a cause in fact, has been eclipsed so that it is not an effective or contributory cause in law."

And Hamblen LJ proceeded at [28] to observe that where the allegation involved intervening conduct, a relevant factor may be:

> "The degree of unreasonableness of the conduct – in general, the more unreasonable the conduct, the more likely it is to be a *novus actus interveniens* and a number of cases have stressed the need for a high degree of unreasonableness."

247. The contributory negligence allegation amounts to the contention that any damage suffered by the Claimants was the result of their own "fault", as it is expressed at para 83M of Servier's Defence.

248. However, the focus of the trial was on mitigation. I agree with submission in Servier's skeleton argument that:

> "… of the possible tools available to the Court by which it might seek to analyse the prescribing argument, the doctrine of mitigation offers an analytical and conceptual framework that maps most straightforwardly on to the actions that Servier contends the Claimants ought to have taken in order to avoid their losses."

249. I consider that the standard of unreasonableness is probably higher, and certainly is no lower, for the alternative defences of causation and contributory negligence. It is therefore appropriate, and sufficient, to consider issue (c) in terms of the principles governing mitigation.

The factual context

250. Servier stressed that over the Relevant Period attention was being devoted to cost-effective prescribing. The GMC guidance on *Good Medical Practice* (2006) states at para 3(j) regarding clinical care that the doctor should "make good use of the resources available to you."[18] The importance of promoting cost-effective prescribing was noted in the Audit Commission report of 1994 and its bulletin on *Primary care prescribing* prepared for PCTs in 2003, although the emphasis of the latter was largely on the avoidance of over-prescribing (e.g. of antibiotics and ulcer healing drugs) and of prescribing drugs which have limited clinical value. Audit Scotland's report, *Supporting prescribing in general practice – a progress report* (June 2003) was similarly concerned with the importance of PCTs promoting cost-effective prescribing in Scotland.

251. Ms Kerr and Prof Chapman, the two experts on this area of the case, agreed that the role of medicines management is to encourage safe, appropriate and cost-effective prescribing. Prof Chapman noted that the medicines management team often also had

[18] The previous, 2001 version of the GMC Guidance was to similar effect.

responsibilities for the proper control of controlled drugs, which was regarded as particularly important after the Shipman scandal.[19]

252. Ms Kerr explained that medicines management evolved over the Relevant Period. There were relatively few engaged in medicines management within PCTs at the start but many more came through over this period and the role itself evolved. Discussing that development, Ms Kerr added:

> "… also our relationships with GPs, how we were working with practices, what we had learned previously about interactions with GPs and working with secondary care, to actually focus more on cost-effectiveness as well as quality.
>
> So I think in the early days we were focusing on quality, and then much more of a drive, as it evolved, to having more people doing the role - working much closer with GP practices on a sort of regular basis, but also more of a focus around cost-effectiveness."

253. PCTs typically employed medicine management leads and pharmaceutical/prescribing advisers, who were concerned with all aspects of the supply and use of medicines within the PCT area. The position as at 2007 was summarised in the NAO Report (para 154 above), as follows:

> "In order to support GPs in adopting best practice in prescribing, PCTs employ prescribing advisers, specialists with pharmacy qualifications and experience, to advise GPs on current and upcoming prescribing issues, cost-efficient prescribing and the implications of guidance from bodies such as the National Institute for Health and Clinical Excellence for the prescribing of new and existing drugs. There are currently around 1,200 prescribing advisers in England and Wales — about one for every 25 GPs."

254. Ms Kerr herself worked as a pharmaceutical adviser for many years before becoming the commissioning lead pharmacist at West Hampshire CCG. The medicines management team would usually include pharmaceutical advisers and pharmacy technicians but not a doctor, although they may have had access to a medical adviser.

255. Prof Chapman and Ms Kerr agreed that cost-effective prescribing in general terms should have been a priority for PCTs and Health Boards throughout the Relevant Period. In October 2006, the NHS Institute for Innovation and Improvement, which had been established as a Special Health Authority, introduced 13 "Better Care, Better Value" ("BCBV") indicators, primarily aimed at commissioners in PCTs and hospital trusts, to provide national level information that those bodies could use to benchmark their performance and introduce other areas of improvement. The indicators sought to highlight variation in performance, identify savings opportunities and inform local improvement planning. The first indicators included admission rates for selected

[19] Dr Shipman was convicted in January 2000 and the final report of the Shipman Inquiry was released in January 2005.

procedures where surgery was unnecessary and prescribing lower cost statins that were available generically. In March 2009, further indicators were introduced, including for drugs affecting the renin-angiotensin system showing the proportion of ACEIs prescribed, as compared to ARBs.

256. In the late 1990s, the Government decided to introduce National Service Frameworks ("NSFs"), intended to set national standards and define service models focused on the four areas of illness having greatest effect on national mortality: cancer, coronary heart disease ("CHD") and stroke, accidents, and mental illness. The first NSF was produced in March 2000 and concerned CHD. The recommended standards under the NSF included that GPs and primary care teams should identify all people with established CHD or at significant risk of CHD and offer them appropriate treatment. For people with diagnosed CHD, the recommended interventions included statins and for patients who also had left ventricular dysfunction, ACEIs. Further, GPs and primary care teams should offer people with suspected heart failure appropriate investigation and the recommended clinical management included initiation on an ACEI. As would be expected, it is clear that the CHD NSF led to a significant increase in the prescribing of drugs for CHD, including ACEIs.

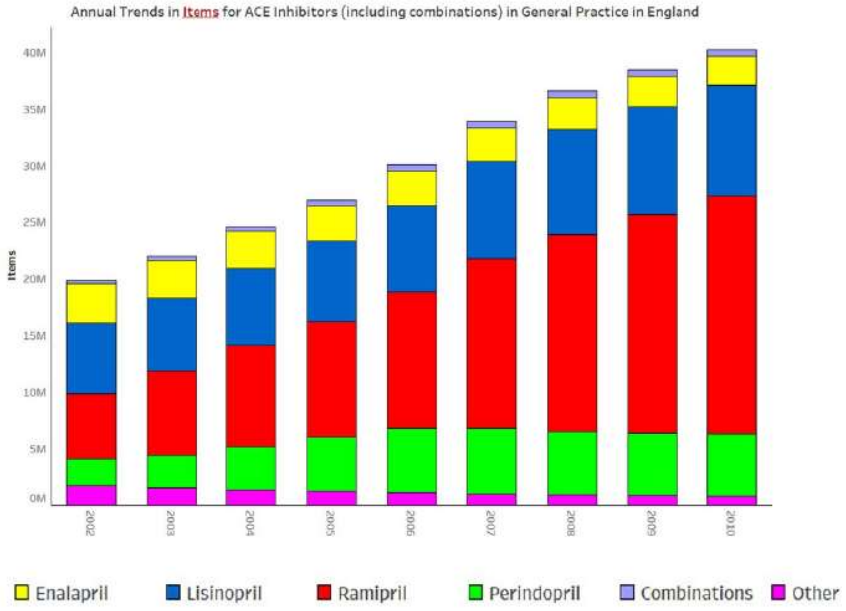
257. Before addressing the particular steps which Servier alleges the Claimants should reasonably have taken to encourage prescribing of alternative ACEIs to perindopril, it is relevant to consider the degree of perindopril prescribing and the relative financial impact, compared to other ACEIs over the Relevant Period.

258. Dr Duerden provided detailed figures showing the trends in prescribing of ACEIs and the proportion accounted for by perindopril, by volume of GP prescriptions for each of the four nations. I reproduce below the chart that is at Figure 1 of Dr Duerden's first report, that illustrates the volume data for England.[20]

[20] The same data is presented in a different form at Appendix B to Dr Duerden and Prof Brown's joint statement.

Figure 1.

Annual trends in items for ACE inhibitors (including combinations) in General Practice in England



259. In Appendix 2 to his report, Dr Duerden presented similar charts for the other three nations and set out the underlying data. The trend and proportions are very similar and it is not necessary to lengthen this judgment further by including all that information.

260. It is clear that the total number of ACEI prescriptions increased significantly over this period. In England, the number of GP prescriptions for ACEIs increased from 22.1 million per year in 2003 to 38.5 million per year in 2009.[21] As well as the national emphasis on CHD to which I have just referred, the reasons included increased familiarity with their use, the publication of studies providing evidence of the benefits of different ACEIs and the various guidelines which increasingly favoured their use for a wider range of indications, in particular hypertension and also heart failure. However, perindopril never accounted for more than 20% of GP prescriptions.[22] Throughout the Relevant Period, it was the third most popular ACEI, behind lisinopril and ramipril (which three drugs together accounted for about 85% of all ACEI prescriptions). In any year, the volume of prescriptions for ramipril was twice the volume written for perindopril.

261. The position as regards the share of spend on ACEIs prescribed by GPs in England is set out in a corresponding chart that is at Figure 4 of Dr Duerden's report.

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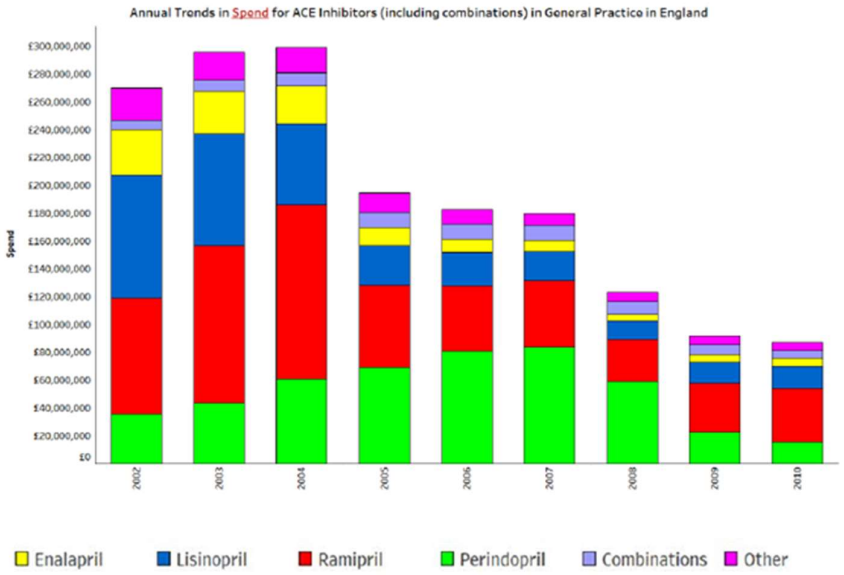
[21] The comparable figures for the other nations are: Wales: 1.9m in 2003; 3.1m in 2009; Scotland: 2m in 2003; 3.2m in 2009. For N Ireland, information as to GP prescriptions is available only for the quantity prescribed not the number of prescriptions: 30.7m in 2003; 44.2m in 2009.

[22] In Wales the proportion peaked at 19% in 2007 and in Scotland its share was never more than 17%. As explained in fn 21, comparable figures are not available for N Ireland but viewed by number of items it reached 23% in 2007 and 2008 and then 24% in 2009. Mr Brogan presented higher figures but those appear to cover all prescriptions in N Ireland not just prescriptions in General Practice. Reconciliation of the figures was not explored at trial.

Figure 4.

Trends in spend for ACEIs (including combinations) in General Practice in England 2002-2010: Costs



262. Given the volume of prescriptions shown in the first chart above, it is clear that the sharp decline in expenditure on ramipril and lisinopril was due to the change in the NHS Tariff price following generic entry. The expenditure on perindopril reached a peak of £80.7 million and £83.5 million in 2006 and 2007 respectively, which was close to 50% of the total, and then steeply declined to £22.7 million in 2009. The trends are again similar in the other three nations.

263. It should be noted that all these figures are national figures. As Servier emphasised, there were significant variations at the local level. For example, in some PCTs the proportion of perindopril as a total of all ACEIs prescribed was considerably higher than the national average.

264. Given my findings on substitutability set out above, another important context is the degree to which perindopril was being prescribed for the different indications.

265. Prof Brown and Dr Duerden agreed that about 10-15% of the UK adult population take medicines for hypertension. However, the so-called Barnett study of GP prescribing in Scotland in 2007 found that of patients with hypertension, only 22% suffered exclusively from hypertension; the rest had other co-morbidities.[23] I do not think that this figure in itself is very relevant since, as Dr Duerden accepted in cross-examination, the 78% could have a wide range of other conditions some of which are wholly unconnected to hypertension or treatment with ACEIs. But Dr Duerden gave evidence of a follow-up study which found that about 18% of patients with hypertension had CHD, while 10% were post-stroke/TIA.[24] He put forward what he accepted was a crude estimate that about 30% of patients with hypertension also suffer from stroke or other cardiovascular conditions such as coronary artery disease or heart failure. Of course,

[23] Barnett et al, "Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study", *The Lancet*, vol 380:37 (2012).
[24] Guthrie et al, "Adapting clinical guidelines to take account of multimorbidity", *BMJ* 2012:345.

Dr Duerden's estimate related to all patients with hypertension not specifically to patients being prescribed ACEIs. Servier pointed to a NPC reference sheet from 2004 reporting that 73% of patients receiving ACEIs were being treated for hypertension. Neither of those figures relate only to patients prescribed perindopril. However, on that basis they seem to me broadly consistent with Servier's internal figures which indicated that, in about 2005, of all prescriptions for Coversyl, just under 25% related to conditions other than uncomplicated hypertension.[25]

266. A further relevant consideration is the proportion of prescriptions for perindopril written in General Practice that were for patients being initiated on this drug, as opposed to repeat prescriptions. ACEIs were well-established as first-line use in the treatment of hypertension by the start of the Relevant Period. It was common ground that once a patient is stabilised on their treatment (i.e. blood pressure is controlled and the patient is tolerating the drug), they will probably remain on that treatment for many years. Dr Duerden said that it is well recognised that about 75% of all prescriptions are repeat prescriptions (i.e. prescribed without further face-to-face contact between patient and prescriber) but considered that as ACEIs are prescribed for persistent, long-term conditions, the proportion for those drugs is about 95%. In his first report, Prof Brown expressed a similar view. He said:

> "The prevalence of hypertension means that in any one year the number of newly diagnosed hypertensive patients is probably [less than] 5% of all hypertensive patients on the practice register."

However, in his second report Prof Brown relied on the General Court judgment to assert that:

> "… every year during the Relevant Period, … one third of patients being treated with perindopril had been initiated on perindopril that year."

267. The passage in the General Court judgment on which Prof Brown relied was itself based on a study prepared by IMS Health Ltd for Servier in 2013 ("the IMS Study") which, somewhat surprisingly, Prof Brown had not looked at before expressing himself in this way in his report. In cross-examination about this passage in his report, Prof Brown readily explained:

> "This isn't my opinion, this is me summarising what I thought I read in the report [of the judgment]."

In fact, as the Claimants pointed out, the IMS Study shows that whereas in the three years 2003-2005, respectively 38%, 39% and 34% of patients on perindopril were new patients that year, thereafter the proportion of new patients sharply declined to 13% in 2008.[26]

[25] Of all prescriptions for Coversyl, 16.8% were for patients with CAD, 2.8% for patients with stroke, and 5.2% for patients with heart failure: Servier's Orientation Plan 2006.

[26] The figures for the intermediate years are: 2006 – 28%; 2007 – 18%. Since the level of ACEI prescribing increased markedly over the Relevant Period (see the chart at para 258 above) and the Study found that 43% of

268. The IMS Study, on which counsel for Servier submitted a helpful explanatory note at the end of the hearing, also showed (on a 2003 baseline) that 44% of patients prescribed perindopril take the drug for less than two years.

The alleged failures

269. Servier's Amended Defence sets out various steps which it is alleged the Claimants reasonably should have taken. Servier added by way of skeleton argument and Further Information further steps which the Claimants should reasonably have taken. Some are at national level and others at more local level. I shall address each one accordingly, by reference to the pleaded case.

National level: guidance

270. Servier alleges that the Claimants should have "[i]ssued national guidance encouraging a switch from perindopril to the prescription of cheaper alternative ACEIs in generic form": Amended Defence, para 83C(b). This allegation was developed in Servier's response to a request for Further Information on 18 May 2021 (the "18 May FI") and was further clarified in a letter from Servier's solicitors dated 28 May 2021:

> "… it is the Defendants' position that the Claimants in all four nations ought to have used national targets, indicators and benchmarks to encourage the use of low cost ACE inhibitors. As to when that ought to have been done, the Defendants contend that (subject to any other national priorities, such as encouraging a switch in statins in the case of the English Claimants …), such indicators ought to have been used to incentivise a switch from perindopril to other generic ACE inhibitors from the point in time when those indicators were introduced or became available in each nation."

England

Better Care Better Value indicator

271. As noted at para 255 above, the first BCBV indicators were introduced in October 2006, following the establishment of the NHS Institute for Innovation and Improvement the year before. In February 2007, the DoH and the NHS Institute ran a 3-week consultation to help shape the development and expansion of the BCBV indicators. Ms Kerr in her evidence did not suggest that a BCBV indicator to prescribe an ACEI other than perindopril should have been introduced before this consultation. Her contention was that, given the time of the consultation (60-90 days), such an indicator should have been issued in the next financial year which began in April 2007.

272. However, by April 2007, Apotex had attempted to enter the UK market with generic perindopril and, although restrained by an interim injunction, the trial of Apotex's challenge to the validity of Servier's patent had concluded in the Patents Court and was awaiting judgment.[27] In accordance with the view of Prof Chapman, I consider that it

patients prescribed perindopril continue to take the drug for 3 or more years, by the end of 2008 a substantial majority of patients on perindopril had been initiated on the drug at some point during the previous 6 years.
[27] The trial before Pumfrey J finished on 20 March 2007.

was entirely reasonable to await the judgment and not to introduce an indicator which might have influence only for a very limited period. Instead, it was appropriate to concentrate on the ongoing 'big ticket' items. That included the proportion of ARBs compared to ACEIs prescribed as drugs affecting the renin-angiotensin system; and in due course a BCBV indicator was introduced addressing that issue. By 2006/07, this had cost implications which exceeded potential savings regarding perindopril: see paras 336-339 below. Moreover, by mid-2007 the number of patients being initiated on perindopril was declining: see para 267 and fn 26 above. And on 11 July 2007, the judgment invalidating the perindopril patent was issued whereupon generic perindopril entered the market. I therefore reject the allegation as regards a BCBV indicator.

NICE

273. Since NICE is not a defendant to these proceedings, the allegation is that the Secretary of State should have told, or requested, NICE to include such guidance in the context of the 2006 CG34 update of its guidance on hypertension. Specifically, Ms Kerr said that NICE should have recommended that a lower cost ACEI should be prescribed to new patients (i.e. patients being initiated on an ACEI). She explained that she did not suggest that NICE should have made a recommendation about switching.

274. In the first place, as Ms Potter explained, one of the purposes of NICE was to provide independent assessment of drugs free from commercial or political pressure. Although the DoH used to agree with NICE the topics on which it would work, ministers never sought during the Relevant Period to influence its findings or recommendations or to give it directions to give guidance on the use or non-use of specific licensed drugs. I regard that position as entirely reasonable and, in my judgment, it cannot be said that the 'duty' to mitigate required ministers to depart from this policy and, exceptionally, to have "directed" NICE to include a recommendation on the lines suggested by Ms Kerr and as alleged by Servier in the 18 May FI.

275. That is sufficient to dispose of the allegation concerning NICE. But in any event, I accept the evidence of Prof Chapman that NICE was extremely cautious about making a recommendation that would be understood as being against the use of a specific drug, in the absence of a head-to-head study, as that could expose it to legal challenge. I therefore further hold that there was nothing unreasonable about NICE's approach. I would only add that Servier will be well aware that this concern was not far-fetched: in 2009 SLL brought judicial review proceedings challenging NICE's decision to recommend an alternative to its drug (strontium ranelate, sold as "Protelos") for general use in treatment of osteoporosis in menopausal women, and that challenge succeeded before the Court of Appeal: *SLL v NICE* [2010] EWCA Civ 346. Prof Maskrey gave evidence that NICE had indeed been threatened previously with judicial review by another pharmaceutical company.

276. As to the allegation that if NICE could not be directed by ministers then they should themselves have issued "including through some other appropriate body if necessary" equivalent national guidelines (18 May FI), it does not appear from Servier's closing submissions that this is pursued beyond reliance on BCBV indicators, which I have addressed above. Any contention otherwise would be manifestly unsustainable. There was a well-established system for issuing guidelines through NICE and in the form of BCBV indicators. Beyond that, if NICE as the expert body did not consider it

appropriate to issue a guideline specifically regarding perindopril, in my judgment it cannot be suggested that it was unreasonable for ministers not to do so.

The NPC

277. The NPC was also entirely separate from the DoH and is not a Claimant in these proceedings. Servier's position is that the Secretary of State "could exercise control (alternatively, significantly influence) over the NPC": 18 May FI. I accept, on the basis of the evidence of Prof Maskrey, that the DoH had influence over the NPC regarding the topics on which it would focus and on its budget.

278. However, the NPC did in fact produce a number of reference sheets and training materials making some of the points on which Servier seeks to rely, i.e. that perindopril was not superior to other ACEIs. Some of those documents are indeed cited by Servier in its closing submission in support of its contentions on the first two preliminary issues. As I understand it, Servier does not suggest in those submissions that the NPC failed to act reasonably in any respect other than as regards the patent information provided to PCTs and GPs in *Prescribing Outlook*: see para 147 above.

279. *Prescribing Outlook* was produced by the UKMi, and until 2005 that was done in cooperation with the NPC. Prof Maskrey, who was cross-examined about this, was unable to explain what was said about the perindopril patent in *Prescribing Outlook* in 2003-2004, but he said that most of the resources to produce the publication came from UKMi and the role of the NPC was confined to checking the UKMi draft against the information which the NPC had gathered. Prof Maskrey said that the resources which the NPC devoted to this was confined to a single, very experienced pharmacist.

280. I accept the point put by Mr Saunders in cross-examining Prof Maskrey that information about patent expiry set out in *Prescribing Outlook* could well have a real effect on medicines management since it would be relied on in planning the strategy of PCTs and Health Boards. However, the patent position regarding perindopril was not straightforward. As explained above (see paras 91-93), the primary patent for perindopril indeed expired in June 2003. Although Servier had obtained three other patents (including Patent 341) which expired only in 2008, those were process patents and it is well recognised that generic manufacturers may be able to design 'around' a process patent to avoid infringement. Indeed, it appears that this is what Apotex did, since Servier did not rely on those process patents in its infringement case against Apotex. In its internal business analysis for Coversyl for 2004/05, Servier significantly identified "perindopril generics (if any)" as one of the threats to its product. And by mid-2004, Niche had applied for a marketing authorisation for generic perindopril in the UK and was restrained from launching its product by an injunction obtained by Servier relying on the three process patents; and the case then settled by one of the agreements which the EC Decision found contravened competition law. There was also the 947 Patent which was the basis of Servier's infringement case against Apotex. Thus, the correct position as at late 2003-2004 was that the primary patent had expired, that there remained extant process patents which might or might not preclude generic entry, and that Servier had a secondary product patent for a crystalline form of perindopril.

281. I recognise that it can be said that UKMi and/or the NPC should have got this right, and *Prescribing Outlook* should certainly not have said that generic perindopril was on the

market when that was not the case. However, in the first place, UKMi, which was primarily responsible for *Prescribing Outlook*, was not part of the Claimants and Servier does not suggest otherwise. Secondly, I do not consider that the influence which ministers through the DoH had over the NPC extended to detailed operational matters such as the resources which it devoted to horizon scanning of patent developments. Prof Chapman and Ms Kerr notably agree in their joint statement that the content of *Prescribing Outlook* "could not/would not have been dictated by the [DoH]."

282. Thirdly, and in any event, where the wrong for which the Claimants claim damages is the entry by Servier into anticompetitive agreements to exclude generic entry by protecting its patents from challenge, including a patent which the Court of Appeal condemned as "a try-on" and "the sort of patent which can give the patent system a bad name", when addressing the fundamental question of the extent of loss for which Servier should be held liable, I do not consider that the principle of mitigation here means that the Claimants' loss falls to be reduced on the basis that they should reasonably have taken more thorough steps to investigate the complex patent position. There is a significant chance that generic entry would indeed have occurred much earlier if it had not been for Servier's anti-competitive agreements.

283. I should add, for completeness, that given the existence of *Prescribing Outlook*, which was available to all PCTs, I do not think it was unreasonable that the Claimants did not establish a separate operation to conduct horizon scanning and provide information on future patent expiry.

Scotland

284. In Scotland, the bodies responsible for issuing national guidance in the Relevant Period were SIGN, the Scottish Medicines Consortium ("SMC"), and NHS Quality Improvement Scotland ("QIS"). However, it was clear from the evidence of Prof Timoney, who has been closely involved with the SMC since its inception and is the current chair of the SIGN Council, that it would have been outside the remit of those bodies to issue the sort of guidance for which Servier contends.

285. Prof Timoney's evidence was unchallenged that SMC guidance was concerned exclusively with newly licensed medicines, new formulations of existing medicines and major new indications for established products, and was given in response to manufacturers' submissions. Although the SMC carried out horizon scanning of drugs expected to enter the market, that also was concerned only with new drugs and not existing drugs coming off patent. From Servier's closing submissions, it does not appear that any allegation concerning the SMC is maintained.

286. As regards SIGN, Prof Timoney explained that SIGN guidelines did not make recommendations based on relative drug cost but only on clinical considerations, and that it has not been concerned with choices between branded and generic drugs. She also said that although NICE has no formal status in Scotland, Scottish clinicians have regard to NICE guidance and SIGN therefore may consider it inappropriate to issue its own guidance on a subject recently covered by NICE. SIGN had issued guidance on Treatment of Hypertension in Older People in 2001 (when a recommendation to use only generically available ACEIs would in any event have been inappropriate since at that time none of lisinopril, ramipril and perindopril were available generically); and then updated NICE guidance was issued in 2006. Altogether, I do not think it

unreasonable that the Scottish Government did not ask SIGN to act outside the scope of the guidance which it normally issued, to address the high cost of perindopril. There were other areas where the price discrepancy as between branded and generic drugs had much more significant financial consequences, notably statins, and, as with the Secretary of State and NICE in England, the 'duty' to mitigate did not require the Scottish Government to make an exceptional change to its general policy concerning its dealings with SIGN.

287. As regards the QIS, which was established in 2003, Prof Timoney explained that a recommendation in favour or against specific drugs was not normally within the various categories of guidance issued by the QIS (into which both the SMC and SIGN were absorbed from 2004 and 2005, respectively). I note that Servier's closing submissions did not suggest that it was unreasonable that QIS did not issue guidance on this matter.

288. However, Servier's solicitors' letter of 28 May 2021 identified two other sources of potential national guidance in Scotland on which it relies: (i) Audit Scotland and (ii) PRISMS data reports; and further reference is made to Audit Scotland in Servier's closing submissions.

i) *Audit Scotland*

289. Audit Scotland is a statutory body that is, in effect, the Scottish equivalent of the NAO in England. It is independent of the Scottish Executive, is not part of NHS Scotland and is not a Claimant in this case. In June 2003, Audit Scotland published *Supporting prescribing in general practice – a progress report*, so-called because it was addressing the situation since a 1999 report by the Scottish Accounts Commission. This 98-page report considered how prescribing quality and efficiency may be measured, discussed the forces that influence prescribing quality and cost, and looked at the potential for further efficiency savings. The report noted, inter alia, that expenditure on ACEIs had increased by 25% between 2001 and 2002. The report set out a range of measures of prescribing efficiency, including: use of established therapies as a proportion of established and new medicines; prescription of generic medicines as a proportion of all medicines prescribed; medicines considered to be of limited value; substitution of premium priced products with cheaper standard formulations; substitution of expensive medicines with therapeutically cheaper products.

290. The report included 9 indicators of prescribing quality (in Appendix A) and 15 indicators of prescribing efficiency (in Appendix B) for use at national and local level, by reference to the measures discussed in the report, and the report also provides estimates of potential savings. The efficiency indicators did not include an indicator of ACEIs available generically but of ACEIs as a percentage of ACEIs + ARBs. As a class, ARBs were significantly more expensive than ACEIs and Audit Scotland evidently regarded that as of greater significance. Since Audit Scotland is independent of the Claimants, it cannot be said that the omission from this report of an indicator focused solely on ACEIs was a failure by the Scottish Claimants to mitigate their loss.

291. Moreover, I do not in any event regard the decision not to select the proportion of ACEIs prescribed generically as in any way unreasonable. Audit Scotland were conducting a comprehensive and independent review of the measures that NHS Scotland could take to reduce prescribing cost. The report shows, first, that Audit Scotland did not consider the issue of prescribing ACEIs available generically to be a

priority, at least in 2003, relative to a host of other potential measures for the purpose of cost-effective prescribing, including an emphasis on prescribing generically; and secondly, the wide range of other drugs to which attention should be given to achieve cost savings. Those included: the substitution of diclofenac MR with diclofenac standard (potential savings of £2.7 million); discontinuation of topical non-steroidal anti-inflammatory drugs ("NSAIDs") (potential savings of £1.2 million); substitution of salbutamol dry powder and automated inhaler devices with Metered Dose Inhalers and the substitution of minocycline with oxytetracycline (potential savings of £1.1 million in each case); and among anti-depressants, the substitution of non-fluoxetine SSRIs with fluoxetine (with a total spend on SSRIs of £8.5 million but since this could be done only for new patients Audit Scotland did not estimate the potential savings).[28]

292. The indicators in the report were recommended to the Health Boards, and although not all the Health Boards chose to adopt every indicator, I do not see that it can possibly be regarded as unreasonable that the Scottish Ministers at national level, or the Health Boards at local level, did not seek to adopt yet additional indicators which had not been considered appropriate by Audit Scotland, in particular an indicator for the proportion of ACEIs prescribed that were available generically.

293. Servier drew attention to the statement in the report that:

> "GPs said a definitive statement or policy on what should – or more particularly should not be prescribed for certain conditions, would be useful when they consult with patients. A well-developed and easily accessed formulary and related policies or guidelines could provide these statements."

But Audit Scotland's specific recommendation following that discussion was that "PCTs should develop area-wide formularies." Therefore that relates to steps at local not national level, and it is not in dispute that development of formularies by PCTs and hospitals was in general an important part of effective medicines management. I address the position regarding local formularies below.

(ii) *PRISMS data*

294. The Prescribing Information System for Scotland ("PRISMS"), introduced in 2004, is a web-based system collating information on dispensed prescriptions by electronically scanning every prescription dispensed in Scotland. Mrs Ryan explained that although in principle GPs could directly obtain access to PRISMS for their own practice's prescribing information, in practice that rarely happened due to the time and expertise required to produce prescribing reports and that it was much easier for GPs to ask their pharmaceutical adviser to provide the information if required. But in any event, PRISMS did not involve the provision of any guidance or indicators or contain any targets: it was designed as a means of providing information to facilitate good decision making. It is unclear if Servier maintains any allegation based on PRISMS, but if it does then that is misconceived.

[28] The report did not include an estimate of the potential savings from the ARBs/ACEIs substitution.

295. I should add that insofar as it is contended that better training on prescribing should have been provided for GPs in Scotland, Prof Timoney explained that in Scotland such training was the responsibility of local Health Boards and not provided at national level.

296. Servier's closing submissions also included the general assertion:

> "[Servier] contends that Scotland [*sic*] ought to have taken at least some steps to promote cost-effective prescribing of ACEIs nationally."

I do not regard such a vague and sweeping allegation as acceptable. There was an abundance of evidence at trial (and probably more material in the disclosure) as to the organisation of the health service in Scotland and the various bodies involved. For the contention that the Claimants in the Scottish proceedings failed to mitigate their loss, Servier needs to specify which of the Scottish Claimants ought reasonably have taken what steps.

Wales

297. In 2002 the AWMSG was established as a Welsh Assembly sponsored public body to provide advice to the Welsh Minister for Health and Social Services, initially on new technologies and new drugs. The AWMSG was described by Mr Hayes, who became a non-voting member in 2003, as the Welsh equivalent of NICE, with which it cooperated. AWMSG concentrated on the appraisal of new (or recently launched) drugs that had not been appraised by NICE or where a NICE appraisal was not expected for a considerable time. Since perindopril had already been on the market for some time, this process did not apply to perindopril.

298. However, in late 2003 the AWMSG also began work on developing a system of National Prescribing Indicators ("NPIs") for Wales. That work was taken forward by the AWPAG. The first indicators were issued in 2005. The NPIs were reviewed or revised on an annual basis. The NPIs were directed at all issues concerning prescribing, and therefore addressed quality and safety as well as cost. They were intended to set targets for the Health Boards in Wales. One of the principles applied in selecting NPIs was that indicators should be clear, easily understandable and achievable.

299. The five indicators issued for 2005/06 covered: (1) a target of 78% for generic prescribing; (2) reduction of inappropriate generic prescribing; (3) hypnotics and anxiolytics; (4) co-proxamol; and (5) NSAIDs. Only the first of those concerned cost; indicators (2) and (3) were directed at quality and indicators (4) and (5) concerned safety. Mr Hayes explained the thinking at the time that:

> "If there were too many NPIs, there would be a risk of losing credibility and buy-in from prescribers."

300. The NPIs for 2006/7 were unchanged. Mr Hayes observed that the fact that the indicator relating to co-proxamol was carried over to a second year, even though the marketing authorisation for that drug had been withdrawn because of concern over a link to suicide, shows the difficulty NHS Wales faced in getting some doctors to change their prescribing behaviour.

301. In 2007/08, the NPI for co-proxamol was removed and replaced with a statin indicator requiring the prescribing of simvastatin as a percentage of all statins prescribing. That followed the NICE technology appraisal of statins in 2006.

302. In 2008/09, the number of NPIs was increased to six by adding an indicator that the percentage of ARBs prescribed should be reduced towards 20% of all drugs affecting the renin-angiotensin system. That meant that doctors were being encouraged to prescribe ACEIs instead of ARBs. The introduction of that NPI relied on the NICE CG34.

303. Challenged as to why the AWMSG/AWPAG did not introduce/recommend a NPI in the later years setting a target for lower perindopril prescribing as a proportion of all ACEIs, Mr Hayes explained that as a general matter the selection reflected what were seen at the time as the national priorities in Wales. The AWPAG review had concluded that that potential saving from a switch to simvastatin was £7 million p.a. In comparison, even if every patient on perindopril switched to ramipril the saving would be only £3.7 million p.a. Moreover, AWMSG was very reluctant to make recommendations about individual medicines unless there was a clear evidence base to support this, as there was with simvastatin and the NICE appraisal of statins. Thus although a document produced by AWPAG in September 2006 recommended that ARBs should be reviewed to arrive at a recommendation of the ARB that was the most clinical and cost effective agent, that suggestion was not adopted by the AWMSG.

304. In my opinion, there was nothing remotely unreasonable about this approach. On the contrary, it reflects a reasonable assessment of the national priorities in Wales and of the number of indicators that could practically be introduced. Further, I accept Mr Hayes' evidence that there was concern about the reaction from pharmaceutical companies:

> "… at the time it appeared to be that a threat of judicial review always seemed to be hanging over lots of our drug appraisal work, and that is something that we wished to avoid, so that set the tone for our national stance on our relationship with pharmaceutical companies."

I consider that caution was reasonable in the circumstances (cp para 275 above) and I therefore reject Servier's submission that this amounted to "an extraordinary dereliction of duty" on the part of AWPAG and the AWMSG. Moreover, any drafting of an indicator relating to perindopril would have been complicated by the fact that there were a range of circumstances in which it was not unreasonable or inappropriate for a clinician to prefer perindopril to other ACEIs, as set out above. I should add that I do not think the fact that the September 2006 AWPAG document referred only to the RCP Stroke Guidance and not to the wider hypertension guidance discussed above affects this conclusion.

305. Servier also alleges that the Welsh Claimants should have adopted NICE guidance. As explained by Mr Hayes, the AWMSG did not seek to replicate the work of NICE but would defer to NICE's appraisal and guidance. In effect, NICE guidance was accordingly applied in Wales and there is nothing in this point.

Northern Ireland

306. Servier's closing submissions regarding action which it alleges should have been taken at national level refer expressly only to England, Wales and Scotland. As I understand it, this allegation is no longer pursued as regards Northern Ireland. In any event, the Central Services Agency in Northern Ireland which at the time issued guidance in the form of so-called COMPASS Therapeutic Notes to GPs, was not part of the N Irish Claimants. When the DHSSPS itself issued clinical guidance covering ACEIs and ARBs in May 2008, following the advice of its Cardiology Expert Group, perindopril was available in generic form.

307. I address the issue of incentive schemes separately in the context of the QOF.

Local formularies

308. Servier alleges that the Claimants should have "[r]emoved perindopril from local formularies": Amended Defence, para 83C(a).

309. By the end of the Relevant Period, virtually all PCTs and many of the Health Boards in Wales and Scotland had produced formularies listing the drugs recommended for prescribing by GPs and most hospital trusts (or groups of hospitals in an area) maintained their own formularies. The hospital formularies effectively directed what drugs doctors at the hospital could prescribe since they dictated what would be stocked by the hospital pharmacy. The PCT formulary had more of an advisory function: as Ms Kerr put it, "a local formulary is a list of those medications recommended for routine prescribing within a locality", and it "could also contain information to assist with the prescribing of those drugs". There was nothing to prevent a GP from prescribing a drug that was not on the formulary and, as Prof Chapman explained, GPs did not tend to consult the local formulary for drugs with which they were already familiar and some did not use a formulary at all. But such formularies clearly were influential, and they also gave valuable support to the PCT or Health Board pharmaceutical adviser in the discussions he or she had with GPs about their prescribing practice. The inclusion of a drug on the formulary, and similarly the exclusion of a drug from the formulary, could therefore have a significant impact. Sometimes a few PCTs had a joint formulary, and in some areas the PCT and local hospitals produced a joint formulary but that was not the norm in the Relevant Period although apparently it became more common thereafter.

310. Local formularies were prepared by the Drug and Therapeutic Committee ("DTC") of the PCT or Health Board. The DTC typically included GP representatives, one or more of the pharmaceutical advisers, consultants from local hospitals and lay representation. The preparation and subsequent revision of a formulary was a formal process, involving intensive review and discussion: the DTC would receive submissions from consultants in the area and may well proactively seek advice from consultants specialised in the field at which a particular drug was targeted. As Ms Ryan put it, "there is a lengthy governance process to be followed to agree formulary changes." Although towards the end of the Relevant Period the formularies were electronic, in the earlier years they were printed and accordingly not amended so frequently. Often an annual review would be concentrated on one area of treatment because of the work involved.

311. Prof Chapman said that it was not unreasonable not to remove perindopril from a PCT/Health Board formulary. Ms Kerr in her first report expressed the view that "as a minimum" all PCTs/Health Boards should have included on their formulary a generic

ACEI as "a preferred option", indicating this on the formulary; and that they "could also have removed perindopril from the formulary." In her oral evidence, she explained that you need to have a choice within the formulary of, typically, 2-3 drugs. She said that her preferred approach would have been to leave ramipril and perindopril on the formulary along with enalapril and lisinopril, and then take perindopril off when ramipril came off patent.

312. Accordingly, there is no basis on the expert evidence for finding that perindopril should have been removed from the formulary at the start of the Relevant Period. Nor does Ms Kerr's evidence, as I understood it, provide support for the contention that it was unreasonable to leave perindopril on the formulary. That would in any event be a difficult conclusion to sustain when the *Guidelines for the Management of Hypertension* produced for GPs, nurses and hospital doctors in the Cambridgeshire region by the department of Clinical Pharmacology at Cambridge University, of which Prof Brown was the head at the material time, continued in the January 2006 edition to list perindopril as an alternative to two 'first-line' ACEIs, lisinopril and ramipril.

313. Prof Brown said that although he is named on the introductory page of the Guidelines, he had no part in preparing them (which of course I accept) and that it was not reasonable of his colleagues to have included perindopril in the list. However, if clinicians in the specialist department of a major teaching hospital considered it appropriate to maintain perindopril in a list of just three ACEIs being recommended to GPs, in my view, and however much Prof Brown may have disagreed with them, it cannot be unreasonable for PCTs and Health Boards also to have retained perindopril and not to have removed it. The fact that Servier can identify some PCTs which did remove perindopril from their formulary of course does not mean that the many PCTs/Health Boards which did not do so were acting unreasonably.

314. Servier also advanced at trial an alternative and lesser contention that local formularies should have contained an indication that one or more ACEIs which were available generically (and therefore not perindopril) were the preferred option or 'first line' ACEIs. Given the chronology of when generic lisinopril and ramipril became available, that effectively means that this should have been done in about 2004.

315. That was of course possible and Servier could point to a number of formularies that did so. But the question in this case is whether that was reasonably required. In my judgment, it was not, for a number of reasons:

    i) Over the Relevant Period the use of local formularies was in the process of development. In 2003 many PCTs/Health Boards did not have a formulary and formularies were introduced in different areas at different times. There was a wide diversity in the style and content of local formularies. Many simply listed drugs in alphabetical order (usually by treatment area) without comment or distinction. Although Servier in its skeleton argument listed five formularies as examples of those failing to comply with what it contended was a reasonable requirement to show the non-generic ACEIs as second line choices, four of those five provided simple alphabetical lists of the drugs within each treatment area; only the formulary for Fife (2005 version) went further. As GPs could not be compelled to adhere to the formulary, it was important to achieve their 'buy-in' and Dr Hurding explains how the Highland Area Board ("NHS Highland"), where he worked at the time, undertook a 'road show' to meet GPs and explain

the rationale of the formulary. I think there is force in his observation that the variation in the approach of different formularies reflected in part the culture among local prescribers and that in some areas the introduction of a formulary that was seen as too prescriptive would have encountered considerable resistance.

ii) I think that for a PCT/Health Board issuing a formulary to go further than selecting the recommended drugs so as to set a preference between them imposed a significant additional burden, especially as such an approach could not normally be confined to ACEIs. The Plymouth Area Joint Formulary, which as its name suggests covered both primary and secondary care, did adopt this approach, and Mrs Watson described in some detail the discussion and debate in the relevant sub-group and then in the full Plymouth Area Joint Formulary Committee prior to the decision to demote perindopril to a second-line ACEI in early 2006. Therefore, while some PCTs could undertake this work, there was no established standard at the material time and in my view it cannot be said that those PCTs/Health Boards which did not do so were acting unreasonably.

iii) As effectively indicated by Ms Kerr, before lisinopril and ramipril came off patent it would not have been reasonable to indicate that generically available ACEIs should be the preferred choice or first line. Of the five formularies identified in Servier's skeleton argument as examples of an unreasonable approach, all but one appear to be from 2003. And by the time of preparation in 2004 of a formulary, or the revision to a formulary, for release in 2005, insofar as the DTC wished to take account of the patent position the PCTs will have received indication through *Prescribing Outlook* that perindopril was off patent: see para 147 above. I consider that it was reasonable for a PCT/Health Board to rely on this information and I note that Ms Kerr described it as "our key resource to do our horizon scanning with." Although it would have been evident that generic perindopril was not yet available, it could reasonably be expected to become available in the near future if the drug was no longer under patent.

iv) In July 2007, after Patent 941 was held to be invalid, generic perindopril entered the market. At that point it was clear that the price of perindopril would come down. While some formularies did 'demote' perindopril, I do not consider that those DTCs which did not do so were acting unreasonably.

v) DTCs often included local consultants, and any proposal to change the recommendations in the local formulary regarding a drug used in the cardiovascular area would often involve consultation with local consultants specialised in that field. That was obviously appropriate, and I consider that it was eminently reasonable to give considerable weight to the views which those specialists expressed. Although the pharmaceutical adviser may have taken a different view, where local consultant(s) supported the inclusion or retention of perindopril as a first line drug, in my view the PCT/Health Board was not acting unreasonably if it followed the advice of the hospital consultants specialised in the particular field and not the pharmaceutical adviser. Mrs Watson gave an example of exactly this happening in Plymouth in 2002.

vi) Servier had the point in (v) very much in mind. It was very alert to a threat to remove or 'demote' perindopril from local formularies and developed a strategy

to mobilise support from local cardiologists to counter this threat. Thus an internal Servier document produced following the price reductions for generic ramipril and lisinopril included a spreadsheet listing 403 PCTs and Health Boards, colour-coded to reflect the estimated degree of risk to Servier's business, and set out a series of bullet points setting out the steps which Servier's PCT-focused and hospital-focused medical reps should take, including the following:

> "• High level of activity with key secondary care targets who could be involved in PCO decision making protocols, or sit on the APC
>
> • Especially Cardiologists as these will be the advisors to the PCO about CV drugs. If the PCO wants to stop recommending Coversyl in favour of ramipril or lisinopril, there is a high likelihood that they will ask a cardiologist for advice or opinion.
>
> • We need to know who that cardiologist is likely to be and whether he/she is favourable to Coversyl and will champion Coversyl ahead of other ACEi
>
> • For this reason it is essential that they know how to differentiate Coversyl from other ACEi and know the evidence in favour of Coversyl. They need to be able to argue against a class effect of ACE inhibitors
>
> • We need to identify, and develop if necessary, the key cardiologist in all areas where business intelligence suggests we may face a problem."

Mr Falcand explained this in his evidence:

> "Q. First, Servier carefully monitored which PCTs and health boards which PCTs and health boards were taking action to limit Coversyl prescriptions, didn't it?
>
> A. Yes. I think I remember having seen a system with a colour code where basically I think we were monitoring the PCTs what we would call a threat of delisting Coversyl, yes.
>
> Q. Secondly, in the areas that were identified as at risk, Servier sought to mobilise its supporters in secondary care to lobby on behalf of Coversyl, didn't it, Mr Falcand?
>
> A. I think one of the actions was definitely to mobilise the secondary care specialists because they are close to the data, and the way to do it was really to give them evidence and all the evidence that we have already provided before. Usually I think because they were the care specialists they were closer

> to the data and keen to maintain the freedom to prescribe, and then it was up to their decision basically to - - in that committee which we were not interviewing.
>
> …
>
> Q. Servier at the time was contacting key secondary care targets, that is health professionals in secondary care, is that right?
>
> A. Yes - - well, not all of them. We were contacting the ones who were advisers in those formulary committees.
>
> Q. And you were finding out whether they were favourable to Coversyl and whether they would champion Coversyl ahead of other ACE inhibitors, that is right, isn't it?
>
> A. I think we would not ask them to champion Coversyl, we would ask them to champion the fact that Coversyl remained in the formulary."

Of course, Servier's efforts were not necessarily successful. But I do not accept the submission made for Servier that what it did at the time is irrelevant to the question before the Court. In my judgment, in the context of this case, such a strategy on Servier's part is very material to the determination of whether a PCT or Health Board was acting unreasonably in failing to mitigate its loss recoverable from Servier because it did not decide to mark perindopril as a second line or less preferable choice of ACEI on its formulary.

316. In Northern Ireland, the evidence was that before the mid-2000s it was more common for formularies to exist at GP practice level than at the level of the four area Health Social Services Boards. Mr Brogan explained how he was active in developing a single formulary for the Western Area Board that was progressively expanded to cover different conditions, relevant to both primary and secondary care. The formulary covering CV-related illnesses was issued in April 2008, but by that stage perindopril had been off patent for some nine months and generic perindopril was widely available. I do not think it is suggested that, as part of a duty to mitigate, the HSSBs in Northern Ireland should have introduced formularies earlier than they did: such a contention would be untenable.

317. As regards hospital formularies, in the light of the conditions for which perindopril prescribing occurred in secondary care and my conclusions on preliminary issues (a)-(b), and the fact that hospital doctors were effectively confined to prescribing medicines on the hospital formulary, I consider that it was not unreasonable to retain perindopril on the formulary without any 'demotion' or express preference for alternative ACEIs.

Local guidance

318. Servier alleges that the Claimants should have "issued local PCT guidance encouraging a switch from perindopril to the prescription of cheaper alternative ACE inhibitors in generic form, including through meetings with GPs, through newsletters and through meetings with individual PCT pharmacists or agents": Amended Defence, para 83C(d). Although expressed in terms of PCTs, I understand the allegation to apply also to the relevant Health Boards in the other three nations.

319. This is a somewhat compendious allegation which I think needs breaking down for the purpose of analysis. For "guidance" in the form of recommendations within a formulary, see paras 309-316 above. Meetings with GPs are addressed below in the context of the QOF, since they seem to me distinct from the issue of guidance across a PCT/Health Board.

320. Although some local guidance documents were issued, such as *the Greater Manchester Stroke Guidance* and the *Cambridgeshire Guidelines for Hypertension* discussed above, there was no evidence that it was the general approach at the time for such full guidance documents to be issued, which clearly required substantial work. More realistically, in Servier's closing submissions, reliance was placed on newsletters to GPs. It is clear that it was the frequent practice at the time for the pharmaceutical advisers to send out regular newsletters, on paper in the earlier part of the Relevant Period moving to electronic communication by the end. As Ms Kerr observed, that was "a very easy thing to do."

321. I accept that this could have been done and in many cases it was done. Servier could point to examples of newsletters that drew attention to the price difference between lisinopril and/or ramipril as compared to perindopril and urged GPs prescribing an ACEI to choose one that was available generically. Effectively, this means that the allegation concerns steps that should have been taken from about early 2004.

322. However, the evidence was also that GPs, who are of course very busy people, receive a vast amount of written communications and generally more than they can absorb. Therefore, to be effective, a newsletter from the pharmaceutical adviser had to be short. Ms Kerr said that the monthly newsletters which her team produced were two sides of A4, and Mr Brogan, who was involved in the newsletters sent out from the Western HSSB in Northern Ireland, similarly observed that they were typically no more than two pages long. As a result, the medicines management team had to be very selective as to what matters to address in their newsletter. In large part, this issue therefore relates to the broader question of priorities, which I discuss below.

323. Moreover, on the evidence it is unclear that newsletters alone were very effective. Servier's own assessment, set out in its Coversyl Orientation Plan for 2006/2007, was that they "have very little impact on overall actions of GPs". Prof Chapman said that the evidence about their effectiveness is mixed and Ms Kerr significantly said:

> "We wouldn't use [a newsletter] to for new messages but we would use it to back up [a] formulary decision" or topics we had had at discussion face-to-face with them generally."

324. Accordingly, I consider that the allegation about newsletters effectively goes together with the broader allegation concerning the QOF and personal engagement of the pharmaceutical advisers with GPs, as well as local incentive and switching programmes.

The QOF and local programmes

325. Servier alleges that the Claimants should have used the QOF to incentivise a switch from perindopril to the prescription of cheaper alternative ACEIs in generic form": Amended Defence, para 83C(d). Servier's pleading proceeds to state that QOF

incentivised GPs from 2004 to meet their pharmaceutical adviser and review all patients on repeat prescriptions.

326. As explained at para 49 above, the QOF was introduced in April 2004 as part of the new GMS contract across the whole of the UK. It is not suggested that a change in the prescribing of ACEIs should have been introduced as a specific indicator under the QOF. But the QOF indicators included one for meeting with the pharmaceutical adviser at least once a year when three actions relating to prescribing should be agreed, and another for evidence subsequently that those actions had been carried out. It was clear from all the evidence at trial that the QOF had a pronounced effect in facilitating access by the local pharmaceutical adviser to GPs. Ms Kerr said the pharmaceutical adviser would typically meet the GPs in each practice for an hour (in some cases 90 minutes), usually over lunch. He or she would be able to give them written reports and have available the data on the record of prescribing by the practice. The experts agreed that these face-to-face meetings with pharmaceutical advisers were probably the most important means of seeking to influence a GP's prescribing practice. Targets set pursuant to the QOF could be linked to an incentive scheme and the enhanced contact between pharmaceutical advisers and GPs following the QOF enabled discussion and promotion of a switching programme.

327. Accordingly, I think that there are three aspects to consider, which are related but conceptually distinct:

i) individual QOF targets;

ii) incentive schemes; and

iii) switching programmes: i.e. for GPs to switch patients already on perindopril to a generically available ACEI.

328. Before addressing each of these more specifically, I consider that there are five important, over-arching considerations.

329. First, the question under the third preliminary issue is not asking what a PCT/Health Board reasonably *could* have done. It is addressing the question of what they reasonably *should* have done, in the sense that it was unreasonable of them not to do so, having regard to the established principles of mitigation as applied to the present case. The latter question is a very different question from the former.

330. Secondly, the two relevant experts, Ms Kerr and Prof Chapman agreed that:

> "During the material time [i.e. the Relevant Period] [the] Claimant health bodies had multiple competing priorities in relation to safety, therapeutic quality, and cost-effectiveness of prescribing in relation to a variety of medicines."

331. The point about competing priorities was a theme of virtually all the factual evidence from those who worked in medicines management or as pharmaceutical advisers. Although the focus of this trial has been on ACEIs, and on perindopril in particular, that should not obscure the fact that the medicines management teams were concerned with a wide range of issues around GPs and patient care, even going beyond the

question of what drugs should or should not be prescribed, and that when it came to drug prescribing they were of course concerned with a wide range of medicines. It is appropriate to consider what were the relevant priorities in prescribing at the time.

332. The two experts agreed that an overriding priority was to increase the extent of generic prescribing, i.e. for GPs to write a prescription for the generic formulation and not by reference to the branded drug. If a GP prescribed the branded drug, the pharmacist was obliged to dispense it and could not give the patient a generic. The initiative to move all GPs to generic prescribing therefore applied across all drugs and was a priority at the time in all four nations.

333. The experts also explained that other priorities in medicines management in the Relevant Period were:

i) Antibiotics: a consensus had developed that there was over-use of antibiotics in primary care for common viral conditions (coughs, cold, flu, etc). This had both safety and cost implications as excessive antibiotic prescribing would lead to antibiotic resistance, making them less useful for the conditions where they were needed. Prof Chapman said this was "a huge agenda" at the time. And Ms Kerr added that there was also an initiative to get GPs who were properly prescribing an antibiotic to use less augmentin, which was more expensive, and prescribe instead amoxycillin.

ii) Benzodiazepines: that was a tranquilizer drug that had been significantly over-prescribed and had become addictive for patients. There was an effort to move patients away from those drugs, which was challenging, and also to persuade GPs not to initiate any patients on them. That was a safety/quality issue and did not concern cost.

iii) Statins: this was the number one priority as regards cost. There was a fortunate confluence of quality and cost considerations since simvastatin, which was off patent and markedly cheaper, also had a much better evidence base than atorvastatin.

iv) Proton pump inhibitors ("PPIs"): expenditure on PPIs was significant, so there was an effort to get GPs to prescribe one of the PPIs which was available generically.

v) ARBs: as explained above, ARBs were newer drugs for treatment of the renin-angiotensin system. ARBs were expensive drugs as they were all on patent (until at least 2010) but the consensus among CV specialists was that it was only necessary to treat patients with an ARB when they did not tolerate an ACEI, e.g when the ACEI gave them a cough. However, ARBs were being heavily promoted by their manufacturers and prescribing of ARBs by GPs was often significantly above the level justified by adverse reactions to ACEIs.

334. Ms Kerr expressed the view that selection of a generically available ACEI instead of perindopril was the second most significant cost item at the time, after statins. Prof Chapman disagreed and considered that PPIs came well above ACEIs, and that the proportion of ARBs out of ARBs plus ACEIs was just as significant if not more so.

335. An indication of the *relative* cost implications of statins and PPIs compared to ACEIs out of the above list can be gained from various sources. In 2005, the Prescribing Support Unit ("PSU"), which was then part of another body sponsored by the DoH, prepared a "Switching Analysis" which showed that switching to generics would produce savings of £248-£347 million for statins, £136 million for PPIs and £46-£57 million for ACEIs. That suggests that PPIs were markedly more significant than ACEIs in relative terms. I should add, however, that the actual figures set out in that paper were based on the assumption of 100% switching from drugs under patent to the cheapest generic in that drug group which, the paper observes "is unlikely to happen in practice". Indeed, the analysis includes the further caveat that:

> "… generics may not cover all the licensed indications of the branded medicine. Hence the cheapest product may not be an appropriate substitute and a more expensive generic or indeed the brand might be more appropriate."

That is a very pertinent observation since Annex C to that analysis, setting out the substitutions applied, shows that for Coversyl the substitution used was enalapril, which I have found above could reasonably be considered an inappropriate ACEI to use in many cases. Accordingly, although I think this paper is helpful in showing the relative position, I consider that little reliance can be placed on the calculated figure for savings as regards ACEIs.

336. The PSU paper was concerned with switching products in patent to generics within a given drug group and therefore did not consider ARBs. However, Ms Kerr in her first report referred to (and relied on) the annual surveys in *Prescribing Outlook* of the national cost of treatment in primary care (based on prescription data for England). They show that whereas expenditure on ARBs was well below ACEIs in 2004/05, by the following year it had increased markedly and overtaken it, although it remained overshadowed by expenditure on statins:

Expenditure (£ millions) in primary care in England

Year April-March	*2004/05*	*2005/06*	*2006/07*	*2007/08*
Statins	637.9	490.9[29]	502.4	444.3
ACEIs	265.8	157.3[30]	171.6	154.9
ARBs	190.1	211.4	239.5	248.9

337. As regards ARBs, *Prescribing Outlook* comments that the relative level of use should approximately equal the level of ACEI intolerance. The 2006 edition of *Prescribing Outlook* states that this is about 10%, but the 2007 edition puts the proportion at about 20%, and since 72% of renin system prescribing was for ACEIs it notes that "about 30% of prescriptions for [ARBs] may be deemed inappropriate." The 2008 edition notes that the proportions are unchanged. The NPCi *Hypertension data-focused*

[29] *Prescribing Outlook* indicates that this decline from the 2004/05 may be due to the fall in the price of simvastatin as it became available generically.
[30] *Prescribing Outlook* indicates that this decline from the 2004/05 may be due to the fall in the prices of lisinopril and ramipril – presumably since they became available generically.

commentary produced in 2007, which Prof Maskrey explained in cross-examination was primarily intended for the prescribing (i.e. pharmaceutical) advisers and GP prescribing leads in each area, states that the level of ACEI intolerance should be assumed to be 10%. Using that lower figure, the NPC considered that about 60% of the ARBs being prescribed in England were inappropriate. Depending on whether the 10% or 20% intolerance figure is used, correct prescribing would have avoided expenditure on ARBs of about £57-£114 million in 2004/05, £63-£127 million in 2005/06, £72-£144 million in 2006/07 and about £75-£149 million in 2007/08.

338. Dr Duerden's figures for the total spend on perindopril prescribed in primary care in England, presented on an annual basis, are as follows:

Annual spend on perindopril in General Practice in England (£ millions)

2005	69.0
2006	80.7
2007	83.5
2008	59.0

339. Servier's internal figures estimated that about 25% of prescriptions of Coversyl were not for uncomplicated hypertension but related to other conditions (para 265 above), where treatment will probably have originated in secondary care and for which I have found that GPs would not reasonably change to another ACEI. Although calendar year figures cannot be directly compared with financial year figures, and only broad estimates can be made, in my view the figures set out above show that a medicines management team could very reasonably have considered that reducing the level of ARBs prescribing was a greater priority than reducing prescriptions for perindopril in the Relevant Period. Although the above figures relate to England, there is no reason to suppose that the relative figures were significantly different in the other three nations.

340. Unsurprisingly, Servier was well aware of this point at the time. The most popular ARBs were materially more expensive than Coversyl, and Servier's internal strategy document, from which I have quoted at para 315(vi) above, included a further bullet point:

> "In some cases with prescribing advisors we may need to position Coversyl against ARBs — we know that ARBs are over-used and very expensive — by switching to Coversyl from an ARB, there are potentially far bigger cost-savings to be made than switching from Coversyl to a generic ACEi."

341. It is self-evident that the extent of saving from reduced prescribing of ARBs would depend on which ACEI was prescribed instead, and similarly that the extent of savings from reduced prescribing of perindopril does not equate to the expenditure on perindopril but must take into account the cost of prescribing the alternative ACEI. But the point made in Servier's contemporary strategy document, i.e. that ARBs were significantly more expensive than perindopril, was not disputed. I therefore reject Servier's submission at this trial that: "Promoting ACEI v ARBs in isolation from cost-effective prescribing of ACEIs was … irrational."

342. Accordingly, while some PCTs and Health Boards may have chosen to include the level of perindopril prescribing as a priority from about 2004, when ramipril became available generically, I think it was eminently reasonable for others to decide that not only statins but also PPIs and ARBs were greater priorities. It follows that I do not accept Servier's contention, as set out in its closing submissions, that:

> "in every case where a PCT/HB sought to promote the prescribing of ACEIs in preference to ARBs …, the PCT/HB ought also and in that context to have promoted the initiation of cost-effective ACEIs such as lisinopril/ramipril."

343. The reference above to 2004 points to the third general issue, which concerns timing. The Relevant Period runs from 2003 to 2009. The benefit of any target or programme to encourage prescribing of alternative ACEIs to perindopril was directly related to the patent position and the subsequent fall in price following generic entry. As set out above, there were material changes in the price of the other ACEIs over the Relevant Period. And following the judgment invalidating Servier's patent in July 2007, generic perindopril promptly entered the UK market, although the English and Welsh NHS Drug Tariff price for perindopril was not reduced to a generic "Category M" price until October 2008, and the price in the Scottish and NI Drug Tariffs was reduced only in April 2008.[31] The operating year for PCTs and Health Boards was to 31 March and it appears that programmes or schemes were set accordingly. Therefore:

i) As to the time when any steps might have been instigated, given my findings in answer to questions (a)-(b), I consider that it was entirely reasonable for those concerned with medicines management not to take steps to encourage prescribing of an alternative ACEI to perindopril until after generic ramipril entered the market in early 2004. Although Servier submitted that since it was known that ramipril would come off patent in 2004, a programme should have been introduced for the 2003/04 year on the basis that the majority of patients remained on an ACEI for a long time, the source of information about the ramipril patent was *Prescribing Outlook* which also advised that the perindopril patent would expire in June 2003. As there was no reason for the PCTs/Health Boards not to rely on *Prescribing Outlook* at the time, I reject that submission.

ii) By the time of planning for the 2007/08 year, it was known that Apotex had briefly entered the market with generic perindopril in July 2006, and a trial to determine its right to do so and the validity of Servier's patent was to be held in the High Court in March 2007. Prof Chapman said it would then have been reasonable to await the outcome of the trial but Ms Kerr's evidence was that targets or schemes to encourage GPs to prescribe alternative ACEIs should have been pursued until the price of perindopril actually fell, which was not until mid/late 2008.

a) I cannot accept Ms Kerr's view as regards the position once the patent was held to be invalid in July 2007 and generic perindopril promptly

[31] The allegation that the Claimants should have reduced the tariff price earlier constitutes a separate ground of Servier's mitigation case but forms no part of the preliminary issues.

entered the market. As Mr Saunders put it in cross-examination of Prof Maskrey:

> "There is not much point … leaving your switching until the last minute if … the patents are just about to expire?"

Prof Maskrey agreed with this proposition.

b) As to the position for the 2007/08 year, before the outcome of the trial was known, I do not suggest that Ms Kerr's approach was itself unreasonable, but given the effort involved in launching and supporting any prescribing scheme, I regard Prof Chapman's view as entirely reasonable.

344. A fourth general consideration is the internal organisation and structure of the PCT/Health Boards. Medicines management was a relatively recent development which was evolving over the Relevant Period. The experts agreed that there was a great diversity between PCTs as regards medicines management in the resources available, the number of staff and the experience and training of those staff. In response to many of the steps which Ms Kerr took and said should have been taken by others, Prof Chapman did not suggest that they were in any way inappropriate but responded that they were a counsel of perfection. I have no doubt that Ms Kerr was genuine in her view and that she has herself been a very effective and impressive pharmaceutical adviser. But as I observed in my general comments on the expert evidence, I found that Ms Kerr's opinions were based very much on what her medicines management team had done and documents shown to her by Servier's solicitors for the purpose of preparing her reports, whereas Prof Chapman displayed a wider knowledge of practice across the country, based on both his engagement with PCTs and hospital trusts in the advisory work done by the Department of Medicines Management at Keele University and his academic research. I therefore was more impressed by Prof Chapman's evidence on this point.

345. Moreover, although Ms Kerr said that the NHS was always reforming, I accept Prof Chapman's evidence that in England the reduction of the 303 PCTs to 152 PCTs with wider jurisdiction in 2006 caused particular disruption as the size and composition of various PCT committees was changed, some staff were transferred to new roles and new procedures had to be agreed or adopted. For many, that accordingly delayed the establishment of new initiatives in the reformed PCT.

346. Fifthly, the PCTs/Health Boards all had an internal governance structure and any initiative concerning GP prescribing involved a process of discussion and consultation in the individual PCT/Health Board. When a proposed initiative concerned a particular area of drugs, local consultants specialised in that area would generally be consulted and could in any event make representations. If a consultant supported the use of perindopril (possibly he or she was one of the KROLs or KLOLs identified by Servier: para 167 above), Ms Kerr's evidence was that it was part of the pharmaceutical adviser's job to engage with them and confront their opinion, drawing attention to the various studies and national guidance to show that alternative and cheaper ACEIs were equally suitable. But she accepted that this could be difficult and she acknowledged that some consultants would, in effect, not take kindly to having their clinical view of

the merits of particular medicines challenged by a pharmacist, however well qualified he or she might be. I have no doubt that, realistically, the view of local consultants would be a significant factor in determining what initiatives could effectively be pursued.

347. The above observations reflect also the recommendations in the NAO Report (para 154 above), at para 16(j)) that PCTs should:

> "Support prescribing advisers in seeking to influence GPs' prescribing behaviour in targeted areas by:
> - keeping messages clear and simple, focused only on a small number of key prescribing priorities;
> - emphasising that value for money in prescribing includes quality of outcome as well as economy, and that there remains scope for practices to use more expensive drugs when that is clinically appropriate; and
> - backing up key messages with endorsement from senior management and local clinical opinion leaders."

And the NAO's communication plan for prescribing (pharmaceutical) advisers in PCTs, *Influencing Prescribing Cost and Quality in Primary Care*, published alongside its main report, stated:

> "… it is critical to ensure that the key messages you are trying to communicate with the GPs are effective. It is important not to use up valuable time with information which will only cloud the argument as GPs have limited time to process all the material they receive related to prescribing….
> Most GPs in the focus groups, conducted by RAND Europe as part of the NAO study, felt their practice was only able to focus on two or three issues in prescribing at any one time."

348. In the light of those general considerations, I address the three particular aspects on which Servier relied.

QOF targets

349. The QOF was introduced in April 2004. It envisaged setting a very limited number of targets: that was doubtless for good reason, in order to maximise effectiveness. The medicines management team would have had to consider what were their priorities within that framework.

350. As regards the conditions for which I have found in addressing issues (a) and (b) above that it would have been reasonable or appropriate to prescribe a generically available ACEI instead of perindopril, I have no doubt that such a course of action could reasonably have been undertaken under the QOF between April 2004 and about the end of 2007: e.g. as regards the initiation of new patients prescribed an ACEI for uncomplicated hypertension.

351. However, as set out above, there were other priorities in prescribing on which pharmaceutical advisers could reasonably have chosen to concentrate in their limited meetings with GPs and the setting of targets under the QOF. Accordingly, I do not think that it was in any way unreasonable if they chose not to make ACEI prescribing a priority.

Incentive schemes

352. Uniquely among the four nations, in Northern Ireland the DHSSPS, concerned about the relatively high expenditure on drugs prescribed in primary care in the province compared to the rest of the UK, launched a national incentive scheme in July 2006 for implementation by each of the (then) four area Health and Social Services Boards. Called the "Regional Prescribing Incentive Scheme ("PIS"), this was based around a points and payment system and Mr Brogan said that it was designed to complement the QOF. He explained that the QOF changed the culture among GPs and made it much easier to implement this kind of financial scheme.

353. The initial, "interim" PIS for 2006/07 incorporated 14 prescribing indicators. They included one global indicator for the proportion of generically available drugs, and indicators relating to the proportion of prescriptions for PPIs, ACE inhibitors, statins and SSRIs written for specified generically available drugs. The generic ACE inhibitor indicator set the target that at least 70% of ACEIs prescribed should be "prescribed as generic ramipril, lisinopril or enalapril". The list of therapeutic prescribing indicators included an indicator that ACEIs should be at least 77% of all ACEIs and ARBs combined.

354. Servier expressly does not allege that the N Irish Claimants should have gone any further at national level, and indeed relies on the N Irish scheme as an illustration of what could be done. However, although the interim PIS in Northern Ireland included a specific indicator of the kind that Servier argued should have been used, the subsequent evaluation of the results of the interim PIS estimated that out of projected savings of between £3.2 and £5.1 million,[32] the ACEI generic indicator accounted for less than £82,000.[33] That was one of the lowest of all the 14 indicators and is to be compared with savings of over £1 million from statins, £433,500 from PPIs and over £580,000 from SSRIs. Moreover, the ACEI/ARB indicator was estimated to produce savings of over £153,000, well above the level resulting from the ACEI generic indicator.

355. In Wales, the AWMSG introduced an "All Wales Prescribing Incentive Scheme" in 2005/06, but that was more a common structure with some common elements, which would then be adapted with further elements by the individual Health Boards when they implemented the scheme. Thus the scheme incorporated the five national indicators adopted for Wales (of which, as already noted, only one concerned cost): para 299 above; and the Health Boards would add further indicators addressing local prescribing priorities. Only half of the potential remuneration under the Welsh scheme was determined by those indicators; the balance was based on a "Learning Portfolio"

[32] Annualised figures extrapolated from the first three months of the scheme. The lower total excludes savings from the general generic prescribing indicator since it was difficult to estimate the extent to which the figure for that indicator (£1.8 million) was attributable to the PIS; the higher total includes it.

[33] The ACEI generic indicator was removed from the PIS for 2007/08, apparently because the number of indicators was reduced and generic perindopril was soon to become available.

comprising continuing therapeutics education: the GPs were required to participate in a study programme, including attendance at training meetings.

356. There were also very many incentive schemes introduced at local level. They existed prior to the QOF and no doubt could be effective. But in my judgment it was not unreasonable if, either at national or more local level, the Claimants did not include within such a scheme the prescribing of ACEIs that were available in generic form:

i) Because of the financial aspect, such a scheme has to be very clear in its terms and would need to allow for a proportion of perindopril prescribing to reflect the use of perindopril for conditions other than uncomplicated hypertension and the limited circumstances where even for hypertension there were good reasons (aside from cost) for the prescriber to choose perindopril as set out in my findings on issues (a)-(b) above. The N Irish PIS set that proportion at 30% and Servier does not suggest that this was unreasonable. On that basis, the N Irish example shows that the gains to be expected from inclusion of this element in such a scheme were very limited.

ii) Although Servier submitted that action should have been taken from at least early 2004, when ramipril became available generically as it could be anticipated that the price of ramipril would fall substantially, in fact that fall in price occurred only at the end of March 2005. I think it would have been reasonable in any event not to introduce a financial incentive scheme before there was an actual price differential such that implementation of the scheme would bring significant financial benefit. Although Servier pointed out that most patients would remain on an ACEI for several years, the IMS Study suggests that over 40% of patients prescribed perindopril took it for no more than two years: para 268 above.

iii) When a PCT/Health Board introduced an incentive scheme, I think it would have been entirely reasonable to limit it to those areas of much greater financial benefit (e.g. statins and PPIs) and/or on the basis of prescribing quality and safety (e.g. benzodiazepine and co-proxamol).

iv) Dr Duerden gave evidence that in 2006 Pfizer challenged the use of incentive schemes to switch patients from its patented atorvastatin to the much cheaper simvastatin. Pfizer's objection was taken up by the ABPI, which brought judicial review proceedings contending that schemes set up by PCTs and Health Boards that sought to reward the use of particular medicines as against others from the same therapeutic class infringed EU Directive 2001/83. That led in due course to a reference by the Administrative Court to the CJEU, which gave its ruling (holding that such schemes were not unlawful) only on 22 April 2010: Case C-62/09 *R (on the application of the ABPI v Medicines and Healthcare Products Regulatory Agency*, EU:C:2010:219. I do not suggest that any PCT/Health Board should have suspended or avoided introducing an incentive scheme while this challenge was being resolved and it may have been able to distinguish its scheme from those under challenge. But I accept Dr Duerden's evidence that while this matter was pending many PCTs and Health Boards were very cautious about introducing financial incentive schemes relating to specific drugs. In my judgment, given the high financial stakes and commercial resources of pharmaceutical companies compared to the limited resources of the

PCTs/Health Boards, that was not an unreasonable position. And although a scheme might be framed in terms of the proportion of ACEIs prescribed generically, if perindopril was by then the only ACEI on the local formulary that was not available in generic form, the reality of such an incentive is that it would be targeted specifically at Coversyl.

Switching programmes

357. There is an obvious difference between a programme concerned with the initiation of new patients and a programme concerned with switching existing patients away from perindopril onto another ACEI.

358. Ms Kerr accepted that getting doctors to switch patients who were stable on their existing medicines to an alternative drug was much more challenging. Such programmes were instituted, but their design required careful consideration of what patients or conditions should be excluded. They also involved the provision of support to GP practices in terms of identifying and communicating with all relevant patients. That is expressly acknowledged in the further allegation at para 83C(f) of the Amended Defence, which states that the Claimants should have:

> "Provided additional support reasonably necessary to facilitate the switching of patients from Perindopril to cheaper alternative ACE inhibitors, including by providing patient information leaflets and/or template letters for use by GPs when switching patients;…"

359. However, Servier's Coversyl Orientation Plan 2006/2007 recognised that:

> "… many PCTs do not have the infrastructure to be able to carry out any switch programmes"

Such programmes not only required time and cost to prepare and deliver but they also imposed additional work on GP practices. As the NAO's guidance to prescribing advisers, para 347 above, stated:

> "Changing patients can incur costs, both of time and money for the clinicians and it is critical to understand these as part of the 'investment'."

Therefore even if the PCT had the resources to implement a switching programme, the programme had to be selected with care and the number of such programmes that could be introduced was limited.

360. It was also necessary to obtain the 'buy-in' of GPs, who retained their prescribing autonomy and would be very influenced by the prescribing practices of local consultants: if GPs saw that their patients were being initiated on a particular drug in secondary care, which meant that the drug had the 'endorsement' of specialist consultants, many would be reluctant to seek to move patients to a different drug even if the treatment was not for an identical condition. This was referred to by Prof Chapman as the 'halo' effect on drugs of consultants' prescribing choices.

361. As for the QOF and incentive schemes, there was also the issue of timing and, above all, of priorities. For all the reasons set out above, I think it was not unreasonable if a PCT or Health Board did not introduce a switching programme to discourage perindopril prescribing in 2005/06 and 2006/07. (From Servier's closing submissions, it does not appear that Servier now suggests that this should have been done before early 2005.)

362. My conclusion is reinforced in the context of this case by the fact that Servier was active in seeking to dissuade PCTs/Health Boards from introducing such schemes for perindopril. In June 2006, it produced an internal document with the objective: "To set in place a pro-active call strategy for negating PCTs that are focussing on a switch from Coversyl to Lisinopril/Ramipril usage." The 12 page document set out a comprehensive strategy, both proactive and reactive, involving contact with GPs, with PCTs and the use of KOLs to engage with pharmaceutical advisers. The document summarises relevant clinical arguments (with charts, graphs and footnote references to academic studies), practical arguments in terms of titration and dosages, "deflection strategies" (pointing out the significantly greater savings from switching among statins or away from ARBs) and further that emphasis can be placed on the GP workload which such a switching programme imposes. Further, in September 2006, when several PCTs in the London area appeared ready to implement a policy of seeking to switch patients on perindopril to one of the ACEIs available in generic form, Servier's strategic response highlighted the fact that the first generic perindopril had just appeared on the UK market – a reference to the short period of supply by Apotex – and that "it is expected that there will be increased generic availability within the UK in the near future".

363. I do not suggest that a PCT or Health Board should necessarily have been influenced by such efforts on the part of Servier. But, in my judgment, when assessing what the Claimants should have done to mitigate the damages which they can claim from Servier as the result of Servier's anti-competitive conduct, the Claimants were not reasonably required to do precisely what Servier made sustained and calculated efforts to dissuade them from doing.

ScriptSwitch

364. Servier alleges at para 83C(e) of the Amended Defence that the Claimants should have:

> "Introduced or encouraged the introduction and use or further use of software such as 'ScriptSwitch' which provides a visual prompt for the NHS prescribers in order to highlight the availability of an alternative, more cost effective treatment."

365. ScriptSwitch is a software programme that became available in the early 2000s. It could be purchased by PCTs and then downloaded onto the computers of GP practices. It had not been introduced in the Relevant Period in Scotland or Northern Ireland as apparently it was not compatible with the computer systems used there. Servier did not put forward evidence that software other than ScriptSwitch was available or suggest that there was something else that should reasonably have been obtained. This allegation was therefore restricted to the English and Welsh Claimants.

366. A PCT could programme ScriptSwitch with the prescribing messages that it wished to convey to GPs at the time when they wrote particular prescriptions. For example, if the GP was typing in the prescription for a particular drug that was not on the local formulary, a message could pop up on the screen suggesting that he or she prescribes instead one of the drugs that was on the formulary. Accordingly, as Ms Kerr observed, this could be an efficient way of influencing GP prescribing at the point of decision-making.

367. Over the Relevant Period, ScriptSwitch was far from being used universally in England and Wales. It was reported that by December 2005 it was being used by over 50 out of the 303 PCTs in England. Ms Kerr did not support any suggestion that it was unreasonable for a PCT to decide not to purchase ScriptSwitch: she said it was not cheap and the PCT might prefer to spend the money on another pharmacist for its medicines management team. Servier in its opening skeleton accordingly adopted her view that where a GP practice had ScriptSwitch, then it was unreasonable for the PCT not to use it to encourage prescriptions of less expensive ACEIs available in generic form instead of perindopril, at least for all new patients.

368. However, it was noted at the time that it was important "to avoid bombarding GPs with messages". The experts agreed that there was a potential for ScriptSwitch to create 'alert fatigue' which would lead GPs to turn off the alert function. Ms Kerr said in cross-examination:

> "Q. Going back to ScriptSwitch, I think you recognised a moment ago that there was a risk of alert fatigue and you had therefore to decide which warnings it was appropriate to show?
> A. Yes, because there could be over 300 warnings you could put on.
> Q. And that would rapidly lead to alert fatigue on the part of the doctors?
> A. Yes.
> Q. And would damage your goodwill with the doctors with whom you had to work closely?
> A. Yes."

369. It was not clear on the evidence whether ScriptSwitch would distinguish the indication for which the prescription was written; I presume it could not, since the programme would see what was being prescribed, not the diagnosis, although it would see the dosage. But it clearly could have been used to trigger an alert whenever a GP wrote a prescription for perindopril. Therefore, I fully accept that when a GP was about to initiate a patient with uncomplicated hypertension on perindopril, ScriptSwitch could be a useful tool in encouraging the GP to prescribe an alternative. But whether it was unreasonable not to use it for that purpose comes down again to a matter of priorities, given the need to avoid alert fatigue, the fact that Ms Kerr considered that the real value would come as regards new patients, and that there was a range of conditions for which it may not have been reasonable or appropriate to select another ACEI. Taking all this into account, I do not consider that it was unreasonable if the medicines management team chose not to include alerts for perindopril on ScriptSwitch.

370. I have addressed in turn all the various steps identified by Servier as each needs separate consideration. However, there are many common themes to the analysis and to some extent the steps have to be considered together as several were mutually supportive and it would be realistic to use them in conjunction with one another. For example, if a

PCT had an incentive scheme, that could be featured in a newsletter and also be the basis for inserting an alert on ScriptSwitch, and the pharmaceutical advisers in their meetings with GPs would discuss the evidence base and savings that underpinned those steps so that the GPs would appreciate and support the objective. I found persuasive the evidence of Prof Maskrey from his experience at the NPC and study of the literature that to change GPs' prescribing practice was complex and did not involve just one kind of approach. This was appreciated by the medicines management teams who gave considerable thought to selecting and developing their strategies. Some PCTs and Health Boards considered it appropriate and important to take steps to encourage or reward prescribing of other ACEIs instead of perindopril at certain times during the Relevant Period, but choices had to be made and others saw their priorities elsewhere, possibly because of the influence of local consultants or a belief that the entry of generic perindopril was not far off. That reasoning applies also to those PCTs/Health Boards with higher than average levels of perindopril prescribing. As Prof Chapman put it during cross-examination:

> "… you may recognise there is an area of particularly aberrant prescribing, but you may not choose to direct your resources to that because there are greater gains elsewhere."

In my judgment, that was entirely reasonable.

SHAs

371. SHAs were part of the structure of the NHS in England at the Relevant Time. There were no equivalents in the other three nations.

372. It was not altogether clear whether Servier pursues an allegation that SHAs should have taken any of the specific steps which it alleges should reasonably have been taken by way of mitigation. Unlike PCTs, SHAs are not referred to in para 83C of the Amended Defence which sets out the prescribing argument, and Servier's skeleton argument for this trial also did not refer to them but, as regards action to be taken at local level, focussed on the PCTs and Health Boards. There was very limited reference to SHAs in Servier's closing.

373. I consider that Servier was right to focus on the PCTs and Health Boards. As Prof Chapman explained, the role of the SHAs was to set the strategy implementing broad health policies. They would set performance indicators, which might include such matters as waiting times at A&E or cancer referral rates. An SHA could set a performance indicator for the level of prescribing of particular drugs, but that would be agreed with the PCTs. Ms Kerr explained that the SHAs had regional pharmaceutical advisers and could effectively highlight to the PCTs areas of high spend on medicines that were of concern. Her view was that for the 2006/07 year, since it had become clear that perindopril was not imminently coming off patent, all SHAs should have set an indicator for the level of prescribing of generically available ACEIs compared to perindopril, because in each area there would be likely to be some PCTs with higher spending in that field; and then the SHA should have monitored the performance of those particular PCTs. This is something that could have been done, as the example of the South West SHA demonstrates. However, here too, I consider that it was a question of priorities which the SHA would assess and I do not think that SHAs were reasonably required to include perindopril prescribing as a priority. Ms Kerr in her oral evidence

accepted that if a particular PCT had a high spend on perindopril that could be dealt with by the SHA's pharmaceutical adviser interacting with that PCT rather than the SHA issuing area-wide guidance. On that basis, the relevant role for the SHA does not take the matter much further, since Servier's case is that the PCT should have taken one or more of the various alleged steps to reduce perindopril prescribing.

Steps to monitor and ensure compliance

374. Servier's final allegation in para 83C(g) of the Amended Defence is that the Claimants should have:

> "Taken all reasonable steps and allocated reasonable resources to ensure that the foregoing measures were complied with, including monitoring compliance and taking further steps in circumstances of non-compliance."

375. This allegation appears to be contingent upon the prior allegations. If the Claimants were not reasonably required to take the previous steps, then it was not unreasonable if they did not seek to ensure that those steps were taken. Moreover, I have placed emphasis in a number of respects on the need for PCTs, Health Boards and indeed SHAs to determine their priorities. It is well-known that the NHS in all four nations is under constant financial pressure. To the extent that priorities, and the expected effectiveness of potential measures which therefore fed into the setting of priorities, were affected by limitation on financial resources, the allocation of more resources to one area meant a corresponding reduction in the resources available for another. As Dr Hawkins, who was head of medicines management at a Welsh Local Health Board over the Relevant Period, put it:

> "You have a finite resource and you have priorities to do. So, whereas we could have made interventions on perindopril earlier, it would have been at the expense of something else, because the resource and the capacity that you would have used to do that wouldn't have been allocated to the other work that you were doing. So, yes, you would have made the savings sooner but it may well have come at a cost of either a qualitative or a safety issue or potentially even cost savings in another area, because you have to prioritise what you think is the most important thing at the time."

376. As for the Claimants' higher level decisions concerning the extent of their budget which was devoted to medicines management as opposed to other areas of health provision, I would reject any suggestion that this could be unreasonable in terms of mitigation of loss caused by Servier's anti-competitive conduct. I should make clear that no such contention was advanced in Servier's written or oral submissions for this trial, and rightly so: such an allegation would in my view be hopeless.

Servier's FI Response

377. The unreality of the case which Servier advanced was demonstrated by their criticisms of documented switching programmes that were introduced by PCTs, as pleaded in Servier's FI Response which forms part of the third preliminary issue:

i) *Greenwich PCT – September 2006*

378. This was a switching programme for patients on perindopril for heart failure or hypertension. The aim was to review those patients and "where clinically appropriate" change them to ramipril or lisinopril (or enalapril in primary care). Servier alleges in its pleading that this programme was "inadequate and unreasonable" in that it expressly aimed to switch 80% of patients prescribed perindopril for those conditions, "which is too low".

379. However, when this was put to Ms Kerr, the expert called by Servier, she said:

> "… 80% would be a standard target when we are looking at switching patients. Anywhere between 70 and 80 is kind of where we tend to go with these switches, unless we really feel it is not achievable and we might put it a bit lower."

See also my observations at para 356(i) above.

380. I should add that the programme is illustrative of the work involved in such a general switch. The methodology to be applied included the following:

> "If a switch is made, monitor patient within 2 weeks to check blood pressure and that they are tolerating the new ACEI. Check U[rine] and E[electrolytes] at 2 weeks."

ii) *West of Cornwall PCT – January 2006*

381. This set out the procedure for a medication change from perindopril to lisinopril or ramipril. It does not specify which groups of patients were included or for what indications they were being treated. Ms Kerr observed that there would have had to be prior discussion to determine the types of patients to be switched. But again this programme illustrates the extent of the work involved:

> "• Searches carried out to identify any patients within the practice currently prescribed perindopril with a view to changing them to the more cost effective formulary choice, lisinopril tabs / ramipril capsules.
>
> • The patients computer records to be reviewed by a clinician and doses of lisinopril / ramipril to be used for each patient noted on the medication change sheet. (The doses calculated using the conversion table included in the South West Medicines Information and Training letter below.)
>
> • Authorised changes implemented by two members of the Prescribing Support team.
>
> …
>
> • One Prescribing Support member will make the changes and the other member is to check that all changes are correct on the computer.

> • All changes will be noted on the patients consultation screen, along with a request that the patient should attend the practice 1 week after they begin their new medication to have their U & Es checked (optional)….."

382. Servier alleges in its pleading that this was "inadequate and unreasonable" because it did not set out a time frame for implementation. However, when that was put to Ms Kerr, she responded:

> "We generally don't give timeframes…. Reality is it takes as long as it takes in the NHS. Normally activities like this are expected to happen within the course of that financial year. So we would expect things to be done within that year.
>
> Q: But that is a general expectation?
>
> A: Yes. Generally we wouldn't say: oh, and this has to be done by this date. Because, yes, there are too many variables."

iii) *Hampshire PCT – October 2006*

383. These are guidelines for practices to switch patients with a diagnosis of essential hypertension from perindopril to ramipril or lisinopril, designed as a template for adaptation by the practice and with the option to consider whether to include also heart failure patients. I have previously referred to these guidelines for the list of exclusions from the recommended switch: see para 228 above.

384. Servier alleges in its pleading that the switching programme set out in these guidelines was "inadequate and unreasonable" for several reasons, including that it was limited to essential hypertension patients, that it did not set out a timeframe for implementation and because of various excluded categories: see the list quoted at para 228 above.

385. However, when asked about the approach of these guidelines in limiting the switch to essentially hypertension patients but giving guidance and a warning for practices that might wish to switch heart failure patients, Ms Kerr responded that this was a reasonable approach and "a very fair way" of doing things. She further said that the specified exclusions were reasonable. As to Servier's criticism on the ground that the guidelines lacked a timeframe, see para 382 above.

Conclusion on Issue (C)

386. The answer to issue (c) is of course affected by my conclusions on issues (a)-(b). Taking account of those conclusions, for all the reasons set out above I do not consider that the Claimants from any of the four nations failed unreasonably at national level to take steps to encourage clinicians to prescribe other ACEIs instead of perindopril.

387. By the end of the trial, Servier's approach to mitigation measures at the local level had considerably shifted. It submitted that the Claimants should have taken steps to ensure that *new* patients were initiated on a generically available ACEI in all cases (except where the patient was allergic to or could not tolerate alternatives to perindopril), but that a programme to switch *existing* patients on perindopril to an alternative ACEI

should have been undertaken only by PCTs/Health Boards with a high level of perindopril prescribing. Servier did not suggest that all the pleaded steps should reasonably have been taken in every local health area. But it contended that: "at least some of these steps should have been taken by each PCT/HB in the UK." For the reasons I have fully set out, I reject that contention.

388. However, Servier developed an alternative contention that even if not all PCTs and Health Boards should reasonably have taken some steps, those with "higher" rates of perindopril prescribing should have done so. Servier accepted that the standard of the required reasonable conduct which the Court has to apply is a general one across all PCTs and Health Boards, but submitted that what constituted reasonable conduct that complied with this standard varied as between different PCTs and Health Boards according to their individual circumstances.

389. This allegation was not pleaded in Servier's Amended Defence. Servier did not put forward any clear criterion according to which "higher" perindopril prescribing PCTs/Health Boards would be distinguished – whether it would be any that were above the national average, or only those exceeding the national average by some unspecified margin. Nor did Servier say whether for this purpose it was sufficient for that higher level to apply in one year or whether it had to be for two or more consecutive years, given that most of the measures Servier argued should have been adopted took several months to prepare. If this allegation had been pleaded, I expect such matters might have been the subject of a CPR Part 18 Request. But as I understood it, the argument was that the third preliminary issue should be resolved in such a way as to allow the prescribing argument to proceed to trial, at least for "higher" perindopril prescribing PCTs and Health Boards, so that they (or the various successor bodies to which their documents have passed) would provide disclosure to reveal what steps each of them took regarding ACEI prescribing, their individual assessment of their other priorities at the time, the resources and experience of their then medicines management teams, the extent of any opposition from local consultants to any proposal to discourage perindopril prescribing and any other reasons why they did not take various other steps which it is alleged they should have taken. Indeed, Servier's closing submissions assert:

> "Without giving proper disclosure, [the Claimants] cannot prove that every PCT and Health Board that had high levels of perindopril prescribing did so because of local factors that could not be overcome by modest and obviously sensible steps."

390. However, the burden of showing a failure to mitigate (or contributory negligence) rests on Servier. I observed at the outset that this trial was not a general inquiry into the operation of medicines management in the NHS in the four nations over the Relevant Period. The question is, to adopt the language of Lord Nicholls in the *Kuwait Airways* case, what is the extent of the loss for which Servier ought fairly or reasonably or justly to be held liable, given the reasons why the law has recognised a cause of action for anti-competitive conduct in the form of agreements between a patent-holder and generic suppliers whereby the generics stayed out of the market and the high patent price of a drug was maintained. Servier's rights to raise mitigation and contributory negligence defences must be observed. But as Green LJ recently observed in the Court of Appeal as regards a mitigation defence to a competition damages claim:

> "… where a claimant has a justiciable right the procedural and evidential rules governing the enforcement of that right must not be allowed to become so onerous that they undermine or weaken the very right itself by making it too hard to vindicate."
> *NTN Corp v Stellantis NV* [2022] EWCA Civ 16 at [26].

391. Unless Servier can show that the Claimants, at least to some extent, failed unreasonably to observe clear standards in the provision of medicines management which applied at the time, then given Servier's efforts not only to persuade clinicians to prescribe perindopril but to forestall any initiatives by PCTs and Health Boards to dissuade them from prescribing perindopril, I consider that it would not be fair or reasonable or just to reduce by reason of Servier's prescribing argument the amount which the Claimants would otherwise recover for purchasing perindopril at the higher prices which resulted from Servier's actions to delay generic entry. Far from finding that there was such a failure to do what was reasonably required, I found that the evidence from all four nations demonstrated a considered and thoughtful effort to apply the evolving approach of medicines management to promote more cost-effective prescribing, within the limits of their resources and taking account of national and local considerations and priorities. And I do not consider it either proportionate, necessary or just to postpone an answer to the third issue to allow for detailed disclosure from individual PCTs and Health Boards. Accordingly, my answer to the question in the third preliminary issue is: No.

POSTSCRIPT

392. I express my appreciation to all Counsel for the skilful and efficient way in which they presented, in written and oral submissions, the mass of often complex written material deployed in evidence. I have no doubt that for the legal teams involved, this trial was a heavy burden.