

Annexe M

Current price inefficiencies and potential benefits of value-based pricing

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1 INTRODUCTION

- 1.1 A basic concern with the PPRS is that it does not help secure prices that reflect the value of drugs. Other annexes in this report discuss the mechanics of the scheme in detail but a relevant conclusion here is that neither of the principal features of the PPRS – the profit cap or the one-off price cuts imposed across a company's portfolio of products – addresses the therapeutic benefits of individual products.

Overview of exercise

- 1.2 The profit cap essentially remunerates on the basis of inputs (costs) rather than outputs (useful drugs). However, there is little systematic link between the costs and outputs of innovative activity in the pharmaceutical sector – through skill and ingenuity different firms will enjoy very different levels of success in producing useful drugs from a given level of expenditure on R&D. Similarly, the one-off price cuts are imposed across all a company's products, irrespective of their value. One supplier's prices may be cost effective while another's may not, but under the PPRS both must reduce their average prices by the same percentage.
- 1.3 This annexe explores what could be gained from reforming the PPRS to set the prices of branded drugs in relation to their therapeutic benefits. It should be stressed that the object of this exercise is to provide only an initial indication of some of the gains that could be achieved through adopting a value-based approach to pricing. To do so we have considered the list prices of both on-patent and off-patent branded drugs as of late 2006 and their clinical efficacy relative to substitute products.
- 1.4 There is a strong case that off-patent branded drugs should be priced in line with (usually cheaper) bioequivalent generics when available because generics are identical to brands of the same drug.¹ The case for pricing on-patent brands with some regard to the cost of generics of different but substitutable drugs depends on the degree of substitutability. In this annexe we focus on a few brands for which publicly available information suggests that prices are clearly out of line with clinical value. If the prices of such products were reduced to be more commensurate with therapeutic benefits delivered the results would be significant, suggesting potentially hundreds of millions of pounds of expenditure per year that could be more effectively spent by the NHS, giving patients access to the treatments they need.
- 1.5 We should also make clear that it is not the role of the OFT to provide a definitive view of the appropriate prices of drugs. Neither is it our role to provide advice on prescribing to the NHS. Both these roles would fall to appropriate expert bodies under any revised pricing arrangements.² We recognise that some companies may have different views to those set out here or may be able to produce additional evidence to inform the debate. It is entirely appropriate that any such evidence be taken into account by the relevant

¹ Nonetheless, there are some practicalities to be considered, which are taken up in Chapter 3.

² Annexe L considers in detail how existing NHS institutions such as NICE, SMC, AWMSG and officials from the UK Departments of Health could administer value-based reforms to the PPRS.

body under any value-based reform of the PPRS. **We stress that this annexe should not be considered as guidance to prescribers. All views are those of the OFT and do not override the conclusions of other expert bodies following a detailed review of the available evidence, including NICE, the SMC, NHS Quality Improvement Scotland and the All-Wales Medicines Strategy Group. In particular, this annexe does not alter the obligations of Primary Care Trusts in England to provide funding for treatments consistent with guidance issued by NICE.**

- 1.6 We do feel, however, that this annexe provides compelling evidence that reform should take place, in the interests of ensuring the best healthcare outcomes for patients as well as appropriate and stable incentives to invest for companies.

Structure of the annexe

- 1.7 The rest of this annexe is structured as follows:
- 1.8 **Chapter 2** explores in greater detail the different ways in which value-reflective prices could help improve outcomes in the short run (by alleviating the impact of rationing decisions within the NHS) and the long run (by giving companies stronger and more stable incentives to invest in the areas of greatest clinical need).
- 1.9 The remainder of the annexe calculates savings that could be spent more efficiently if value-based prices were applied to a number of drugs that we believe are inefficiently priced under current arrangements. The products discussed are all substantially more expensive than close clinical substitutes, which explains why we consider their prices to be inefficient: it neither promotes value for money for the NHS nor provides good investment incentives to pay significantly more than the lower price in each case to achieve essentially the same clinical outcomes.
- 1.10 **Chapter 3** reviews the specific case of off-patent brands for which entirely equivalent generic products are available. The chapter defines equivalence and calculates savings that could be made across the UK by reimbursing off-patent branded drugs in line with equivalent generics. We explain how, for off-patent originator brands, 'in line' reimbursements may not be identical but instead comprise a small premium for off-patent brands over generics in order to preserve the stability of generics markets. For the reasons set out in Annexe L we consider only brands that have Category M equivalents on the market.
- 1.11 **Chapters 4 to 9** review clinical evidence relating to a number of on-patent branded drugs (and two therapeutic classes). The products reviewed in Chapters 4 to 8 appear not to offer value for money as currently priced. Chapter 9 looks at a drug for which the current price structure may be inefficient.
- 1.12 A concluding **Chapter 10** looks beyond the drugs considered in this annexe in two ways. Firstly it suggests some further areas where current prices may not be value-based but where more investigation is needed. Secondly, to give an indication of how some of the efficiency savings identified might be spent, it reviews a number of therapeutic areas where important drugs are at present under-prescribed despite offering apparently good value for money.

Interpreting savings estimates

- 1.13 For the drugs we have reviewed, we identify indicative annual savings on prescribing volumes from 2005. It must be noted that we would not expect gains estimated on the basis of prescribing volumes observed in 2005 to persist indefinitely. The products considered in this assessment will go off patent in a few years and, indeed, one of the PPIs lost patent protection in December 2005. Further, as noted in the body of the text, the UK Departments of Health are aware at least one of the drugs explored in this annexe may not offer value for money at current prices – and the issue is beginning to be addressed by switching patients to a better-value therapeutic substitute. We would argue that, in the absence of a value-based approach to pricing, there is a greater possibility of drugs continuing to be prescribed in the future at prices that do not reflect their value, but it is difficult to speculate on medium term outcomes at this point.
- 1.14 Therefore it is important to recognise that the estimates above represent a snapshot view, as of 2005. They are indicative of how outcomes for some drugs might be different under a value-based pricing scheme. We must stress again that it is not the role of the OFT to provide a definitive view of the appropriate prices of drugs. We have tried, rather, to assess to what extent prices under current arrangements may not be value-reflective and hence whether there is a case for reform. We feel that our assessment provides strong evidence that reform should take place, in the interests of ensuring the best healthcare outcomes for patients as well as appropriate and stable incentives to invest for companies in the long term.
- 1.15 As well as focusing on savings, we also attempt to give due consideration to the possibility that there is some 'value in variety' provided by similar drugs in the same therapeutic class. That is, different drugs may have differential benefits for certain types of patient in ways that have not been demonstrated in clinical trials and formal cost-effectiveness analysis – for example because effects occur in subgroups that are too small to be considered significant in broad population trials, or because benefits (such as additional patient convenience) are difficult to capture in QALY measures. Hence the savings calculations show the impact of reimbursing each drug at 50 per cent more than the cost of the alternative. (Because the comparators to each drug assessed in Chapters 4 to 9 are generics, these reimbursement premia could also help maintain the stability of generics markets – the same issue encountered in Chapter 3 for off-patent brands).
- 1.16 It is important to remember that, if the PPRS were reformed to employ a more value-based approach, the savings estimated in Chapters 4 to 9 could be reallocated to funding new treatments to which access is rationed under current arrangements.

A note on viewpoints and processes

- 1.17 We expect that the arguments presented in Chapters 4 to 9, that the NHS does not obtain value for money on some widely used on-patent medicines, could be controversial. This calls for a number of remarks about the views we express and the processes we followed in order to arrive at them.

- 1.18 For each drug and class explored in Chapters 4 to 9, evidence is presented for and against the view that it is clinically equivalent to the suggested alternative. We then estimate the savings in NHS expenditure that could be achieved if total UK prescribing in primary care³ for each drug was reimbursed in relation to the list price of the more cost effective alternative rather than at its own current list price. We emphasise that a number of other drugs were initially considered during this analysis but excluded because the evidence on value for money was insufficiently clear.
- 1.19 The process we undertook to identify the drugs covered in Chapters 4 to 9 and evaluate evidence on them was as follows. To identify areas where value for money may be a concern we first spoke to a number of prescribing advisers from PCTs in England, hospital pharmacists from around the UK, professors of pharmacology at UK universities and a retained adviser to the study, Dr Neal Maskrey of the National Prescribing Centre.
- 1.20 Also as part of the process of identifying drugs, we conducted a literature search that included referencing publications such as the '*Drugs and Therapeutics Bulletin*' and reviews available through the National Electronic Library for Medicines, the Cochrane Database of Systematic Reviews, PubMed and other sources. Several publications have in the past expressed value for money concerns about each of the drugs covered by this annexe.
- 1.21 The drugs covered in this annexe were mentioned frequently by sources. Those we met and asked, as an open question, if they could identify any areas where there are likely concerns over value for money each mentioned a number of the drugs covered without prompting.
- 1.22 Having identified a list of drugs in this way, we assessed the degree of substitutability between each drug and potential therapeutic alternatives by reviewing evidence produced by: NICE or SMC, pricing authorities in other countries, other NHS bodies (such as local drugs review groups and academic centres) and clinical trials directly. We subsequently took advice from a panel of medical experts that we consulted to discuss the drugs and test our views. The panel consisted of:
- Dr Ross Breckenridge: Consultant, Vascular Medicine, UCL Hospital;
 - Professor Steve Chapman: Head, School of Pharmacy, Keele University;
 - Dr Neal Maskrey: Director of Evidence-based Therapeutics, National Prescribing Centre;
 - Professor Ron Purkiss: Clinical Director, Medicines Management and Pharmacy, Sheffield Teaching Hospitals;
 - Dr Michael Scott: Chief Pharmacist, Antrim Area Hospital.

³ We do not consider the hospital sector, where transaction prices often differ from list prices. Individual hospitals and procurement consortia obtain highly variable, but sometimes large, discounts to list price. The hospital sector accounts for an estimated 25 per cent of the branded drugs bill in 2005. (Hospital procurement is discussed in Annexe A of this report). To the extent to which list prices do constrain hospital transaction prices, the estimates in this annexe will therefore understate the true savings that would be realised for the NHS.

Also by correspondence on separate occasions:

- Dr Ruth Lopert: Principal Adviser, Pharmaceutical Policy Taskforce, Australian Department of Health and Ageing;
- Professor Tom Walley: Professor of Clinical Pharmacology, Liverpool University.

- 1.23 The panel was not appointed by a formal process. Rather, we met the individuals concerned, and many others, in the course of our research and asked a manageable number to advise us. The panel helped us to interpret the publicly available information sources we had used to form initial views on the drugs covered by our annexe. Importantly the panel advised us as to the limits of statistical analysis and the various ways in which results can be presented and received. Beyond this, the panel explained how in some cases clinicians and procurement managers in the NHS (and abroad) have interpreted publicly available information on clinical efficacy.
- 1.24 As a final stage we asked Dr Neal Maskrey to review a draft of this annexe and suggest amendments as necessary on matters of fact and the interpretation of clinical trials. We informed companies concerned of this exercise and gave them a period of 14 working days to submit any comments. We only contacted companies whose products were assessed on an individual, named basis – that is, we did not contact companies whose products were part of a broad category or class or drugs reviewed, such as off-patent brands with Category M generic substitutes (Chapter 3), the proton pump inhibitors or angiotensin-II receptor antagonists.
- 1.25 Dr Maskrey assisted us in amending the annexe in order to address matters raised in submissions.

2 SHORT- AND LONG-RUN BENEFITS OF VALUE-BASED PRICING

- 2.1 As noted in the introduction, value-based pricing can have positive short-run and long-run effects. In this chapter we explore these effects in greater detail, considering first how inefficient prices can distort company investment decisions (long-run effects) and second how they can undermine value for money and exacerbate rationing in the NHS (short-run effects).
- 2.2 We believe these inefficiencies could be addressed by adopting a value-based approach to pricing. A range of detailed options and choices are set out in Annexe L, but most options comprise two key principles:
- Set prices for off-patent branded drugs in line with equivalent generics. It is hard to argue in principle that the NHS should pay significantly more for a brand name than identical ('bioequivalent') products available at much cheaper prices.
 - Set prices for on-patent branded drugs in recognition of the incremental clinical benefits they deliver compared to therapeutic alternatives. An important new drug might be a breakthrough therapy for a previously untreated condition, or improve the level of patient care provided by existing (perhaps more invasive or inconvenient) non-drug interventions. Other new drugs sometimes help patients more than similar drugs that may or may not be available generically. In each case, an efficient price for a branded product should reflect the availability and prices of viable substitutes.

Long-run effects – investment incentives

- 2.3 If the prices of drugs do not reflect their value to patients and broader society companies will be given inefficient incentives to invest in pharmaceuticals in the future. These issues are addressed in greater detail in Box 2.1, which reviews some therapeutic areas in which there is unmet demand, shows the importance of UK prices in global demand and hence demonstrates how a value-based approach to pricing could improve incentives to invest in these and other priority areas. Such gains would in part depend on the particular pricing method employed, for which various options are explored in Annexe L of this report.

Box 2.1: Potential gains from value-based pricing in the long term

When the prices of medicines do not reflect relative therapeutic benefits the investment incentives of firms can be distorted. Specifically, companies may not face strong incentives to invest in drugs that are most beneficial to society and may conversely be encouraged to spend large sums developing products that offer unclear improvements to patients over existing alternatives. This can be bad for public health in the long term, leaving patients without effective treatments to combat their diseases.

The World Health Organisation has identified many 'pharmaceutical gaps' in serious conditions where it is not profitable for private sector companies to research effective treatments.⁴ Some examples of missing medicines according to the WHO are:

- An effective treatment for acute stroke;
- New antibiotics to replace older products rendered ineffective by overuse (and associated microbial resistance);
- Antidepressants with proven efficacy in children and the elderly;
- Effective antibacterials for a number of conditions prevalent in developing countries including: malaria, tuberculosis, leishmaniasis and trypanosomiasis;
- Technologies to complement drugs in many areas, such as a heat-stable formulation of insulin or better diagnostic tools for Alzheimer's (for insights into how the onset of the condition differs from the usual process of ageing, which could improve understanding of the current generation of controversial drugs where efficacy is debated).

The recent Cooksey review of the UK health research funding also identified several priority therapeutic areas that are likely to present increasing health challenges in the UK, such as cancer, mental health, diabetes, asthma and arthritis.

Against this backdrop of need, the drugs that generate the biggest revenues globally tend to be for conditions that are chronic, non-fatal (at least for many patients for a long time) and for which there are several substitute therapies with similar characteristics and efficacy. Examples of such conditions include dyspepsia and high cholesterol. Commentators sometimes call these sorts of pharmaceuticals 'me-too' drugs. We do not think it is useful or accurate to divide drugs crudely into 'innovative' versus 'me-too' categories. Many innovations are incremental in nature, bringing benefits to patient groups that may be poorly served by existing drugs. Such benefits can take the form of more effective treatments or reduced side effects and it is key to securing value for money that any such incremental benefits be reflected in prices.

The concern we address in the main part of this annexe is that, for some drugs we review, relative price differences do not appear to reflect relative incremental benefits. To the extent to which this is true, prices will be out of line with value and will not give helpful incentives to companies to invest in drugs in the future.

Value-based prices might bring huge gains over time to the extent to which they could drive investment in areas of clinical need. Such gains are clearly difficult to quantify, however, since we do not know today what drugs could be produced tomorrow under helpful incentives. We also recognise that improving investment incentives depends on many variables, not least how pricing regimes around the world interact with countries' science policies. As well as pricing, other factors in the profitability of drug development include the cost of R&D, which is determined by the regulatory process in leading markets, notably the US and Europe. In the UK the Cooksey review has considered how costs of development could be reduced, and public funds better targeted, so as to improve success prospects for new medicines in some therapeutic areas.

But price is undoubtedly a central concern in getting investment incentives right. UK prices are particularly important in this regard. Annexe D of this report investigates the effect of UK

⁴ See for example: WHO (2004), 'Priority medicines for Europe and the world', Department of Essential Drugs and Medicines policy, document WHO/EDM/PAR/2004.7

prices on the incentives of global firms to invest in new drugs. Although the UK is a small market in terms of prescription volumes, it exerts a disproportionately strong influence on global prices due to the fact that public health services in many other countries follow the UK's lead in pricing new drugs. Countries accounting for around 25 per cent of world pharmaceuticals sales reference the price of a proportion of their products to prices in the UK. Ways in which an improved PPRS might leverage this are discussed in Annexe L that assesses possible options for reform of the scheme.

Short-run effects – value for money and patient access to healthcare

- 2.4 When the prices of prescription medicines do not reflect their relative therapeutic benefits the NHS may obtain poor value for money in the short run. At present, the profit-cap and price-cut mechanisms of the PPRS do not take account of therapeutic value. As a result, similar drugs can carry very different prices – and the NHS does not always obtain value for money. This is a problem because the UK drugs bill is around 12 per cent of the total NHS budget. Obtaining poor value for money on some drugs leads to restrictions on their use and can mean needlessly diverting limited resources from other drugs and non-drug interventions.
- 2.5 Box 2.2 below investigates the question of how expenditure on some drugs might constrain healthcare budgets that could be put to other uses – and exacerbate problems of rationing in the NHS. But it should be stressed that implementing value-based prices would not simply achieve savings on the drugs bill to be spent on other interventions. Savings on poor value drugs might also release resources for other valuable, but high-cost, medicines.

Box 2.2: The effect of inefficient drug prices on access to healthcare

The resources available to the NHS for expenditure on drugs and other healthcare interventions are limited. This implies that, if the price of a treatment is out of line with its relative therapeutic value, the NHS is not making the best use of its funding to improve patients' health. More value-reflective prices would achieve a better outcome for patients, allowing wider access to therapies on a timely basis. The precise mechanisms by which resources are allocated in the NHS and access to treatments may be restricted are complex. This box highlights some concrete ways in which inefficient prices can detract from patient welfare.

It should be noted that drugs budgets are not fixed. Primary care organisations (PCOs)⁵ receive needs-based funding which they have discretion to allocate to a number of uses, including primary care prescribing and hospital commissioning, according to local requirements. We have heard from PCOs that, in attempts to balance their budgets, they sometimes respond to high drug prices by rationing access to other forms of healthcare. Such rationing can affect commissioning of simple elective procedures in hospitals (such as hip operations or cataract removals, which may either be cut or have waiting lists extended) as well as services directly provided by PCOs.

For many drugs prescribed in primary care, a high price will not necessarily result directly in curtailed use. The fact that some of the drugs reviewed in this annexe enjoy very high

⁵ Primary Care Trusts (PCTs) in England and ('Local' or 'Area') Health Boards in Wales, Scotland and Northern Ireland.

prescribing rates despite doubts over their cost effectiveness demonstrates this. Evidence provided in Annexes A and C shows that GPs are not generally sensitive to (or at times aware of) the prices of some of the largest-selling drugs in the UK. The situation may be different for prescribers in hospitals, who are more likely to be sensitive to prices.⁶

There are some categories of drugs where rationing does take place on cost grounds. For example, it is likely that access to 'high-cost' drugs (meaning high cost per patient rather than by total expenditure) may be directly curtailed as a result of inefficiently high prices. PCOs have mechanisms for restricting access to certain high-cost drugs (in some cases requiring approval of prescribing decisions on an individual basis or only agreeing to fund a certain level of prescribing over a given period). If, as some predict⁷, drugs become increasingly tailored to smaller patient groups (for example specific genetic profiles) this rationing of access to expensive therapies is likely to become a more significant issue in the future. To ease access it will not only be necessary to ensure that the prices of such drugs are set at a cost effective level, but also to address the prices of less cost effective treatments that are nonetheless prescribed in very large volumes.

For other drugs, the means by which PCOs are able to constrain expenditure are likely to vary by locality. These approaches, including the use of prescribing advisers and financial incentives to affect prescriber behaviour, are discussed in Annex A.

While PCOs' ability to constrain expenditure varies significantly, there is some evidence to suggest that this behaviour has, in aggregate, had a material impact on patients' access to drugs. For example, during 2003 several pharmaceutical companies expressed concerns at variations in the use of cancer drugs between the 34 cancer networks in England. In response, the Secretary of State asked the National Cancer Director to investigate. Updates issued by the investigation between 2004 and 2006 found that prescribing of cancer drugs has generally increased following positive NICE appraisals but that noticeable variations in usage remain.⁸

A more specific example of restricted access is provided by the anti-TNF α therapies for inflammatory arthritis. In March 2002, NICE approved the use of the 'anti-TNFs' for people with severe rheumatoid arthritis for whom alternative treatments had failed. But a survey in 2005 by the British Society for Rheumatology⁹ found that a third of rheumatologists consulted were prevented from prescribing anti-TNFs in accordance with NICE guidance by PCTs, which usually cited resource constraints. In Chapter 10 of this annexe we consider a number of other specific drugs that may be under-prescribed, given estimates of clinical need, whether or not resource constraints can be shown to be the direct cause.

At a more general level, in August 2006 the King's Fund published a report¹⁰ highlighting large variations in the amount different PCTs in England spend on three major disease areas in which drugs are a central part of treatment: cancer, heart disease and mental health. In each area the difference in expenditure between low-spending and high-spending PCTs was around eight-fold. The report observes that PCTs are allocated funds by the Department of Health on the

⁶ The issues are complex, and taken up in Annex A. Hospital doctors, as employees of the institution, can generally be bound by procurement decisions made by hospital pharmacy departments. By contrast, contact between GPs and community pharmacies that procure and dispense prescription medicines is often minimal.

⁷ See for example the recent Cooksey review of the public funding of healthcare research.

⁸ See for example Department of Health News Release (2006/0314), 20 Sept 2006.

⁹ The survey was conducted jointly by the BSR and the Arthritis and Musculoskeletal Alliance (ARMA). See www.rheumatology.org.uk/public_affairs/armabsrtnfsurvey/

¹⁰ King's Fund (2006), 'Local variations in NHS spending priorities'. The report uses official data from the Department of Health's National Programme Budget Project.

basis of local health and demographic needs so it is natural to observe some variations in expenditure. Heart disease, for instance, might be more prevalent in one PCT population than another. But even after adjusting for needs, the report observes that a high-spending PCT can devote four times more resources to cancer, heart disease or mental health than a low-spending peer.

These differences in needs-adjusted expenditure could reflect many factors. High-spending PCTs may face local needs or costs that are not taken into account accurately enough by the resource allocation formula. Or they might achieve better health outcomes than are required by the government's National Service Frameworks for major diseases, perhaps reflecting the preferences of local populations. But variations are also consistent with PCTs attempting to restrict access to drugs on expenditure grounds.

While practice varies between PCTs, many companies have suggested to us that the mechanisms they employ focus more on reducing cost in the short term rather than achieving value for money. This is one of the motivations for using cost-effectiveness assessment to inform prices directly – to give local decision makers greater assurances that drugs prescribed are cost-effective at prevailing prices and to avoid the need for using volume controls to contain expenditure.

The recent financial problems of the NHS have led to a situation in which rationing decisions have become ever more acute. The Service built up a deficit of £500 million in 2005, but the Secretary of State has instructed it to achieve a surplus in 2007. In this context, it is all the more important that scarce resources be allocated to uses that deliver the greatest clinical benefits to patients.

3 OFF-PATENT BRANDS WITH GENERIC EQUIVALENTS

Introduction

- 3.1 The present and following chapters consider whether the prices of drugs may be out of line with their relative therapeutic benefits under current pricing arrangements. In the following chapters this involves assessing to what extent on-patent drugs deliver equivalent clinical outcomes to generics with different active ingredients – that is, evaluating degrees of therapeutic substitutability. In this chapter we consider a much closer concept of equivalence – that between off-patent brands (originator products and so called 'branded generics') and generic versions of them, which have the same active ingredient.
- 3.2 In most cases, generic versions of an off-patent brand are considered completely equivalent to it such that a significantly higher price for the brand would not be value-reflective, with the implications for value for money discussed in the previous chapter. That is why, in Annexe L of this report, we propose reimbursing off-patent brands with appropriate generic equivalents in line with generic prices.¹¹
- 3.3 Prior to continuing with this discussion we note that, for certain types of products, generics are not considered substitutable. Therefore, in the rest of this chapter, we briefly review the concept of equivalence between a brand and generic versions of it, before estimating savings that would accrue from our proposals.

Therapeutic equivalence

- 3.4 In the UK, the MHRA licenses new chemical entities on the basis of their efficacy, safety and quality of manufacture. These criteria are also used in determining whether to license manufacturers to produce generics.¹² To demonstrate safety and efficacy, generic manufacturers are generally able to draw on pre-existing clinical data and are not usually required to repeat trials on animals and humans. Rather, the focus is on demonstrating that a generic is 'essentially similar' to the relevant existing brand. The particular criteria that apply for establishing whether a generic is equivalent to a branded product are set out in Box 3.1.

Box 3.1: Definition of equivalence between an off-patent brand and a generic

A generic drug is defined as an 'essentially similar product.'¹³ The requirements to prove essential similarity are as follows:¹⁴

- The active substance for the two products must have the same qualitative and

¹¹ The definition of what we consider to be an 'appropriate' substitute is something considered briefly in this chapter but explained in greater detail in Annexe L of this report.

¹² The following points also apply to biological similar products.

¹³ EC Directive on the Community Code relating to medicinal products for human use: Directive 2001/83/EC; article 10.1 (a) (iii), as amended.

¹⁴ CHMP Note for Guidance on the Investigation of bioavailability and bioequivalence. (CPMP/EWP/QWP/1401/98).

quantitative composition;

- The pharmaceutical form must be the same;
- Where necessary bioequivalence may need to be demonstrated from bioavailability studies.

Bioavailability studies show the rate at which a substance is delivered from pharmaceutical form and becomes available at the site of action. To establish bioequivalence, studies must show that after administration two products have essentially the same effects with respect to both efficacy and safety.

Factors other than the active ingredient can affect bioequivalence. If different salts, esters, complex derivatives, or other chemical modifications are used, it must be demonstrated that the safety and efficacy is the same to claim essential similarity. Neither is essential similarity a given between different oral forms (for examples, capsules, tablets) with the same active substance.

Granting a licence for the production of a generic drug therefore implies that a switch to the generic version should be possible without causing any therapeutic problems. A generic drug can be authorised without its own pre-clinical and clinical data if the existing branded product has been authorised for at least six years. The applicant company must have the consent of the patent holder to refer to their pre-clinical and clinical data.

If essential similarity cannot be proven, then appropriate pre-clinical tests and clinical trials must be provided and the product will not be considered as a generic medicinal product. A common reason why drugs based on the same chemical and exhibiting similar clinical efficacy may not be judged essentially similar is when one or more is a modified-release (MR) formulation. MR formulations typically release more slowly than standard versions of a chemical, which can change their side-effect profile in particular. For this reason, the MHRA usually requires that all MR versions of a drug be marketed under separate brand names and advises that doctors also prescribe by brand name so as to avoid possible confusion for pharmacists in deciding which product to dispense. Some MR products are considered in a subsequent chapter of this annexe.

Biological products are more difficult to compare than chemically derived medicinal products (that is, pharmaceuticals). The molecular composition of biologicals can be complex due to the substances and technologies used (for example, recombinant DNA, blood- or plasma-derived products, gene and cell therapy, etc). Tests for biological products are based on comparability studies to prove similar safety, efficacy and quality. As a result the data requirements are different for such drug applications.¹⁵

Potential savings on the remuneration of off-patent branded drugs

- 3.5 Although any generic licensed by the MHRA has been deemed bioequivalent to the relevant off-patent originator product, generics and off-patent brands are currently reimbursed under different arrangements. An off-patent brand is reimbursed under PPRS so long as it is prescribed by brand name. The NHS list prices of generics, however, are set according to mechanisms that audit pharmacy transaction prices and adjust reimbursement prices as pharmacies negotiate dispensing margins with suppliers.

¹⁵ CHMP Guideline on similar biological products (CHMP/437/04).

- 3.6 The majority of generics (90 per cent) are listed on the UK Drug Tariffs under Category M that has led to strong competitive pressures on prices over time.¹⁶ Annexe L of this report, which sets out proposals for reform of the PPRS, recommends that off-patent brands should be reimbursed in relation to the price of an equivalent Category M generic, where available. Once the NHS has achieved a commodity price for a drug after its patent has expired – having allowed price protection under the PPRS for on average 12 years – it is inefficient to pay high premium rates for a product for which much cheaper equivalents are available.
- 3.7 As discussed in Annexe L, it may nonetheless be desirable to pay a small premium on off-patent originator brands to preserve the stability of generics markets. The Category M mechanism is designed to use competitive pressures to deliver savings to the NHS over time, but can allow prices to rise when there are supply shortages. Pricing off-patent originator brands at a small premium to generics would preserve incentives for the NHS to use generics, thus helping to allow adequate volumes to sustain competition between generic manufacturers.
- 3.8 We have undertaken an analysis of the savings that could be generated if all off-patent prices (originators and branded generics) were brought closer in to line with generic reimbursement rates listed on the UK Drug Tariffs. In our recommendations in Annexe L, we propose that only originator brands receive a (maximum) 25 per cent premium to generic rates and that branded generics be priced at parity with equivalent generics. However, it is difficult to identify all non-originator brands from Prescription Cost Analysis (PCA) data used to calculate the savings. Because applying the premium to all off-patent brands underestimates potential savings, to correct for this effect we have also estimated savings from remunerating all off-patent brands at the price of an equivalent generic, where available, but applying no mark-up. The true magnitude of potential savings under our recommendations would lie between savings estimated with, and without, adding the 25 per cent premium to generic prices applied to both originator brands and other branded generics. The description of our calculations below focuses on the case where generic prices plus 25 per cent were applied to brands but the same steps were undertaken in the calculations applying no premium.
- 3.9 Brands and generics were compared at the presentation level (that is, using the same forms, strengths and pack sizes). Using dispensing volumes from PCA data for 2005, we compared actual expenditures on off-patent brands prescribed by name to what would have been paid had each item been reimbursed at 125 per cent of the Tariff price of the exactly matching generic.
- 3.10 Our analysis considered three scenarios. First, prices of off-patent drugs were compared with prices (up rated by 25 per cent) of any generic equivalent appearing in any category in the UK Drug Tariffs.¹⁷ This estimate is our upper bound for savings that could be generated.

¹⁶ Annexe A describes Category M and the other generics categories in some detail.

¹⁷ Separate analyses were undertaken for each of England, Wales, Scotland and Northern Ireland. Tariff prices can in principle vary across countries though in practice they tend to be the same. To take a

- 3.11 The second set of figures is based on changing reimbursements only for off-patent products for which there are Category M equivalents. In total, around 300 off-patent drugs (and roughly 540 presentations) were identified using this approach. As noted in Annexe L, **this is the option we are recommending and hence is the most relevant savings estimate.**
- 3.12 Our final estimate still considers brands with Category M equivalents alone, but takes into account the fact that manufacturer list prices for some off-patent brands are below equivalent Category M prices by subtracting from overall savings the 'loss' of increasing reimbursement of these brands. This may appear to be the most accurate savings estimate, since we are not recommending reimbursing brands at the lower of the prevailing brand or Category M price, but rather uniformly reimbursing at the Category M price plus a maximum of 25 per cent. However, we do not believe these apparent losses will be realised in practice, at least for the NHS as a whole.
- 3.13 This merits some further explanation. As set out in Annexe A, under current reimbursement arrangements generic list prices include a significant mark-up to audited pharmacy transaction prices (often more than 50 per cent over the rate achieved from suppliers) to achieve the annual aggregate £500 million margin settlement for pharmacies agreed as part of the most recent Pharmacy Contract. It is this factor that sometimes causes Category M prices to exceed PPRS list prices for equivalent originator products. But linking the reimbursement prices of off-patent brands to Category M rates would increase the volume of many products contributing to the fixed £500 million settlement, thereby permitting some lower Category M prices and hence avoiding greater costs for the NHS. **We therefore consider the middle estimate set out below to be the most accurate estimate of likely savings.**

Savings results

- 3.14 Table 3.1 below shows that **a total of around £64 million in savings could be generated each year if all off-patent drugs with category M equivalents were reimbursed at generic list prices plus 25 per cent.** As mentioned above, savings under our recommendation, to apply a premium only to originator brands and not other branded generics, would be slightly higher than this figure. Table 3.2 below shows the savings that would be generated if all off-patent brands were remunerated at the prices of equivalent generics without applying the 25 per cent premium. Savings under our recommendation would fall between the estimates in Tables 3.1 and 3.2 – that is, between £64 million and £83 million.
- 3.15 On this basis, savings from England would have been between £34 million and £44 million in 2005. In Scotland savings would have been in the range of £15 million to £20 million. Savings in Wales would have been around £3 million. In Northern Ireland,

conservative view, we did not calculate potential savings from remunerating modified release formulations of drugs, where available, at the price of generics of the standard-release chemical. Many clinicians consider that many MR formulations (that often appear near the end of the patent life of an originator product) offer no benefits over standard-release chemicals. But some MR drugs seem to offer distinct benefits. The issues are taken up in Chapter 9.

savings would have ranged from £11 million to £15 million. Potential savings are high in Northern Ireland relative to the size of the market partly due to the fact that, as noted in Annexe A, there are high levels of branded prescribing for off-patent drugs.

Table 3.1 – Savings from reimbursing off-patent brands at generic list prices plus 25 per cent in 2005 (£ millions)

Country	Take account of any generic equivalent	Take account of Cat. M equivalents only	Category M only and include dissavings*
England	£41.1m	£34.7m	£30.6m
Scotland	£20.4m	£15.4m	£9.2m
Wales	£2.9m	£2.7m	£1.4m
Northern Ireland	£11.2m	£11.0m	£6.8m
Total	£75.6m	£63.8m	£48.0m

(*) Dissavings from branded drugs priced below the generic reimbursement rate.
Source: OFT calculations based on PCA and Drug Tariff data for the UK.

Table 3.2 – Savings from reimbursing off-patent brands at generic list prices (no premium added) in 2005 (£ millions)

Country	Take account of any generic equivalent	Take account of Cat. M equivalents only	Category M only and include dissavings
England	£53.2m	£44.9m	£40.8m
Scotland	£26.5m	£20.2m	£18.8m
Wales	£4.7m	£3.2m	£2.8m
Northern Ireland	£15.0m	£14.6m	£13.9m
Total	£99.4m	£82.9m	£76.3m

Source: OFT calculations based on PCA and Drug Tariff data for the UK.

3.16 Our analysis suggests that in all four countries the top five drugs accounted for around half the savings generated. The top five drug categories in all countries included the calcium channel blockers, the PPIs, the statins and the SSRIs. In the following chapters two of these groups – statins and PPIs – are also examined from the viewpoint of therapeutic substitutability between different chemicals.

Table 3.3 – Savings from reimbursing off-patent brands at generic list prices plus 25 per cent in 2005 (£ millions)

Country	Savings from top 5 drugs (£m)	Savings from top 5 drugs (per cent)	Total savings*
England	£18.1m	52 per cent	£34.7m
Scotland	£8.5m	55 per cent	£15.4m
Wales	£1.7m	63 per cent	£2.7m
Northern Ireland	£7.4m	67 per cent	£11.0m
Total	£35.7m	56 per cent	£63.8m

(*) This table is based on the middle column of Table 3.1 above.
Source: OFT calculations based on PCA and Drug Tariff data for the UK.

Note on savings calculations

- 3.17 In conducting this analysis we had to take account of possible inaccuracies in Prescription Cost Analysis (PCA) data from Scotland, Northern Ireland and Wales.
- 3.18 Nominally each line of data is coded as belonging to one of three classes, to identify products prescribed and dispensed as brands, those prescribed generically but dispensed as brands, and those prescribed and dispensed generically. However, these classifications were sometimes unreliable. For example we found examples of branded drugs still under patent being coded as 'prescribed and reimbursed generically'.
- 3.19 We were concerned not to overestimate possible savings in this exercise.
- 3.20 In order to avoid overestimating savings we included in our analysis only drugs that were clearly identifiable as brands or generics by using a number of checks, for example of the manufacturer listed in the data and of the price (implied by the data) compared to other sources such as the Drug Tariff. Where we were not confident of being able to correctly characterise an item as a brand or generic we omitted it. We also omitted products that consumed low proportions of overall expenditure. This removed several thousand of the lowest-costing products that in aggregate only accounted for a few per cent of total expenditure in each country.

4 STATINS

Background

- 4.1 Statins lower cholesterol and are one of the classes of drugs employed to treat cardiovascular disease (CVD), which is the single greatest cause of death in the UK. The most common manifestation of CVD is coronary heart disease (CHD).
- 4.2 CHD is caused by a narrowing of the arteries supplying the heart and is due to a gradual build-up of fatty material called atheroma. The narrowing can cause heart attacks, angina and other forms of chronic heart disease. Forms of CVD other than CHD include stroke, transient ischemic attack and peripheral arterial disease. Stroke, for example, is a neurological event that is presumed to be of vascular origin.
- 4.3 High levels of low density lipoprotein (LDL) cholesterol in the blood are a well accepted risk factor associated with the build-up of atheroma and onset of CHD. LDL is also a risk factor in the other forms of CVD such as stroke.¹⁸ Statins inhibit an enzyme involved in cholesterol synthesis (HMGCoA reductase) and have a strong, dose-dependent effect in reducing LDL cholesterol.

Box 4.1: Other effects of statins

Beyond reducing LDL, statins have other effects that may be beneficial to cardiovascular health. Statins tend to reduce triglycerides – another lipid, like cholesterol, seemingly involved in the build-up of atheroma – and some increase high density lipoprotein (HDL) cholesterol. There are further, more subtle 'pleiotropic' effects which are only partially understood, such as reducing certain types of inflammation.

It is not at all clear whether the action of statins on triglycerides and pleiotropic effects is clinically significant. On the other hand, it is sometimes argued that elevated HDL cholesterol is associated with improved cardiovascular health.

There are difficulties, however, in teasing out the effect of HDL on cardiovascular morbidity and mortality. Populations with high HDL tend to show lower rates of heart disease but high HDL is often correlated with low LDL (where evidence on cardio-protection is strong) so that attributing independent effects HDL is problematic. Furthermore, according to the OFT panel, the benefits of increased HDL in patients at high risk of heart disease have never been shown conclusively.

- 4.4 Five statins currently have a UK marketing authorisation: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. Pravastatin and simvastatin are off-patent and available generically.

¹⁸ However, the causality between elevated cholesterol and different types of stroke (ischemic and haemorrhagic) is debated.

Clinical evidence

- 4.5 The evidence on the comparative efficacy of the statins is summarised in the NICE Technology Appraisal¹⁹ TA94. The appraisal identifies 31 randomised controlled trials (RCTs) of statins lasting at least six months and specifying clear clinical endpoints. Of these, 28 were placebo-controlled and three were head-to-head trials of two or more statins.
- 4.6 Studies such as those reviewed by NICE (but also many smaller and more observational exercises, some of which are touched on below) have evaluated how effectively statins reduce LDL cholesterol and how they reduce cardiovascular morbidity and mortality. To make sense of what different studies show it is important to examine the link between LDL and cardiovascular disease. Whilst LDL is a major risk factor, the full extent of its causal relationship with CVD is less well understood. There is little doubt that reducing LDL helps prevent cardiovascular events but there is an active debate about the degree of LDL lowering that is effective. It has been asserted, but not proven, that treating to a pre-determined cholesterol target reduces cardiovascular mortality and morbidity, and that using higher doses of statins has a strong evidence base. These issues are taken up in Box 4.2 below.

Box 4.2: Cholesterol reduction and cardiovascular disease

Statins are one of several classes of drug that are used to improve cardiovascular health and survival prospects in patients with different specific forms of heart disease. One immediate effect of statins is to lower LDL cholesterol but that is not a clinical outcome. It is sometimes claimed that cardiovascular risk can be continually reduced along with LDL cholesterol concentrations but credible sources advocate that there are no clear benefits in lowering cholesterol below a threshold (see below). Thresholds, however, vary and depending on which source of guidance a prescribing doctor is minded to follow, the choice of statin may differ. In equivalent doses, rosuvastatin and atorvastatin are somewhat more effective than the other three chemicals at lowering LDL.

Guidelines on cholesterol reduction for patients at risk of cardiovascular disease recommend two main targets.²⁰ One is a total cholesterol (TC) level of 5.0mmol/L or LDL cholesterol of 3.0mmol/L (depending on which is measured and recalling that the HDL cholesterol component of TC is not associated with cardiovascular harm). The other target is for TC 4mmol/L or LDL 2mmol/L.

The '4 and 2' target is recommended by the Joint British Society Guidelines.²¹ The '5 and 3' target is recommended by the Department of Health's National Service Framework on coronary

¹⁹ *Statins for the prevention of cardiovascular disease*, (January 2006).

²⁰ The targets quoted are for primary prevention of CVD in patients who are asymptomatic but assessed as being at elevated risk from one or more risk factors, including raised blood pressure, family history of dyslipidemia or obesity among others. Targets can change for secondary prevention. Risks of developing coronary heart disease (CHD) tend to be lower than those of developing CVD, which is a broader definition of disease. Many sources of guidance confuse CHD risk with CVD risk. Some cardiologists consider that statins have somewhat better evidence against CHD than broader CVD.

²¹ JBS2, developed by the British Cardiac Society, the British Hypertension Society, Diabetes UK, HEART UK, the Primary Care Cardiovascular Society and the Stroke Association.

heart disease (2000) and has been reconfirmed recently as a 'national target' in England by the National Clinical Director for heart disease and stroke, and in Scotland by new guidelines from the Scottish Intercollegiate Guidelines Network (SIGN): *Risk estimation and the prevention of cardiovascular disease*, (SIGN97).

Targets have entered the clinical debate because of the strong link between LDL and cardiovascular disease and a desire to give clinicians a common standard to work towards in reducing cardiovascular risk. But lower targets are controversial and many clinicians are sceptical that '4 and 2' can be achieved, by any statin, in most patients who present with initially elevated cholesterol. In our discussions, the OFT panel made a point that has now emerged in the SIGN guidelines, that 'current clinical evidence does not demonstrate that lipid therapy should be titrated to achieve proposed LDL cholesterol targets (p33, s9.7)'. Evidence of reaching targets (for example by upwards dose titration) is lacking because most randomised controlled trials have tested statins in fixed doses versus placebo or lower doses of another statin.

- 4.7 To summarise briefly the evidence in NICE TA94, pravastatin seems to be the least effective statin in terms of reducing mortality or, more immediately, LDL cholesterol levels. Rosuvastatin appears to be the most aggressive in lowering LDL cholesterol in head-to-head trials against atorvastatin, simvastatin and pravastatin. But although rosuvastatin shows promise there is not yet any clinical endpoint data for its comparative effects on health outcomes such as heart attacks, strokes and death. No evidence is reported on fluvastatin. The statins with the most accumulated evidence are simvastatin (the first chemical launched, appearing in the UK in 1989) and atorvastatin. These are the most commonly prescribed statins and there is debate in the NHS over the extent of their therapeutic substitutability, since simvastatin is now available generically at around one-tenth the cost of atorvastatin.
- 4.8 TA94 reports one head-to-head trial of atorvastatin against simvastatin in patients with pre-existing CVD at study entry.²² The trial compared the two chemicals in doses of 20mg to 40mg and found no significant difference in subsequent cardiac events between patients treated with one chemical or the other. It has, however, been claimed that the study was not powered to show a difference in cardiovascular outcomes between the chemicals because only 552 patients were randomised to receive atorvastatin and 535 to receive simvastatin. If the effects of each chemical on mortality in equivalent doses²³ are similar – as the OFT panel contended they are – a much larger head-to-head trial may be required in order to evaluate small differences in post-treatment event rates.
- 4.9 Beyond the one available head-to-head comparison at similar doses, NICE TA94 also reports on several placebo-controlled trials for each of atorvastatin and simvastatin –

²² The 3T study (2003), *Clinical Therapy*, (25) conducted in patients with existing CVD and dyslipidemia.

²³ Twice the dose of simvastatin can be required to achieve the same LDL-lowering effect as atorvastatin mainly because the half-life in the body of atorvastatin is longer. But 40mg of atorvastatin is considered a high dose and 80mg is rarely prescribed. Equivalent dose ratios between any two statins are not constant as treatment moves from mild to intense. Over 95 per cent of simvastatin is prescribed at ≤ 40 mg, and 85 per cent of atorvastatin at ≤ 20 mg (source: UK PCA data).

but these are not designed similarly enough to permit indirect comparisons of the chemicals at commonly used doses.²⁴

- 4.10 As well as the studies described above, which have compared simvastatin and atorvastatin in 'usual' administered doses (20-40mg and 10-20mg respectively), other trials have evaluated the claim that high-dose atorvastatin may offer benefits as an 'intensive' LDL-lowering therapy which simvastatin is unable to match. Atorvastatin is sometimes recommended in local NHS guidelines (although not uniformly) as a second- or third-line statin in patients who fail to reach low cholesterol targets on other statins.
- 4.11 In the IDEAL trial²⁵ of 8,888 patients with stable CHD, atorvastatin 80mg was assessed against simvastatin 20mg. In patients with previous myocardial infarction (heart attack), 'intensive' lowering of LDL did not result in a significant reduction in the primary outcome of major coronary events, but did reduce the risk of other composite secondary endpoints²⁶ and nonfatal acute MI. There were no differences in cardiovascular or all-cause mortality. An adviser to this study, Dr Neal Maskrey, observes that we should be cautious about accepting secondary endpoints unless they were pre-specified and highly statistically significant. This is because it is possible to perform multiple post-hoc analyses and report only those which are significant.²⁷
- 4.12 In the evaluation of 'intensive' LDL-lowering therapy, both atorvastatin and simvastatin have also been investigated separately in studies looking at higher and lower doses of the same chemical. In the TNT trial,²⁸ 10,003 patients with stable CHD were randomised to receive either atorvastatin 10mg or 80mg. Observed mean LDL cholesterol levels were 2.0mmol/L during treatment with 80mg of atorvastatin and 2.6mmol/L during treatment with 10mg of atorvastatin. A primary event²⁹ occurred in 434 patients (8.7 per cent) receiving 80mg of atorvastatin, as compared with 548 patients (10.9 per cent) receiving 10mg, representing a reduction in the rate of events of 2.2 per cent.³⁰

²⁴ For example, one trial evaluated simvastatin in patients with CHD at study entry, another evaluated atorvastatin in a much larger cohort with no CHD. Both chemicals appear effective in absolute terms.

²⁵ Pedersen et al (2005), JAMA, (294).

²⁶ A composite endpoint is the occurrence of one of several pre-defined events. The statistical analysis of composite endpoints can be more limited than that of single endpoints, particularly when investigators seek to draw inferences about individual events within the composite.

²⁷ To clarify, we consider one of the secondary endpoints to be 'highly significant', that showing occurrence of any coronary event was reported in 1059 simvastatin and 898 atorvastatin patients (HR, 0.84; 95% CI, 0.76-0.91; P<0.001). We would consider another of the secondary endpoints, reported at p=0.02, to be 'significant'. Further endpoints reported at p=0.47 and p=0.81 are clearly not significant.

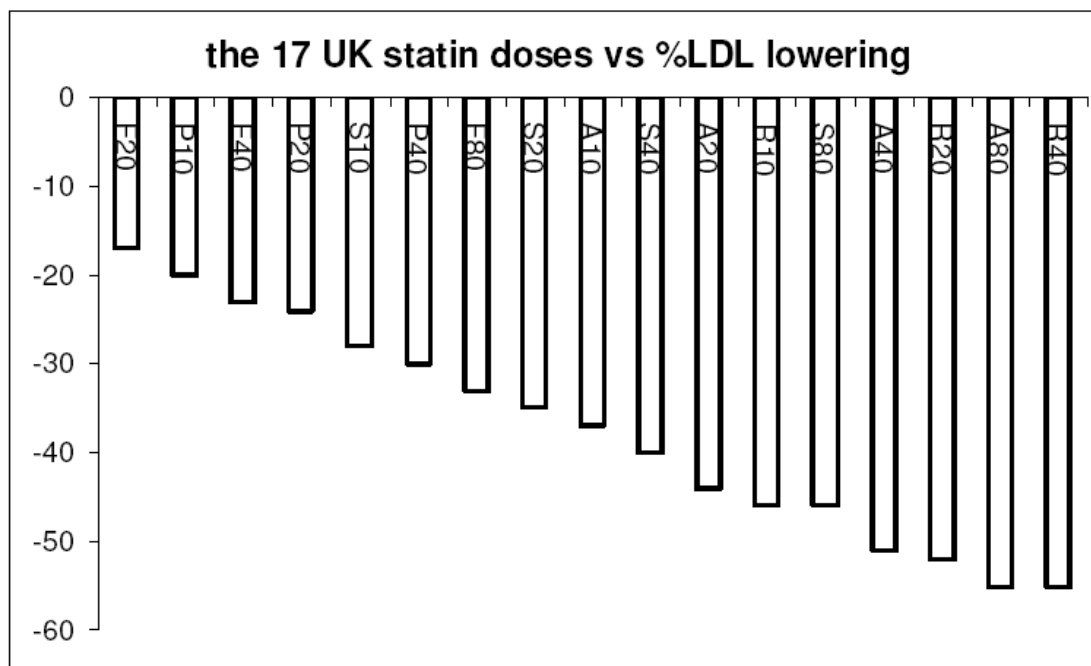
²⁸ La Rosa et al (2005), New England Journal of Medicine, (352).

²⁹ The primary endpoint was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke. Despite a difference in this composite endpoint, there was no difference between the two treatment groups in overall mortality.

³⁰ This result (p<0.001) can be stated as a relative risk reduction of 22 per cent, although out of context this might be taken to imply a greater degree of difference than is the case. Both doses were demonstrated to be effective and the difference between them amounted to a small absolute number of events.

- 4.13 The effect of high- and low-dose simvastatin on cardiovascular events has been compared in the A to Z trial,³¹ which did not reveal significant differences in mortality endpoints between patients treated on either regimen. Dr Maskrey advised us that taking all the results of the high-dose versus low-dose statin trials into account it would be premature to conclude that high-dose therapy is in general more effective than moderate-dose treatment.
- 4.14 To complement the evidence available from trials and sources of NHS guidance such as NICE and SIGN, it is instructive to consider how local NHS bodies have appraised the statins in terms of their therapeutic substitutability. Some NHS trusts and cardiac networks recommend atorvastatin as an 'intensive' LDL-lowering regimen for patients failing to respond to other statins or patients with initially high LDL levels. However, prescribing guidelines from a number of leading hospitals tend towards the view that atorvastatin and simvastatin are close therapeutic substitutes (abstracting from cost). For example, guidelines at one leading trust, University College London Hospital, summarise data from several trials (covered above) that relate specifically to the LDL-lowering capacity of the different statins:³²

Figure 4.1: Excerpt from UCLH statins prescribing guidelines



Key: A = atorvastatin; F = fluvastatin; P = pravastatin; R = rosuvastatin; S = simvastatin

- 4.15 The most potent drugs are on the right-hand side of the chart. There is little difference between high-dose simvastatin (80mg, 'S80') and high-dose atorvastatin (40mg, 'A40') in the right-hand third of the chart. Like the NICE appraisal, the chart implies that pravastatin (or possibly fluvastatin) is least effective, and rosuvastatin most effective, in the intermediate objective of lowering LDL cholesterol.

³¹ De Lemos et al (2004), JAMA, (292).

³² Reproduced by kind permission of Dr James Moon, Specialist Registrar in cardiology, UCLH.

- 4.16 According to the UCLH guidelines, what differences there are in LDL action between simvastatin and the other chemicals should be set against the other advantages of simvastatin. For example, simvastatin 40mg is said to raise HDL cholesterol more effectively than any dose of atorvastatin (although clinical opinions on the significance of this vary). Moreover, the UCLH guidelines deem there to be few significant safety issues in the choice between atorvastatin and simvastatin because both chemicals are metabolised in the same way, giving rise to similar potential side effects and drug interactions.³³
- 4.17 Although the evidence on pravastatin and fluvastatin is relatively scarce, the NICE appraisal and the UCLH guidelines concur that these chemicals may have advantages over the others in terms of side effects and interactions with other drugs. The enzyme that metabolises both atorvastatin and simvastatin (CYP3A4) is quite prone to be inhibited by several other drugs and substances including grapefruit juice. Pravastatin is sometimes indicated in patients for whom other chemicals are not suitable.

Further evidence from other countries

- 4.18 Appraisals carried out in other countries cast more light on the relative efficacy of the different statins. In Australia, for example, the Pharmaceutical Benefits Advisory Committee (PBAC) assesses the clinical and cost effectiveness of drugs before advising the Minister for Health and Ageing on whether individual products should be reimbursed on the publicly funded Pharmaceutical Benefits Scheme (PBS). A PBAC view on a drug is input into a reimbursement price negotiation with the company concerned.
- 4.19 The PBAC considers all the statins to be mutually substitutable in most patients. Until June 2005 atorvastatin was listed at the same reimbursement price as equivalent doses of simvastatin.³⁴ In July 2005, following the presentation of further data, the PBAC took the view that atorvastatin is more effective than simvastatin in lowering LDL and subsequently atorvastatin was exempted from a 12.5 per cent price cut applied to the statins when simvastatin lost patent protection, leaving it at a 14 per cent premium to equivalent doses of simvastatin (both originator products and generics, which are flat-priced in the PBS). However, PBAC provided in that decision the reimbursement price of

³³ For clarification, the view of the NHS National Prescribing Centre on this matter is that both atorvastatin and simvastatin have cautions in their SPCs and in MHRA publications. Prescribers need to be aware of these and recognise that they are different, but it is not clear that any currently marketed statin has a clinically significant record on side effects or safety which should on its own determine prescribing choices.

³⁴ Annexe K provides a detailed case study of the Australian system. Until August 2005, atorvastatin was listed on the PBS on a 'cost-minimisation' basis and subjected to the Weighted Average Monthly Treatment Cost (WAMTC) methodology. Under WAMTC the prices of drugs deemed equivalent are adjusted each year, in the light of emerging evidence on the relative doses at which they are prescribed in clinical practice, so that the average monthly cost to patients on any chemical in the same group is the same. Atorvastatin was subsequently removed from the WAMTC group.

atorvastatin would remain linked to that of simvastatin and would rise or fall, maintaining the 14 per cent gap, on any future changes in simvastatin.³⁵

- 4.20 It is worth noting, however, that simvastatin is more expensive in Australia than the UK, mainly because Australia lacks a well developed generics market. We understand that recent policy proposals have aimed at securing more competitive reimbursement prices for generics and will in the future de-link the price of simvastatin and atorvastatin. Annexe K gives some further details. However, these proposals are very recent and the analysis informing them is not known to us at this stage.

Value for money

- 4.21 In the view of the OFT panel, the evidence on statins summarised by NICE, and the judgements passed by various bodies in this and other countries, do not suggest that any statin achieves significantly better clinical outcomes than simvastatin. This is not to say that all the chemicals are clinically identical. The evidence reviewed, although extensive, is imperfect, issuing from trials of different designs and limitations.
- 4.22 A conservative conclusion is that no comprehensive advantages to any statin over simvastatin have been demonstrated at the population level. Simvastatin is as well metabolised and has as few side effects as any other statin. It is also the product for which there is the most comprehensive evidence in terms of effects on mortality. This conclusion holds for nearly all subgroups. According to the OFT panel, the subgroup in which simvastatin is ineffective (due to genetic factors) is extremely small.³⁶ Where this is the case, pravastatin or fluvastatin are typically substituted.³⁷ Significantly, there is little evidence of significant subgroup differences between atorvastatin and simvastatin, because both are metabolised in the same way, giving rise to similar side effects and drug interactions.
- 4.23 It is nonetheless plausible that different drugs may have different benefits for certain types of patient in ways that have not been demonstrated in RCTs and formal cost-effectiveness analysis. Box 4.3 below takes up the issues.

Box 4.3: Patient-level benefits of statins

Switching studies

A number of small-scale studies have investigated the benefits that different statins provide to individual patients. However, such studies are usually observational (rather than RCTs) and the results of different exercises often conflict. Both the pharmaceutical industry and NHS bodies

³⁵ The Pharmaceutical Benefits Advisory Committee recommended that the only basis for judging whether the price relativity could be further increased would be an incremental cost effectiveness analysis based on major cardiovascular events measured directly in randomised trials rather than based on predictions modelled from surrogate outcomes.

³⁶ As evidenced, for example, in the HPS study (2002), *Lancet*, (360), which evaluated simvastatin 40mg in 20,536 patients, finding significant benefits in a wide range of high-risk patients.

³⁷ Other options include fibrates or ezetimibe.

have funded research. Two recent studies have investigated the effects on LDL control of switching patients from atorvastatin to simvastatin, with contrasting results.

In a recent industry-sponsored study following 100 patients switched from atorvastatin to simvastatin, statistically significant increases in total cholesterol were found, with some patients showing more than ten per cent variation in total lipid levels after switching.³⁸ By contrast in a study partly funded by the NHS (Usher-Smith et al, 2007)³⁹, 70 patients switched from atorvastatin to simvastatin showed no significant changes in mean total cholesterol several months after the switch. One driver behind these variant results could be the way patients were selected to participate in each switch. For example, in Usher-Smith et al (2007), the initial group considered for switching numbered 122 patients but 52 were excluded, 19 for having inadequate cholesterol control (on any statin) before the exercise and a further 16 who were either intolerant to simvastatin or had previously failed to control their cholesterol using simvastatin.

Both of these studies are small and observational and so offer results of limited generalisability. For example Usher-Smith et al (2007) shows 'no significant difference' between atorvastatin and simvastatin if one looks to the 70 patients successfully switched, but some difference if one considers the 16 patients excluded due to simvastatin not being the first choice for them. A further problem is that both studies focus mainly on the effect of statins on cholesterol lowering rather than final clinical endpoints⁴⁰, but a recent review has dismissed the notion of there being a simple linear link between cholesterol levels and cardiovascular risk⁴¹ (see also the discussion in Box 4.2 above).

The evidence reviewed here, though weak, suggests that some price premium for atorvastatin over generic simvastatin might be warranted, to reflect the possibility that the two drugs may have different effects in different patient subgroups. However, the evidence is by no means clear cut and below we argue that such a premium should be lower than the current price gap in the absence of high-grade evidence of the superiority of atorvastatin in large patient populations or well defined subgroups.

Statins and patient subgroups

If, beneath the aggregate population level, different statins display varying efficacy across patient sub groups then some difference in prices could be value-reflective. Often, however, subgroup analyses in clinical trials are not well powered: patient numbers followed up may not be large enough for underlying differences to become easily apparent. One subgroup in which there is some accumulated evidence comparing two statins is patients with diabetes.

Both atorvastatin and simvastatin have good evidence for patients with diabetes. The CARDS study⁴² provides evidence on atorvastatin 10mg (compared to placebo) and specifically

³⁸ Raal (2004), 'A single-centre retrospective observational study to evaluate the change in total cholesterol and LDL cholesterol in hyperlipidaemic patients switched from atorvastatin to simvastatin', *Cardiovascular Journal of South Africa*, (15).

³⁹ Usher-Smith et al (2007), 'Evaluation of the cost savings and clinical outcomes of switching patients from atorvastatin to simvastatin and losartan to candesartan in a Primary Care setting', *International Journal of Clinical Practice*, (61).

⁴⁰ However, Usher-Smith et al (2007) notes that, ten months after the switch, there were no new diagnoses of ischemic heart disease or cerebrovascular accidents among the patients successfully switched to simvastatin.

⁴¹ Hayward et al (2006), 'Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem', *Annals of Internal Medicine*, (145).

⁴² Colhoun et al (2004), *Lancet*, (364).

investigated the effect of atorvastatin in patients with type-II diabetes. Evidence on simvastatin 40mg in patients with diabetes is provided by the HPS study (see footnote 37), which studied treatment effects in a subgroup of patients with type-II diabetes (implying possibly less statistical power than a main group analysis). However in the HPS study there were more patients with diabetes (5,963) than were registered in CARDS (2,838).

- 4.24 In the absence of strong evidence that other statins achieve a better reduction in cardiovascular related death and illness in large populations than generic simvastatin, it seems inefficient for the NHS to pay a heavy premium for them.
- 4.25 Despite this, two on-patent statins – atorvastatin and rosuvastatin – are substantially more expensive than generic simvastatin.⁴³ Atorvastatin costs £18.10 for a 28-pack of 10mg tablets (the most commonly prescribed dose) whilst generic simvastatin costs £1.86 for an equivalent month's treatment (28 pack of 20mg tablets). This has a major budgetary impact because up to 40 per cent of NHS prescriptions for any statin are for atorvastatin.⁴⁴ Rosuvastatin is priced similarly to atorvastatin (£18.03 for 28 tablets, either 5mg or 10mg) but much less prescribed. The financial implications of these disparities look set to be maintained in the future, as the recommendations in NICE TA94 imply that statins should be prescribed to at least one in seven of the adult population on the basis of clinical need.
- 4.26 The simple conclusion from this assessment of relative clinical benefits and cost is that atorvastatin is almost certainly not cost-effective relative to simvastatin at its current price and scale of use. Although the pharmacological differences between simvastatin and rosuvastatin are greater, there is a similar lack of clinical evidence to support the large price differences between the two.
- 4.27 While TA94 appraised the statins in January 2006, it appraised them as a class (against non-statin therapy). Furthermore, during the analysis conducted in early 2005 using prices from 2004, prices of generic simvastatin (then less than one year after patent expiry) were higher than today, and more in line with costs of branded alternatives. The extent of price disparities today would imply extremely high incremental cost effectiveness ratios.
- 4.28 The tables below show the savings that could be made if atorvastatin and rosuvastatin were reimbursed at more value-reflective prices. We have allowed for a brand premium price of 50 per cent above that of generic simvastatin to reflect the idea that different drugs may have different benefits for certain types of patient in ways that have not been demonstrated in RCTs and formal cost-effectiveness analysis.
- 4.29 It should be stressed that that the object of this exercise is not to provide a definitive view of the correct prices of the products reviewed. That role would fall to an appropriate expert body under any revised pricing arrangements, were they to be

⁴³ Prices for atorvastatin and rosuvastatin are from the BNF (52), September 2006. Prices for simvastatin are from the England Drug Tariff, November 2006.

⁴⁴ During 2005 in primary care, around 40 per cent of dispensed prescription items for the statins were for atorvastatin. One prescription item is typically a pack of 28 tablets. Anecdotally, the prescribing rate for atorvastatin is lower in hospitals, but comprehensive data are not available.

adopted at some point in the future. Companies would need to be fully engaged in the process of evaluation and may well be able to produce additional evidence to inform the debate. Our aim, rather, is to provide an indication of the extent to which current prices are not value-reflective and to provide support for the view that there is a substantive case for reform in the direction of value-based pricing.

- 4.30 As with all other estimations in this annexe, savings are calculated on total UK primary care prescribing volumes in 2005 for the relevant drugs (atorvastatin and rosuvastatin). Hence savings are only indicative since prescribing volumes can change appreciably from year to year. For each target, savings are estimated by multiplying 2005 volumes by the difference between the current list price of the target and an eighteen-month average of the generic (Category M) price of the comparator (simvastatin, price up-rated by 50 per cent). Average prices are used for comparator drugs because UK generics prices can exhibit some volatility month by month.⁴⁵ The prices used are for equivalent presentations of the drugs concerned so that, for example, atorvastatin 10mg is hypothetically reimbursed at a 50 per cent premium to simvastatin 20mg. The results do not change significantly if different equivalent doses are assumed.
- 4.31 The tables show that, at 2005 volumes, annual savings from reimbursing atorvastatin and rosuvastatin in line with simvastatin would amount to around £375 million per year, summing over all available strengths. We note that several PCTs have made recent efforts to reduce prescribing of atorvastatin, reflecting concerns about its cost effectiveness at prevailing prices. However, while public data are not yet available, our understanding is that overall prescribing of the drug has fallen only slightly in 2006.

Table 4.1 – Savings from adjusting the price of Atorvastatin – reimbursing 2005 total UK volumes in line with Simvastatin Category M prices (£ millions)

Branded drug		Comparator		Savings from reimbursement
Product	Presentation	Product	Presentation	Generic price plus 50 per cent
Atorvastatin	Tab 10mg	Simvastatin	Tab 20mg	£165.7m
Atorvastatin	Tab 20mg	Simvastatin	Tab 40mg	£124.2m
Atorvastatin	Tab 40mg	Simvastatin	2 x Tab 40mg	£58.9m
Atorvastatin	Tab 80mg	Simvastatin	4 x Tab 40mg	£3.2m

Note: Prices for Atorvastatin are official list prices at November 2006. Prices for Simvastatin are from the England Drug Tariff, average 18 months to June 2006. Simvastatin 4 x 40mg unlikely to be used in clinical practice.

⁴⁵ As discussed in chapter 3 above, because Category M prices reimburse pharmacists at rates reflecting their purchase prices from suppliers they can vary, for example with shortages.

Table 4.2 – Savings from adjusting the price of Rosuvastatin – reimbursing 2005 total UK volumes in line with Simvastatin Category M prices (£ millions)

Branded drug		Comparator		Savings from reimbursement
Product	Presentation	Product	Presentation	Generic price plus 50 per cent
Rosuvastatin	Tab 5mg	Simvastatin	Tab 20mg	£0.01m
Rosuvastatin	Tab 10mg	Simvastatin	Tab 40mg	£21.9m
Rosuvastatin	Tab 20mg	Simvastatin	2 x Tab 40mg	£5.8m
Rosuvastatin	Tab 40mg	Simvastatin	4 x Tab 40mg	£0.3m

Note: prices for Rosuvastatin are official list prices at November 2006. Prices for Simvastatin are from the England Drug Tariff, average 18 months to June 2006. Simvastatin 4 x 40mg unlikely to be used in clinical practice.

Note on all calculations in this annexe

- 4.32 Volumes used in these calculations are taken from Prescription Cost Analysis (PCA) data produced by the Prescription Pricing Division in England, Health Solutions Wales, ISD Scotland and the Central Services Agency in Northern Ireland. PCA data records volumes dispensed by community pharmacies and reimbursed by the NHS in units (for example, tablets and capsules) rather than packs.
- 4.33 By contrast, price sources like the BNF and UK Drug Tariffs quote the cost of packs (usually 28 units where tablets or capsules are concerned). Our approach was to divide prices listed on a per-pack basis by 28 to convert them to a per-unit basis, before multiplying the price difference [target drug – (comparator drug plus 50 per cent)] by the volumes of the target drug to obtain savings.
- 4.34 Sometimes drugs are available in other pack sizes (such as 56) where the price per unit is different from packs of 28. In such cases it would be impossible to predict future expenditure as we do without making assumptions about the pack sizes likely to be dispensed. However, this is not an issue for most drugs considered in this annexe, which in primary care are only available in packs of 28.

Indicative method of implementing value-based pricing: repayments and risk sharing

- 4.35 We recognise that there is a risk that manufacturers would not wish to continue to supply products at the lower value-based prices considered above, given the possibility that doing so could lead to parallel exports from the UK. As discussed in Annexe L, there are potential options, such as the use of side payments that could help address this concern.
- 4.36 Lastly, there is also a possibility that either of the two products reviewed above may, in the future, lead to beneficial outcomes that have not yet been demonstrated in trials data (for example, that the aggressive LDL lowering characteristics of rosuvastatin could lead to enhanced mortality reduction). If there is considered sufficient uncertainty on this front, it would be possible for payers and companies between them to agree risk-sharing arrangements, with repayments or price changes possible after a specified

period contingent on the realisation of certain clinical outcomes. Statins are good examples of the types of drugs that could in principle be suitable for a risk-sharing approach because treatment is undertaken to avoid clear final outcomes (well defined events such as heart attacks, strokes or death) during the progression of a chronic condition where outcomes are only known some time after therapy begins.

- 4.37 Risk-sharing mechanisms of this type could help improve the uptake of both types of drug. In the absence of rational value-based price controls, the NHS often relies instead on quantity rationing applied at a local level. This is likely to be a blunter instrument, focussing on cost at the expense of relative clinical benefits.
- 4.38 If rationing becomes more widespread it may deprive patients of any as yet unproven benefits of rosuvastatin and atorvastatin across large populations – as well as depriving the manufacturers of revenues. But rationing would not seem such a compelling requirement for local NHS managers if the PPRS were able to set prices centrally at value-reflective levels.

5 PROTON PUMP INHIBITORS

Background

- 5.1 Proton pump inhibitors (PPIs) block the secretion of gastric acid in the stomach by inhibiting an enzyme system (the 'proton pump') of gastric parietal cells. PPIs are used in the treatment of various conditions that lead to the symptom of dyspepsia. These conditions are mainly:
- Gastro-oesophageal reflux disease (GORD, resulting in stomach contents rising into the oesophagus);
 - Peptic ulcer disease (gastric and duodenal ulcers are breaks in the lining of the stomach or small intestine);
 - Non-ulcer dyspepsia (often diagnosed when patients present dyspepsia symptoms such as heartburn but have a normal endoscopy);
 - Ulcers caused by use of NSAIDs (a common side effect of which is gastrointestinal bleeding).
- 5.2 PPIs may also be used (typically in combination with an antibiotic) in the eradication of the H-Pylori bacterium that is strongly associated with peptic ulcer disease.
- 5.3 Five PPIs are available in the UK: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. All are different chemicals (of the same class and with broadly the same mode of action) except esomeprazole, which is the left enantiomer of omeprazole (see below). Omeprazole and lansoprazole are off patent and available generically.

Clinical evidence

- 5.4 A review of published evidence found little suggestion of there being significant clinical differences between any of the PPIs. In particular it appears that omeprazole and esomeprazole can be used to similar clinical effect in their shared licensed indications. Also, higher-dose presentations of each chemical may not be significantly more effective than more moderate doses. The OFT panel agreed with all of these findings.
- 5.5 NICE has reviewed the evidence on PPIs in its Clinical Guideline on the management of dyspepsia.⁴⁶ The guideline reports extensively on the many trials and meta-analyses that had evaluated the relative efficacy of different PPIs as of early 2004 and does not highlight any significant differences between any of the chemicals in the treatment of any of the conditions described above.
- 5.6 A review by the London New Drugs Group⁴⁷ in February 2003 evaluates the relative efficacy of omeprazole and esomeprazole. As mentioned above, esomeprazole is the

⁴⁶ CG17, *Managing dyspepsia in adults in primary care*, (August 2004).

⁴⁷ Accessed from the NHS National Electronic Library for Medicines at: www.druginfozone.nhs.uk/Recordper_cent20Viewing/viewRecord.aspx?id=514795

left enantiomer of the omeprazole chemical.⁴⁸ It is known to be metabolised slightly differently to the right-enantiomer of omeprazole or the traditional drug containing both enantiomers (technically known as the racemic mixture, usually referred to as omeprazole). The difference in metabolism could make esomeprazole more potent than the racemic mixture, with the result that its standard dose might be lower.⁴⁹ It has also been claimed that esomeprazole is metabolised more easily in a small minority of patients who are poor metabolisers of omeprazole generally.

- 5.7 Despite the pharmacological differences between esomeprazole and omeprazole, the LNDG review concluded that there may be little clinical advantage to esomeprazole. A trial published in 2000 evaluated the endoscopically-confirmed healing of reflux oesophagitis after eight weeks of treatment on esomeprazole (40mg or 20mg) versus omeprazole 20mg in 1,960 patients.⁵⁰ More patients were healed at week eight with esomeprazole 40mg than with omeprazole 20mg (94.1 per cent vs. 86.9 per cent respectively, $p < 0.001$). This equates to a 'number needed to treat' (NNT) of 14, that is 14 patients would need to be treated with esomeprazole 40mg rather than omeprazole 20mg to produce one additional healed patient at week eight. It is important further to note that this result was obtained by a significantly higher dose of esomeprazole than omeprazole (recalling also that esomeprazole is more potent than the same dose of omeprazole). Healing rates for the comparison of esomeprazole and omeprazole both at 20mg were 89.9 per cent vs. 86.9 per cent ($p < 0.05$; NNT: 33) respectively, again noting that 20mg of both chemicals may not be an equivalent dose. The LNDG review observes that a subsequent study comparing esomeprazole and omeprazole bears a strong resemblance to that discussed here.⁵¹
- 5.8 It should be noted that esomeprazole is the only PPI with a licence for the on-demand treatment of GORD to relieve symptoms in patients who have already completed a course of healing therapy with any PPI. Trials have shown esomeprazole to be effective compared to placebo in this indication. A pharmaco-economic study has shown that the post-healing on-demand use of esomeprazole may be more cost-effective than an

⁴⁸ In chemistry, enantiomers belong to the class of stereoisomers, which belong to the class of isomers. A given molecule may or may not have isomers. When they exist, all isomers of a molecule have the same chemical formula but are different arrangements of the same atoms. In the stereoisomers of a molecule the structure of bonds between atoms is the same but their geometrical positioning in space differs. Enantiomers are stereoisomers that are non-superimposable mirror images of each other. When a molecule has enantiomers the conventions for identifying and naming them vary. Often they are termed 'left' and 'right' enantiomers in reference to their spatial configuration. Another convention differentiates enantiomers according to the direction in which they rotate polarised light.

⁴⁹ Esomeprazole is preferentially metabolised by one of the two enzymes that metabolise both enantiomers. This leads to higher bioavailability and steady-state concentrations. See for example, Äbelö et al (2000), '*Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes*', Drug Metabolism and Deposition, (28).

⁵⁰ Kahrilhas et al (2000), '*Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomised controlled trial*', Alimentary Pharmacology and Therapeutics, (14).

⁵¹ Richter et al (2001), '*Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive oesophagitis: a randomised controlled trial*', American Journal of Gastroenterology, (96). Again esomeprazole 40mg is compared to omeprazole 20mg.

alternative treatment strategy using omeprazole and respecting its product license.⁵² Since the manufacturer has not pursued a licence for on-demand treatment for omeprazole, a licence-compliant strategy would be intermittent treatment (for periods of weeks) on a continuation basis. This can be more costly than on-demand use where a drug is not necessarily taken every day. The study does not, however, account for the real possibility that some patients may already be using PPIs other than esomeprazole effectively in an on-demand manner.

- 5.9 Overall, the OFT panel was comfortable concluding that all five PPIs are highly interchangeable. Participants also felt that more potent chemicals and variants have insignificant advantages since the action of all PPIs is irreversible (in individual gastric parietal cells, hence the effects wear off only as new cells are produced). Thus moderate regimens, so long as they are maintained, control all the main forms of dyspepsia well. This view concurs with findings from a recent Cochrane systematic review.⁵³

Value for money

- 5.10 The evidence presented above does not show conclusively that any PPI provides significant clinical benefits over any other. Despite this, the prices of branded products are substantially higher than generic omeprazole and lansoprazole. The various chemicals have variable potencies, in recognition of which the BNF recommends different doses, which also vary according to indication (such as ulcer healing or symptom control). To simplify the price comparison for expositional purposes, it suffices to note that the cheapest branded product costs over £11.00 for a 28-pack of low-dose tablets (rabeprazole) and the most expensive over £29.00 for a month's treatment (branded omeprazole 20mg capsules or dispersible tablets, packs of 28). In comparison, generic omeprazole cost £4.29 for a 28-pack of 20mg capsules in November 2006, though the price can vary from month to month.⁵⁴ Omeprazole is a good point of comparison because it is the most widely prescribed of any PPI.
- 5.11 The tables below estimate savings that could be made in primary care across the UK if all branded PPIs were reimbursed in line with equivalent strengths of generic omeprazole. To establish equivalent strengths, we used defined daily doses (DDDs)

⁵² Wahlqvist et al (2002), *'Cost effectiveness of proton pump inhibitors in gastro-oesophageal reflux disease without oesophagitis. Comparison of on-demand esomeprazole with conventional omeprazole strategies'*, *Pharmacoeconomics*, (20).

⁵³ Khan et al (2006), *'High-dose versus standard-dose proton pump inhibitors in the short-term management of reflux oesophagitis'*, *Gastroenterology*, (130).

⁵⁴ Prices for branded products are from the BNF (52), September 2006. The price for generic omeprazole is from the England Drug Tariff, November 2006. As mentioned above in the discussion of statins, generics (Category M) prices can be variable. Generic omeprazole is one of the more variable items and the 18-month average Tariff price to June 2006 was around £10.00.

maintained by the World Health Organisation.⁵⁵ A DDD is the assumed average maintenance dose per day for a drug used in its main indication in adults.⁵⁶ For example, according to the WHO the DDD for omeprazole is 20mg so a 40mg tablet would constitute two DDDs. The DDD for pantoprazole is 40mg, so in the analysis below the price of generic omeprazole 20mg capsules is applied to prescribing volumes of 40mg branded pantoprazole. For pantoprazole 20mg the price of omeprazole 10mg is applied.

- 5.12 The broader approach taken below is the same as elsewhere in this discussion. Savings are calculated on total UK primary care prescribing volumes in 2005 of all branded PPIs by considering the difference between list prices for the brands and eighteen-month averages of Category M prices (plus 50 per cent) for generic omeprazole. As elsewhere, the tables apply a brand premium of 50 per cent to branded products to reflect the potential for clinical benefits over omeprazole that have not been formally demonstrated in RCTs.
- 5.13 The tables show that, in 2005, savings from reimbursing branded PPIs in line with generic omeprazole would have been around £91 million. Again, it should be stressed that that the object of this exercise is not to provide a definitive view of the correct prices of the products reviewed, but to provide an indication of the extent to which current prices are not value-reflective and to provide support for the view that there is a substantive case for reform in the direction of value-based pricing.
- 5.14 An important caveat to this analysis is that a large part of the savings are due to lansoprazole, for which the originator manufacturer's Supplementary Protection Certificate expired in December 2005. (All other drugs considered in this annexe are some years from patent expiry).

⁵⁵ See the WHO Collaborating Centre for Drug Statistics Methodology, www.whocc.no

⁵⁶ It is important to emphasize that DDDs are standardised units of equivalence that may not apply for all patients or indications. They do, however, capture how drugs are used across large populations. Most WHO DDDs are the same as maintenance doses recommended in the BNF, although the BNF provides extensive guidance and caveats for clinicians that can make dose comparisons unnecessarily involved for expositional purposes.

Table 6.1 – PPI presentations equivalent to Omeprazole 10mg

Branded drug		Comparator	
Product	Presentation	Product	Presentation
Omeprazole	Cap 10mg	Omeprazole	Cap 10mg
Lansoprazole	Cap 15mg	Omeprazole	Cap 10mg
Pantoprazole	Tab 20mg	Omeprazole	Cap 10mg
Rabeprazole	Tab 10mg	Omeprazole	Cap 10mg

Table 6.2 – PPI presentations equivalent to Omeprazole 20mg

Branded drug		Comparator	
Product	Presentation	Product	Presentation
Omeprazole	Cap 20mg	Omeprazole	Cap 20mg
Esomeprazole	Tab 20mg	Omeprazole	Cap 20mg
Lansoprazole	Cap 30mg	Omeprazole	Cap 20mg
Pantoprazole	Tab 40mg	Omeprazole	Cap 20mg
Rabeprazole	Tab 20mg	Omeprazole	Cap 20mg

Table 6.3 – PPI presentations equivalent to Omeprazole 40mg

Branded drug		Comparator	
Product	Presentation	Product	Presentation
Omeprazole	Cap 40mg	Omeprazole	Cap 40mg
Esomeprazole	Tab 40mg	Omeprazole	2xCap 20mg

Table 6.4 – Savings from adjusting the price of branded PPIs – Reimbursing 2005 total UK volumes in line with Omeprazole Category M prices (£ millions)

Branded drug		Comparator		Savings from reimbursement
Product	Presentation	Product	Presentation	Generic price plus 50 per cent
All branded PPIs	All	Generic omeprazole	Matched by DDD	£91.5m

Note: Prices for branded PPIs are official list prices at November 2006. Prices for Omeprazole are from the England Drug Tariff, average 18 months to June 2006.

Note: Savings are not calculated for a number of presentations of branded PPIs for which there is no generic equivalent. These include special forms of some of the chemicals (such as injections or dispersible tablets) and combination products (usually a PPI plus an antibacterial).

Note: Totals may not be exact due to rounding.

6 CHIRAL SWITCHES

Background

- 6.1 As well as esomeprazole discussed above, a number of other drugs are now available in a form containing only one enantiomer of the active ingredient.
- 6.2 As discussed above, the enantiomers of a molecule have the same chemical formula but a different three-dimensional configuration. Enantiomers usually display identical physical properties such as molecular weight, solubility and melting point. But, in a drug, they may not have the same pharmacological properties because interactions within the body between a drug and the proteins that elicit therapeutic effects and eliminate the drug require a specific three-dimensional configuration of drug and protein.
- 6.3 Often one enantiomer of a drug is inactive because it has less affinity for the drug's target site. Inactive enantiomers can be entirely inert in the body – but they may not be. Typically, the therapeutic effects of a medicine reside in one enantiomer with the other having potentially: no activity; some activity; antagonist activity against the active enantiomer; or entirely separate (beneficial or adverse) activity from the active enantiomer.
- 6.4 The vast majority of drugs are manufactured and marketed as a mix of both enantiomers of the active chemical, with clinical trials having established that inactive enantiomers pose no significant risks. However, relatively recent developments in chemistry have provided the tools to produce single-enantiomer preparations on an industrial scale. This has led to the emergence of a number of such products which are separately patented from their traditional chemical forms containing both enantiomers (so-called racemic mixtures).
- 6.5 In theory, chiral switching could offer therapeutic advantages through increased potency and selectivity, or fewer adverse side effects. Other advantages might be improved onset and duration of effect or a decreased propensity for drug interactions. But using a single enantiomer instead of a racemic mixture is not necessarily beneficial. For example, dilevalol, one of the enantiomers of labetalol, was more toxic than the racemic mixture and never marketed.⁵⁷
- 6.6 Here, we evaluate two single-enantiomer drugs that have come into widespread use: escitalopram (an enantiomer of the antidepressant citalopram) and levocetirizine (an enantiomer of the antihistamine cetirizine). Each single-enantiomer product is on-patent and was developed by the same company that originally pioneered its racemic mixture (now available generically in both cases).

⁵⁷ See Tucker (2000), 'Chiral switches', *Lancet* (355).

Clinical evidence

- 6.7 Escitalopram and levocetirizine have been claimed to offer pharmacodynamic and pharmacokinetic advantages over their traditional alternatives. Both drugs are somewhat more potent than their racemic mixtures which may permit them to be used in lower doses, potentially reducing side effects.^{58 59}
- 6.8 However, on the basis of publicly available information it is more difficult to determine clinical differences between each of these single-enantiomer products and their respective racemic mixtures. The OFT panel was not aware of significant clinical differences although, in the assessment of escitalopram, the panel did not include an expert psychiatrist. In our review of the evidence below we find that there may be clinical differences between escitalopram and citalopram but variable trial design means that these differences may be difficult to quantify. Escitalopram is licensed for certain indications that citalopram is not, which may reflect company decisions on license applications or a lack of available trial data, or both. It is possible that some clinicians may prescribe citalopram off-label for certain of the indications of escitalopram but we cannot determine if such usage is clinically effective without relying on subjective opinions.
- 6.9 Escitalopram is licensed for major depressive disorder (MDD), panic disorder, social anxiety disorder (SAD), generalized anxiety disorder (GAD) and obsessive-compulsive disorder (OCD). Citalopram is licensed for MDD and panic disorder. Comparative evidence on escitalopram and its racemate therefore focuses on the indications of MDD and panic disorder.
- 6.10 A 2003 meta-analysis of comparative studies of escitalopram and citalopram used in depressive illness⁶⁰ claimed some advantages for escitalopram, estimating a between-groups difference in mean change of MADRS score⁶¹ from baseline at eight weeks of 1.02 (95 per cent confidence interval, 95 per cent CI: 0.09 to 1.95). It is unclear

⁵⁸ On escitalopram, see for example: Thase (2006), *'Managing depressive and anxiety disorders with escitalopram'*, Expert Opinion on Pharmacotherapy, (7). The author quotes pooled analyses of studies using citalopram as an active comparator suggesting a modest advantage for escitalopram. The abstract notes that this 'may be attributable to a greater than predicted potency compared with citalopram, presumably as a result of the greater effect of escitalopram at the allosteric binding site of the serotonin transporter.' Below, however, we focus on the demonstrated clinical efficacy of escitalopram compared to citalopram, rather than predictions made on the basis of pharmacodynamics.

⁵⁹ On levocetirizine, we have been made aware of pharmacodynamic data from Devalia et al (2001), European Journal of Allergy and Clinical Immunology, (56). Many endpoints in the pharmacodynamic assessment were unable to show any significant differences between levocetirizine and cetirizine, though levocetirizine did demonstrate greater wheal inhibition 32 hours after dosing than cetirizine ($p=0.018$).

⁶⁰ Auquier, Robitail et al (2003), *'Comparison of escitalopram and citalopram efficacy: A meta analysis'*, International Journal of Psychiatry in Clinical Practice, (7).

⁶¹ The Montgomery Asberg Depression Rating Scale (MADRS) is a commonly used rating scale for depression. Patients with scores between 20 and 30 are sometimes characterised as suffering from 'severe' depression. We are unaware of any agreed methodology for determining the magnitude of change in MADRS scores that can be construed as showing 'response' to treatment, though a recent bulletin by the National Prescribing Centre cautions against assuming that even a 50 per cent reduction in MADRS can be taken as an unequivocal response to an antidepressant (MeReC Extra 18, available online at: www.npc.co.uk/MeReC_Extra/2005/no18_2005.pdf).

whether this is a large difference in clinical terms and, moreover, this analysis is subject to methodological limitations according to a review by the London New Drugs Group⁶², although a subsequent paper based on the 2003 meta-analysis finds similar between-groups advantages for escitalopram and may not be subject to the same limitations.⁶³

- 6.11 Since the 2003 meta-analysis, an eight-week study⁶⁴ comparing escitalopram with citalopram in severe depression reported a between-groups difference in mean MADRS score reduction, favouring escitalopram, of 2.1 points (95 per cent CI: 0.01 to 4.21). A longer-term (24 weeks) study in moderate-to-severe depression reported that the primary efficacy measure (non-inferiority) was similar in the escitalopram and citalopram groups, as was the overall incidence of adverse events.⁶⁵
- 6.12 As regards the relative efficacy of levocetirizine and cetirizine, there has been somewhat less academic interest than for escitalopram/citalopram: as at the end of 2006, we found no studies that have directly compared it with cetirizine in patients with allergic symptoms. One observational study of levocetirizine has been brought to our attention, but this only addressed patients' subjective perceptions of the drug as a useful treatment for allergic symptoms in comparison to previous unspecified therapies.⁶⁶ It is perhaps due to a lack of clinical data that pricing authorities around the world often do not fund levocetirizine. For example, in France, levocetirizine is not listed for public reimbursement. In Australia it is not reimbursed on the Pharmaceutical Benefits Scheme.

Value for money

- 6.13 As before in this annexe, it should be stressed that that the object of this exercise is not to provide a definitive view of the correct prices of the products reviewed. That role would fall to an appropriate expert body under any revised pricing arrangements, were they to be adopted at some point in the future. Companies would need to be fully engaged in the process of evaluation and would be able to produce additional evidence to inform the debate. Our aim, rather, is to provide an indication of the extent to which

⁶² LNDG Briefing (February 2006) available through the NHS National Electronic Library for Medicines at www.druginfozone.nhs.uk/search/product.aspx?id=9. The briefing contends that the 2003 meta-analysis makes no attempt to demonstrate that the authors had not missed some studies, and that some of the sensitivity analyses conducted may have favoured escitalopram by construction.

⁶³ Lançon et al (2006), 'Escitalopram vs. citalopram clinical and cost effectiveness', *International Journal of Psychiatry in Clinical Practice*, (10).

⁶⁴ Moore, Verdoux et al (2005), '*Prospective, multi-centre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder*', *International Clinical Psychopharmacology*, (20).

⁶⁵ Colonna (2005), '*A randomized, double-blind 24 week study of escitalopram (10mg/day) versus citalopram (20mg/day) in primary care patients with major depressive disorder*', *Current Medical Research and Opinion*, (21).

⁶⁶ Klimek et al (2005), '*Patients' perception of the value of levocetirizine in allergic diseases*', *Clinical Drug Investigation*, (25). The study followed 17,500 patients in Germany for mean observation periods of less than 36 days. Around 75 per cent of patients who had taken other (unspecified) medications before levocetirizine expressed the opinion that levocetirizine helped them more.

current prices may not be not value-reflective and to assess the basis for the view that there is a substantive case for reform in the direction of value-based pricing.

- 6.14 The evidence reviewed above indicates that whilst the clinical differences between escitalopram and citalopram are statistically significant, the magnitude of such benefits has been debated. As indicated above, we found no studies that directly compare levocetirizine and cetirizine. Prices, however, are quite divergent. Taking prices from the BNF (52) and England Drug Tariff for November 2006, escitalopram costs £14.91 for a 28-pack of 10mg tablets, compared to £2.69 for the same sized pack of 20mg tablets of generic citalopram. Levocetirizine costs £7.45 for a 30-pack of 5mg tablets compared to £1.47 for a 30-pack of 10mg tablets of cetirizine.
- 6.15 We calculated savings that could be made in primary care across the UK if escitalopram and levocetirizine were each reimbursed at lower prices than today. As elsewhere in this annex, we assume that value-based prices for products concerned by our analysis may be up to 50 per cent higher than current generic reimbursement rates of therapeutic alternatives, even in the absence of demonstrated clinical superiority over those alternatives.⁶⁷ Whilst we have not undertaken a formal cost-effectiveness analysis (modelling the relative costs and benefits of each product and its comparator probabilistically across different indications and patient subgroups)⁶⁸ we believe that in each case a brand premium of 50 per cent above the generic price of equivalent strengths of comparator products fairly captures the notion that different drugs may provide different benefits for certain types of patient in ways that have not been demonstrated in RCTs.
- 6.16 Indicative savings on escitalopram are in the range of £25 million. Those for levocetirizine are just over £3 million.

⁶⁷ A further survey of existing evidence on escitalopram vs. comparators, the more controversial case in this section, appears in NICE's Clinical Guidelines 23, *Depression*, Appendix 20, available at: www.nice.org.uk/page.aspx?o=236692

⁶⁸ We have been made aware of two recent cost-effectiveness studies comparing escitalopram and citalopram, Wade et al (2005), *Current Medical Research and Opinion*, (21) and Wade et al (2005), *Clinical Therapeutics*, (27). Both present models in which escitalopram appears to be a cost-effective alternative to citalopram at current prices. However, neither study has been validated for methodology in an appraisal by NICE or a body of similar standing and we cannot comment on assumptions made in the models. A note on the NHS Economic Evaluation Database on the *Clinical Therapeutics* paper queries a number of the assumptions. See www.crd.york.ac.uk/crdweb/ShowRecord.asp?ID=22005008218. One concern is that remission, discontinuation and response rates were modelled over six months, having been extrapolated from shorter-term data. If either of citalopram and escitalopram were faster acting than the other, but no more effective over a course of treatment, extrapolation from short-term data may obscure clinical comparisons.

Table 7.1 – Savings from adjusting the price of Escitalopram – reimbursing 2005 total UK volumes in line with Citalopram Category M prices (£ millions)

Branded drug		Comparator		Savings from reimbursement
Product	Presentation	Product	Presentation	Generic price plus 50 per cent
Escitalopram	Tab 5mg	Citalopram	Tab 10mg	£1.1m
Escitalopram	Tab 10mg	Citalopram	Tab 20mg	£14.9m
Escitalopram	Tab 20mg	Citalopram	Tab 40mg	£8.9m

Note: Prices for Escitalopram are official list prices at November 2006. Prices for Citalopram are from the England Drug Tariff, average 18 months to June 2006.

Table 7.2 – Savings from adjusting the price of Levocetirizine – reimbursing 2005 total UK volumes in line with Cetirizine Category M prices (£ millions)

Branded drug		Comparator		Savings from reimbursement
Product	Presentation	Product	Presentation	Generic price plus 50 per cent
Levocetirizine	Tab 5mg	Cetirizine	Tab 10mg	£3.4m

Note: Prices for Levocetirizine are official list prices at November 2006. Prices for Cetirizine are from the England Drug Tariff, average 18 months to June 2006.

7 ANGIOTENSIN-II RECEPTOR ANTAGONISTS

Background

- 7.1 The angiotensin-II receptor antagonists (A2RAs) are one of several classes of drugs used in the treatment of high blood pressure (hypertension). Elevated blood pressure is associated with stroke, heart attacks and renal failure.
- 7.2 The A2RAs act on the renin-angiotensin system as do a related class of drugs, the angiotensin converting enzyme (ACE) inhibitors.⁶⁹ The renin-angiotensin system is a hormone system that, when functioning normally, helps regulate blood pressure throughout the body by raising it when it is too low, for example following a haemorrhage. Among other effects, the chemical angiotensin-II causes blood vessels to constrict thereby increasing blood pressure.
- 7.3 A2RAs and ACE inhibitors prevent the action of angiotensin-II. ACE inhibitors block the production of angiotensin II from another chemical, angiotensin I, by inhibiting the enzyme that converts one into the other. A2RAs block the receptor sites of angiotensin II on the muscles surrounding blood vessels.
- 7.4 Other than A2RAs and ACE inhibitors, patients with elevated blood pressure may be prescribed a number of other antihypertensive drugs. Different antihypertensives have various modes of action, for example lowering blood pressure by reducing blood volume or cardiac output rather than via vaso-dilation.
- 7.5 Seven A2RAs are available in the UK: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. None are yet available generically because all are still on patent. Eleven ACE inhibitors are available in the UK, most generically.

Clinical evidence

- 7.6 ACE inhibitors and A2RAs are both widely used for more or less the same indications. Many clinicians, including all those on the OFT panel, consider there to be few differences between the two classes in terms of clinical efficacy. However there is an important difference in terms of side effects. ACE inhibitors are widely reported to cause a persistent dry cough in a significant minority of patients, a symptom which appears to be absent from patients on A2RA therapy.⁷⁰
- 7.7 The cough is not an innocuous side effect: it is irritating and can cause patients to stop taking ACE inhibitors, wasting their prescriptions. This is a temptation because hypertension is often asymptomatic and patients may underestimate the seriousness of their condition.

⁶⁹ ACE inhibitors have a number of other indications in the treatment of cardiovascular disease, and are often prescribed in patients with heart failure, left ventricular dysfunction and diabetic nephropathy.

⁷⁰ The cough is thought to result from the action of ACE inhibitors on one of their chemical pathways. As well as preventing the conversion of angiotensin I to angiotensin II, ACE inhibitors also lower blood pressure by preventing the breakdown of bradykinins, which act as vasodilators. (Bradykinins may also have other cardio-protective properties). Bradykinins are thought to cause the cough in people with certain polymorphisms of the human bradykinin B₂ receptor gene.

- 7.8 The cough has been observed to occur in anywhere between three per cent and 25 per cent of patients taking ACE inhibitors under controlled conditions, although not always seriously enough to motivate treatment withdrawal. In general, the literature suggests that cough occurs slightly more often in females than males, and there may be some ethnic differences as well. A great many studies address the issue. One fairly recent meta-analysis of several previous trials and some other evidence, in 2003, found that patients taking ACE inhibitors over two years for chronic heart failure were slightly more likely than patients on other therapies to have treatment withdrawn due to side effects. Compared to patients receiving standard treatment or placebo, treatment with an ACE inhibitor seemed to lead to an additional three per cent of treatment withdrawals.⁷¹
- 7.9 In the opinion of the OFT panel, dry cough irritating enough to warrant switching occurs in around five per cent of patients treated with an ACE inhibitor.

Value for money

- 7.10 Most A2RAs cost between £10.00 and £15.00 for a month's treatment at typical maintenance doses. By contrast, generic ACE inhibitors are much cheaper. Drug Tariff prices as of November 2006 for two widely prescribed ACE inhibitors are: £2.79 for ramipril (28-pack of 10mg capsules) and £1.98 for lisinopril (28-pack of 20mg tablets).
- 7.11 In view of these price differences, and the suggestion that the most obvious clinical advantage of A2RAs over ACE inhibitors is in the avoidance of dry cough in a minority of patients who take an ACE inhibitor, we calculated the savings that could be made from reimbursing 60 per cent of A2RA prescribing volumes in line with an indicative price for the average generic ACE inhibitor. This proportion merits some further explanation.
- 7.12 We assumed that up to ten per cent of patients where either an A2RA or an ACE inhibitor would be indicated may experience the dry cough on an ACE inhibitor. We assumed ten per cent so as not to overestimate potential savings, recalling that a recent meta-analysis and the OFT panel estimated that around three per cent and five per cent respectively of such patients may experience the cough on an ACE inhibitor. To estimate the proportion of observed A2RA prescribing that may have been motivated by avoiding the cough we took ten per cent of all prescribing of ACE inhibitors and A2RAs. This amounted to slightly less than 40 per cent of observed A2RA prescribing in primary care across the UK in 2005.
- 7.13 As with the PPIs above, savings are calculated here on a class of drugs rather than at the level of individual products. It is therefore necessary to consider the equivalent doses of the various products in the two classes compared. One formal approach would be to calculate a single weighted average price per defined daily dose (DDD) for all generic ACE inhibitors and apply this (with a brand premium of 50 per cent) to

⁷¹ Agusti et al (2003), 'Adverse Effects of ACE Inhibitors in Patients with Chronic Heart Failure and/or Ventricular Dysfunction: Meta-Analysis of Randomised Clinical Trials', *Drug Safety*, (26).

prescribing volumes of A2RA chemicals expressed in DDDs.⁷² The single ACE inhibitor price could be, for example, a volume-weighted average of the prices per DDD of each available generic. It could be compared to the average price per DDD of each A2RA, itself a weighted average of the prices of available strengths and presentations.

- 7.14 A simpler approach is taken below, however. We use a generous indicative price for a 28-pack of ACE inhibitors (tablets/capsules) at typical maintenance dose. At £6.00, this is higher than the Drug Tariff price (at November 2006) of any commonly prescribed presentation of generic ACE inhibitors (most packs cost around £4.00). This price is up-rated by 50 per cent to allow for the possibility that A2RAs may deliver clinical benefits (beyond the avoidance of dry cough when substituted for ACE inhibitors) that have not been demonstrated in RCTs. Ideally, we would compare this price to the current actual pack price of each A2RA presentation and calculate savings over (60 per cent of) 2005 prescribing volumes.
- 7.15 However, Prescription Cost Analysis data used in these calculations⁷³ lists volumes only in terms of units (for example tablets) and provides no information on the pack sizes dispensed by pharmacies. This does not complicate calculations for all other drugs considered in this annexe, which are only available in primary care in packs of 28, but some of the A2RAs are sold in multiple pack sizes where the price per tablet or capsule is not constant. Thus it would not be advisable to convert quantities in the data to packs by dividing by 28 because it is not clear which pack price to compare to the indicative ACE inhibitor price. Therefore as an alternative approach we calculated savings by comparing the average price per unit paid by the NHS in 2005 for each presentation of each A2RA chemical (averaging over pack sizes) with a price of 32.25 pence per unit (£6.00 divided by 28, rounded up and increased by a 50 per cent brand premium) for an indicative ACE inhibitor.
- 7.16 The broader approach taken in the calculations below is the same as elsewhere in this discussion. Savings are calculated on UK primary care prescribing volumes in 2005 of all branded A2RAs. Here, however, 40 per cent of volumes are assumed to be reimbursed at today's list prices on the assumption that those reflect the value of A2RAs to patients who would suffer from the cough on an ACE inhibitor.
- 7.17 Using the methodology described above, potential savings from reimbursing 60 per cent of all primary care prescribing of A2RAs in line with the indicative cost of a generic ACE inhibitor are around £64 million.

⁷² See the section on PPIs above for an explanation of defined daily doses. Essentially, they convert the various presentations of a drug (for example 4mg tablets or an injection at concentration 4mg/ml) into standard units. The definition of 'standard' is a typical treatment maintenance dose in adults.

⁷³ See note on page 32.

Table 8.1 – Savings from adjusting the prices of A2RAs – reimbursing 60 per cent of 2005 total UK prescribing volumes in line with indicative generic ACE Inhibitor prices (£ millions)

Branded drug		Comparator		Savings from reimbursement
Product	Presentation	Product	Presentation	Generic price plus 50 per cent
All branded A2RAs	All oral solid dose forms (tabs, caps)	Generic ACE inhibitor	Indicative price for any (see text)	£64.0m

Note: Chemicals that are the target of savings calculations are: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan.

8 MODIFIED-RELEASE PRODUCTS

Background

- 8.1 Many drugs are available in modified-release (MR) variants, in which the action of the same active ingredient is either extended or delayed. MR products are most common for drugs in oral solid dose form. Usually they work either:
- To extend drug release for a number of hours, either by combining the drug with release-retardant materials to form a matrix core, or by applying release-modifying film coatings to cores containing the drug;
 - To delay drug release for a period of time, typically through the application of an externally applied enteric coating.
- 8.2 In principle, MR systems can offer important benefits in terms of patient convenience by reducing dosing frequency, which can assist compliance with prescriptions and reduce waste. MR systems may also deliver clinical benefits. The action of MR products in the body can be more even than that of standard variants and peak concentration levels can be lower. For these reasons adverse side effects can be reduced. But side effects can also be a function of how long a drug remains in the body with the result that some MR formulations may be less clinically helpful than their traditional alternatives.
- 8.3 We have investigated three MR products: Cardura XL[®] (MR doxazosin, used to treat hypertension and benign enlargement of the prostate); Diamicron MR[®] (MR gliclazide, used to treat Type 2 diabetes); and Lyrinel XL[®] (MR oxybutynin, used to treat urinary incontinence).

Clinical evidence

- 8.4 The OFT panel's consensus conclusions on the three products we asked them to discuss represented the spectrum of possible views about MR formulations. Lyrinel XL[®] was seen as a useful substitute to standard-release oxybutynin. Diamicron MR[®] was seen as a potentially useful alternative to standard gliclazide. Cardura XL[®] was thought to be scarcely different from generic doxazosin.
- 8.5 The panel considered that Lyrinel XL[®] could improve patient welfare when used instead of standard-release oxybutynin by lowering unpleasant side effects. Oxybutynin can have a number of adverse effects including (sometimes severe) dry mouth in a majority of patients. Some on the panel felt that the MR formulation reduces the incidence and severity of such effects, mainly by dint of producing lower peak concentration levels in the body. We note, however, that the panel discussion took place before a recent review of the evidence by NICE that recommends standard-release oxybutynin as a first line.⁷⁴

⁷⁴ CG40, *Urinary incontinence*, October 2006.

- 8.6 The OFT panel did not have strong views on what improvement may be delivered by Diamicon MR[®] over standard gliclazide. Patients with Type 2 diabetes take gliclazide mainly to augment insulin secretion, and one serious (but uncommon) side effect is hypoglycaemia, when therapy to lower blood glucose reduces the level too far. The panel did not express a strong view as to whether an MR formulation significantly changes the probability of hypoglycaemia. But they did not believe that the MR product controls blood glucose significantly better than the standard-release form. They reasoned that this explains why some PCTs recommend against prescribing the MR version on safety grounds. Although it has a similar effect to the standard variant, the recommended dose of the MR product is different, meaning that potentially dangerous confusion could arise if doctors were to prescribe both regularly.
- 8.7 As regards Cardura XL[®], the OFT panel was unconvinced of any advantages over standard doxazosin. Unusually for an MR formulation, Cardura XL[®] releases scarcely more slowly in the body than standard doxazosin. The main difference is that the bioavailability of the MR form is around half that of the traditional generic.^{75 76} For many other drugs MR formulations have both a longer half-life in the body and lower bioavailability, which confers advantages over standard forms which may need to be dosed with much greater frequency to maintain treatment for 24 hours. More frequent doses of standard formulations reaching systemic circulation at higher concentrations can cause greater side effects – particularly when there is a minimum effective dose for a standard form – hence the rationale for MR products in many cases. But since the difference between Cardura XL[®] and standard doxazosin appears to be limited to bioavailability, equivalent safety may well be obtained from either simply by changing the dose.⁷⁷

Value for money

- 8.8 Each of the three MR brands considered here is more expensive than the standard-release form of the generic chemical.⁷⁸
- 8.9 Cardura XL[®] costs £6.33 for a 28-pack of 4mg tablets compared to £4.41 or £2.99 respectively for 28-packs of generic doxazosin at 4mg and 2mg strengths.
- 8.10 Diamicon MR[®] costs £4.40 for a 28-pack of 30mg tablets compared to £1.76 for a month's treatment on standard gliclazide at equivalent dose (28-pack of 80mg tablets).

⁷⁵ Up to 59 per cent according to product characteristics published by Pfizer (February 2006). See www.pfizer.com/pfizer/download/uspi_cardura_xl.pdf

⁷⁶ Bioavailability is the fraction of an administered dose of medication that reaches the systemic circulation. By definition, when a drug is administered intravenously its bioavailability is 100 per cent. But the bioavailability of drugs administered via other routes (such as by mouth) can decrease due to incomplete absorption and first-pass metabolism. Bioavailability is an important consideration when administering drugs non-intravenously.

⁷⁷ The panel was also aware of trials suggesting that there are few differences between Cardura XL[®] and standard generic doxazosin in practice. See, for example: Os and Stokke (1999), 'Effects of doxazosin in the gastrointestinal therapeutic system formulation versus doxazosin standard and placebo in mild-to-moderate hypertension', *Journal of Cardiovascular Pharmacology*, (33).

⁷⁸ As of England Drug Tariff November 2006 and BNF (52).

Lyrinel XL[®] costs £12.34 for a 30-pack of 5mg tablets, versus £3.26 for a month's treatment on standard oxybutynin at equivalent dose (84-pack of 5mg tablets, one tablet taken two or three times daily). However, as there is at least some argument that both of these products may have advantages compared to their non-MR equivalents, we do not include potential savings arising from changes to their reimbursement here.

8.11 The table below shows savings that could have been made in primary care during 2005 across the UK if Cardura XL[®] had been reimbursed in line with equivalent strengths of standard-release generic doxazosin. As with calculations made for other classes of drug above, a 50 per cent brand premium has been applied to recognise potential advantages over the standard-form chemical that have not been clearly demonstrated through trials.

8.12 Indicative savings are around £11 million for Cardura XL[®].

Table 9.1 – Savings from adjusting the price of Cardura XL[®] – reimbursing 2005 total UK volumes in line with Doxazosin Category M prices (£ millions)

Branded drug		Comparator		Savings from reimbursement
Product	Presentation	Product	Presentation	Generic price plus 50 per cent
Cardura XL [®]	Tab 4mg	Doxazosin	Tab 2mg	£5.3m
Cardura XL [®]	Tab 8mg	Doxazosin	Tab 4mg	£5.6m

Note: Prices for Cardura XL[®] are official list prices at November 2006. Prices for Doxazosin are from the England Drug Tariff, average 18 months to June 2006.

9 CLOPIDOGREL

Background

- 9.1 Clopidogrel is an antiplatelet drug. Antiplatelets decrease the aggregation of platelets in the blood and can inhibit the formation of blood clots (thromboses) in the arterial circulation. Antiplatelets are important in the prevention and treatment of cardiovascular disease and in particular for patients having recently suffered ischemic events (adverse consequences of reduced blood supply to tissue or an organ, often brought about by clots – strokes and heart attacks are both forms of ischemic event).
- 9.2 Clopidogrel is licensed for:
- The prevention of ischemic events in patients with a history of symptomatic ischemic disease (specifically for patients suffering from myocardial infarction, from a few days until less than 35 days; ischemic stroke, from 7 days until less than 6 months; or in established peripheral arterial disease).
 - As a combination treatment with low-dose aspirin for acute coronary syndrome. In this case, clopidogrel is approved⁷⁹ for use in patients presenting with or without ST-segment elevation (STEMI and non-STE ACS).⁸⁰
- 9.3 Another antiplatelet, and probably the closest substitute for clopidogrel, is aspirin. Aspirin is the most commonly prescribed antiplatelet agent. Clopidogrel and aspirin have different mechanisms of action.

Clinical evidence

- 9.4 A review of published evidence suggests that, combined with aspirin to treat STEMI or non-STE ACS, clopidogrel offers some therapeutic advantages over aspirin monotherapy. Public information also suggests that as a monotherapy for the secondary prevention of ischemic events clopidogrel may have limited advantages over aspirin, although the evidence of increased therapeutic benefit is substantially less strong in this case and clopidogrel is not recommended by NICE in this indication. Overall, the clinical evidence does not clearly imply that the current list price of clopidogrel fails to offer value for money on average across all prescribing in primary care. However, we do raise the issue that, since the therapeutic value-added of clopidogrel relative to aspirin may be different in the secondary prevention of ischemic events and the treatment of STEMI or non-STE ACS, a value-based pricing scheme

⁷⁹ By the European Medicines Licensing Authority, under the centralised procedure.

⁸⁰ Patients who have symptoms of acute myocardial ischemia (oncoming heart attack) and are given an electrocardiogram (ECG) may or may not have an ST-segment elevation (a rise in a particular portion of their ECG reading). Most patients who have ST-segment elevation (STE ACS) will ultimately develop a Q-wave acute myocardial infarction (heart attack, in this case often termed ST-segment elevation MI or STEMI; the Q-wave is another part of the ECG). Patients who have ischemic discomfort without an ST-segment elevation (non-STE ACS) have either unstable angina, or a non-ST-segment elevation myocardial infarction (NSTEMI) that usually leads to a non-Q-wave myocardial infarction.

could generate efficiencies by publishing a separate value-reflective price for each indication.

- 9.5 Regarding the indication in non-STE ACS, it seems that the best current evidence on clopidogrel is to be found in the CURE study⁸¹ which is cited by most published reviews of clopidogrel, including one by the Midlands Therapeutic Review and Advisory Committee (MTRAC)⁸² in October 2002 and the NICE Technology Appraisal TA80 dated June 2004.
- 9.6 CURE evaluated the addition of clopidogrel to aspirin in over 12,000 patients hospitalised with non-STE ACS for a mean duration of nine months. In the study, patients treated with aspirin and clopidogrel combined were less likely to suffer cardiovascular death, a non-fatal heart attack or a stroke than patients treated on aspirin alone. Around 9.3 per cent experienced an adverse event within nine months following combination treatment, compared to 11.4 per cent following aspirin monotherapy. This 2.1 per cent absolute reduction in risk translates into a relative risk reduction of 20 per cent ($p < 0.001$).
- 9.7 However, the CURE study also uncovered some safety concerns in the clopidogrel arm. The incidence of minor, major and life-threatening bleeding was higher for patients in the clopidogrel group than those in the control group.⁸³ For aspirin plus clopidogrel versus aspirin plus placebo, the rates of major haemorrhage were 3.7 per cent versus 2.7 per cent (absolute risk increase 1 per cent, relative risk increase 37 per cent, $p = 0.001$). The rates for life-threatening haemorrhage were 2.2 per cent versus 1.8 per cent ($p =$ not significant).
- 9.8 The efficacy of clopidogrel ascertained from the CURE study was sufficient that when estimates of relative mortality risk in patients undergoing therapy with clopidogrel and aspirin combined (compared to patients on aspirin monotherapy) were input to NICE's cost-effectiveness model, clopidogrel emerged as a relatively cost-effective option. Incremental cost-effectiveness ratios (ICERs) for clopidogrel in all patient groups considered were below NICE's 'threshold' of £20,000 to £30,000 per QALY, sometimes comfortably so. Accordingly, in TA80 clopidogrel was recommended for use in the NHS as a combination therapy for non-STE ACS for twelve months in patients at moderate to high risk of MI or death.⁸⁴

⁸¹ The 'Clopidogrel in Unstable angina to prevent Recurrent ischemic Events' (CURE) trial is a large and ongoing international study. See for example: Yusuf et al (2001), 'Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation', *New England Journal of Medicine*, (345).

⁸² Based at Keele University, MTRAC is a committee of GPs and other decision makers that reviews selected drugs for use in primary care in the West Midlands, and issues prescribing advice. See: www.keele.ac.uk/depts/mm/MTRAC/

⁸³ Bleeding is a typical side effect of agents that thin the blood and the dangers must be weighed against the benefits of improved circulation.

⁸⁴ It is worth noting, however, that the assumptions used in NICE's model in TA80 have been queried recently, in the light of newly emerged data, by the Scottish Intercollegiate Guidelines Network (SIGN). In National Clinical Guideline 93 (February 2007), SIGN contends that the NICE model could overstate patients' pre-treatment risk of suffering a cardiovascular event. SIGN estimates high 'number needed to treat' (NNT) statistics for clopidogrel in non-STE ACS, indicating that for treatment lasting longer than

- 9.9 To the assessment of the efficacy of clopidogrel for non-STE ACS based on public information the OFT panel added some insights into therapeutic benefits provided in specific contexts. The panel were aware of data from observational studies showing that in patients who had had stents inserted to treat narrowings of coronary arteries dual therapy was generally continued for six to twelve months and the panel did not disagree with this approach.
- 9.10 Regarding its indication for STEMI, evidence supporting the efficacy of clopidogrel is provided by the COMMIT trial.⁸⁵ In that study, 45,852 patients with acute myocardial infarction were randomized to clopidogrel 75mg daily or placebo for a mean 14.9 days. All patients also received 162mg of aspirin daily. The primary outcome was death from any cause, observed in 7.5 per cent of the clopidogrel group versus 8.1 per cent of the aspirin-only group ($p=0.03$, 'number needed to treat', NNT, on clopidogrel to observe one less event: 167). The composite endpoint of death, MI or stroke was also reduced, to 9.2 per cent versus 10.1 per cent in the control group ($p=0.002$, NNT: 111). In terms of safety, major bleeding occurred in 0.58 per cent of patients in the clopidogrel group versus 0.55 per cent in the control group (p =not significant) and the minor bleeding rate was 3.6 per cent versus 3.1 per cent ($p=0.005$, 'number needed to harm', NNH: 200).
- 9.11 Regarding its indication for the secondary prevention of ischemic events, the best evidence on clopidogrel appears to be found in the CAPRIE (1996) trial⁸⁶ which is cited in a review by the London New Drugs Group⁸⁷ in February 2003 and NICE TA90 dated May 2005.
- 9.12 CAPRIE tested clopidogrel head-to-head against aspirin in over 19,000 patients. The efficacy of the two drugs was judged according to the incidence after treatment of fatal or non-fatal ischemic stroke, fatal or non-fatal MI, or vascular-related death. Clopidogrel patients had an annual risk of such events of 5.3 per cent, compared with 5.8 per cent in the aspirin group, implying a relative risk reduction of 8.7 per cent ($p=0.043$).
- 9.13 Overall, the LNDG review concludes that 'there is good evidence that used as a monotherapy clopidogrel is marginally more effective than aspirin in patients with atherothrombosis. However, there is considerable uncertainty about the true size of that additional benefit – the analysis above estimates it to be between 2 and 19 patients per 1,000 patients treated for two years.'⁸⁸ NICE TA90 goes further,

three months hundreds of patients may need to have clopidogrel added to an aspirin regimen before one patient would benefit.

⁸⁵ COMMIT Collaborative Group (2005), *Lancet*, (366). There is also some positive evidence in the CLARITY trial but we were advised that the most positive evidence in that study relates to improvements in blood flow observed via angiography. Improvements in final events such as MI or death were observed but less important. CLARITY was also a smaller trial, in 3,491 patients. See Sabatine et al (2005), *New England Journal of Medicine*, (352).

⁸⁶ See CAPRIE Steering Committee (1996), '*A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events*', *Lancet*, (348).

⁸⁷ Obtained from the NHS National Electronic Library for Medicines at www.druginfozone.nhs.uk/Record_per_cent20Viewing/viewRecord.aspx?id=514848

⁸⁸ Excerpt reproduced by kind permission of David Erskine (review author) and Peter Sharott (LNDG chair).

concluding that clopidogrel has no proven effect on mortality over and above that seen with aspirin as a sole antiplatelet agent.⁸⁹ Accordingly, clopidogrel is not recommended by NICE in this indication except for aspirin-intolerant patients.

Value for money

- 9.14 Clopidogrel costs £35.31 for a 28-pack of 75mg tablets (a month's course of therapy at the typical daily maintenance dose) compared to between 40p and 87p for a month's treatment on aspirin.⁹⁰ Cost-effectiveness modelling carried out by NICE in TA80 suggests that clopidogrel provides value for money as a combination treatment for non-STE ACS for a period of twelve months.⁹¹ However, NICE TA90 did not recommend clopidogrel as a monotherapy for the secondary prevention of ischemic events. NICE has not appraised clopidogrel in STEMI.
- 9.15 It is difficult to appraise the value for money obtained by the NHS on clopidogrel at current prices because it is widely used in primary care, where available data sources do not detail indications prescribed for. However, the OFT has obtained evidence that clopidogrel may be prescribed both for the secondary prevention of ischemic events and for longer than twelve months in non-STE ACS, against the recommendations of NICE guidance.
- 9.16 For example, a PCT in the West Midlands⁹² has provided the OFT with details of an audit of clopidogrel prescribing undertaken in 2005. During the audit period, 193 local patients were taking clopidogrel in combination with aspirin and 187 were taking clopidogrel alone. Of the 193 on combination therapy, 93 had been prescribed it for non-STE ACS but had remained on treatment for longer than the 12 months recommended in NICE guidance. In addition there were 14 patients taking the combination for an unlicensed indication and a further 5 taking clopidogrel as part of an unusual combination, for example with warfarin. Of the 187 using clopidogrel as their sole antiplatelet agent, 94 were taking it either for an unlicensed indication or in a use Sandwell prescribing advisers deemed inappropriate. Overall, the PCT found that around 50 per cent of the observed clopidogrel use was either inappropriate or unnecessary.
- 9.17 Since clopidogrel may not provide unequivocal therapeutic benefits over aspirin in all current primary care prescribing, there may be a case for modelling a value-based price in each of its indications. If it could be reimbursed at a value-based price in each

⁸⁹ TA90, page 16, paragraph 4.3.4. Unsurprisingly, ICERs in many patient subgroups are much higher than observed in TA80, with some breaching NICE's 'threshold'.

⁹⁰ Aspirin: 40p for a 28-pack of 75mg dispersible tablets; 87p for a 28-pack of 75mg enteric coated tablets. Source: BNF (52), September 2006. Prices for clopidogrel were taken from the same source.

⁹¹ It is worth highlighting, however, that there is little evidence that clopidogrel offers long-term benefits when added to aspirin therapy. In the CHARISMA trial 15,603 high-risk primary and secondary prevention patients were randomized to clopidogrel 75mg daily or placebo, in addition to aspirin 75-162mg daily, for a median of 28 months. The primary outcome was MI, stroke or cardiovascular death and there was no benefit with clopidogrel plus aspirin. Adverse events were observed in 6.8 per cent of patients receiving clopidogrel versus 7.3 per cent in the control group but this was a statistically insignificant result ($p=0.22$). See Bhatt et al (2006), New England Journal of Medicine, (354).

⁹² Sandwell PCT. Access to the audit was facilitated by the MTRAC group at Keele University.

indication there would be less scope for inefficient use than at present. Incentives for the product's sponsors to market clopidogrel would be aligned with demonstrated clinical value and any 'overuse' (if it could be so determined) would carry lighter financial implications for the NHS than at present. It should be noted, however, there is some chance that a value-based price for clopidogrel in the treatment of non-STE ACS may be higher than today's NHS list price since modelled ICERs of clopidogrel in TA80 were below NICE's imputed threshold of £20,000 per QALY.⁹³

- 9.18 In order to reimburse clopidogrel efficiently under reforms to the PPRS – by paying a different value-based premium over aspirin in different indications – it would be necessary to estimate the prevalence of non-STE ACS and STEMI in the UK and the typical need for prescribing beyond early interventions in hospital. In TA80, NICE gives some consideration to the prevalence of non-STE ACS but concludes that it is difficult to estimate prevalence confidently using current hospital episode statistics. But in practice it should be possible to use primary care data sources such as the General Practice Research Database (GPRD) and advice from prescribing advisers.
- 9.19 It is important to note that reimbursing clopidogrel at different effective rates for each of its licensed indications would not necessarily require the application of multiple reimbursement prices and consequent administrative complications for the NHS and pharmacies. It may instead be sensible to pay a single NHS list price in primary care, to be agreed with the manufacturer, before using rebates (for example annually) to settle any difference between reimbursements paid and those required by a schedule of notional indication-level prices. The practicalities of rebates are explored in Annexe L of this report, which draws up detailed proposals for reform of the PPRS.

⁹³ It should however, be noted that, as described in Annexe L, the value-based pricing system we propose would set maximum thresholds for prices based on value. Therefore, a company could decide to set a price lower than this maximum.

10 CONCLUSION

- 10.1 The drugs discussed in this annexe are a selection of the areas where the PPRS, as currently constituted, may not secure value-based prices. They were chosen for illustrative purposes because current prices seem in several cases far out of line with value – since each area is served by tried and tested medicines over which newer products do not appear to offer compelling advantages.
- 10.2 Beyond the drugs considered here, the OFT has identified several other broad areas where drugs may not offer value for money and so constrain NHS funds available to pay for greater prescribing of the same or other medicines. These include:
- A number of other examples of the types described above, in particular single-enantiomer products and MR formulations;
 - Metabolites or salts of drugs that are more expensive than the chemicals they are derived from;
 - Combination products, where two (usually, but sometimes more) drugs used as complements in treating a condition are marketed as a single presentation (for example in a single inhaler for asthma) that may not be cost-effective.
- 10.3 We did not conduct a detailed assessment of these areas in the context of this study. However, on the basis of our interaction with NHS stakeholders we do believe there are likely to be other areas beyond those assessed in this annexe, in respect of which prices may not reflect value. Such areas would be captured under any comprehensive value-based pricing scheme of the sort recommended in Annexe L.
- 10.4 Although the analysis in this annexe has highlighted a number of existing medicines that do not appear to offer good value for money, the most important observation that can be made in conclusion is that any savings deliverable by value-based reforms to the PPRS could yield improved access to drugs and other healthcare within current NHS budgets.
- 10.5 In the rest of this chapter we consider therapeutic areas where there may be a case for greater expenditure either today or in the future. By its nature this is a more speculative exercise than the foregoing. For example, to ascertain whether drugs currently available are under-prescribed would require estimates of clinical need. But clinical need is harder to estimate than the effects of a drug in representative samples of the population tested under controlled conditions. Similarly, to say that expenditure may be called for on innovative therapies in the future is inherently speculative since even promising technologies currently in development may turn out to be ineffective.
- 10.6 For these reasons we refer below to several existing drugs where there may be some case for greater use but do not quantify the extent. We also consider some new drugs and related technologies that are in development and could conceivably merit high value-based prices – but we are unable to comment definitively at this stage. The purpose is to provide very preliminary suggestions of areas in which savings under value-based pricing arrangements could be spent. There are likely to be many other areas.

- 10.7 Moreover, we recognise that such savings may also be spent efficiently on greater prescribing of some of the drugs considered earlier in this annexe. We further recognise that the savings calculated in this annexe are only indicative and that value-based prices taking into account factors such as value in variety and the stability of generics markets may be somewhat higher than we have assumed.

Possible under-use of existing drugs

- 10.8 Opinions on priorities between drugs (and trade-offs within the fixed budget of the NHS more generally) tend to vary more widely than views on the efficacy of individual therapies. For this reason, to identify areas of potential under-prescribing we refer here only to estimated projections of clinical need published by NICE in technology appraisals. The thoroughness of the analysis it undertakes puts NICE in perhaps the best position among commentators to make reasonable estimates of need.
- 10.9 Uptake of drugs in line with NICE guidance has been assessed in a number of initiatives and is now being monitored by NICE itself under the Evaluation and Review of NICE Implementation Evidence (ERNIE) program. Earlier published work includes a report by Abacus International.⁹⁴
- 10.10 Implementation of NICE guidance can be difficult to assess because technology appraisals often pertain to specific indications or patient groups for which a drug is licensed whilst aggregate prescribing may be driven by other licensed uses. Nonetheless tentative conclusions are available from the Abacus report and a number of ERNIE reviews which, alongside a number of cases of good implementation, find that some drugs seem to be prescribed at levels below NICE's estimates of clinical need.
- 10.11 The Abacus research looked at the impact of NICE guidance on 28 different disease areas. Of the technologies reviewed 18 were drugs. Uptake was measured by data on sales volumes from a variety of sources and interviews with clinicians. The study also attempted to estimate what uptake should be if the guidance were fully implemented, as a benchmark for evaluating implementation. (The study noted, however, that these estimates were based on projections drawn from small sample sizes).
- 10.12 The study found that implementation varied across disease areas, with 12 of 28 technologies used within reasonable expectations of the guidance (including products with both positive and negative recommendations), 12 technologies being under-implemented and four over-implemented.
- 10.13 In more recent reviews available through the ERNIE database on NICE's website, clinical need is expressed as expected annual expenditure in primary care in England at NHS list prices. By this measure, one potentially under-used medicine is drotrecogin alfa for severe sepsis (having resulted in multiple organ failure). The drug received a positive recommendation in 2004, with NICE estimates of expenditure arising from implementation in the range £11 million to £19 million. In 2004 the NIC amount was

⁹⁴ *NICE guidance implementation tracking, data sources, methodology and results*, Abacus, 2005, available on the NICE website.

just about £5 million but in 2005, this amount had increased to nearly £12 million, close to the lower bound of the NICE range.

- 10.14 An earlier report by the Audit Commission has explored whether drugs are used as widely as NICE recommends, focusing on how financial constraints may prevent PCTs from funding drugs.⁹⁵ The Audit Commission surveyed 27 PCTs spread over ten Strategic Health Authorities. Most indicated they had insufficient resources to fund certain high-cost drugs, including drotrecogin alfa and the anti-TNF α therapies etanercept and infliximab for rheumatoid arthritis.
- 10.15 The 'anti-TNFs' have been investigated by other sources. For example a survey in 2005 by the British Society for Rheumatology found that a third of rheumatologists consulted were prevented from prescribing anti-TNFs in accordance with NICE guidance by PCTs. This proportion was roughly unchanged from a similar survey carried out among rheumatologists in 2003. The majority of respondents identified lack of funding to be the main barrier (either the allocated funds for the year had not been used or PCT had not released funding).⁹⁶
- 10.16 One further source suggesting that positive NICE guidance may not be fully implemented is an ongoing review by the National Cancer Director. During 2003 several pharmaceutical companies expressed concerns at variations in the use of cancer drugs between the 34 cancer networks in England. In response, the Secretary of State asked the National Cancer Director to investigate. Updates issued by the investigation between 2004 and 2006 found that prescribing of cancer drugs has generally increased following positive NICE appraisals but that noticeable variations in usage remain.⁹⁷
- 10.17 Financial constraints (in which expenditure on some drugs assessed in this annexe may play a part), as well as challenging the implementation of individual pieces of guidance from NICE, SMC or AWMSG, may also exert pressures on the evaluation bodies themselves. Box 10.2 below considers an argument that the cost-effectiveness threshold that NICE applies in rejecting some expensive new drugs for NHS provision may be stricter than it needs to be because the institute cannot assess all drugs. Under value-based reforms considered in Annexe L of this report, we explain how NICE, SMC and AWMSG could in principle assess all drugs, rather than just a subset. Assessing all drugs for cost effectiveness might help to alleviate restrictions in use.

⁹⁵ *Managing the financial implications of NICE guidance*, Audit Commission, (2005).

⁹⁶ In TA36 (March 2002), NICE approved the use of etanercept and infliximab for people with severe rheumatoid arthritis for whom alternative treatments had failed. The survey was conducted jointly by the BSR and the Arthritis and Musculoskeletal Alliance (ARMA). It also investigated the use of adalimumab, a third anti-TNF α , which was licensed after the NICE guidance was issued. In November 2006, NICE published a Final Appraisal Determination for a review of TA36, recommending infliximab, etanercept and adalimumab for NHS use on the same terms. The original BSR/ARMA survey is available at: www.rheumatology.org.uk/public_affairs/armabsrtfnfsurvey/

⁹⁷ See for example: Department of Health News Release (2006/0314), 20 Sept 2006.

Box 10.2: Decisions by NICE to reject drugs for NHS use

In Technology Appraisals, NICE, SMC and AWMSG sometimes reject drugs on the basis of unacceptable cost effectiveness rather than purely on the grounds of insufficient clinical efficacy. As of late 2006, NICE has rejected a number of new cancer drugs partly on the basis of cost (some pending appeal, and the uncertainty of clinical evidence also being a factor in decisions). Recent rejections include: bevacizumab and cetuximab for metastatic colorectal cancer, pemetrexed for mesothelioma, gemcitabine for breast cancer, erlotinib for lung cancer and bortezomib for multiple myeloma.

The incremental cost-effectiveness ratio (ICER) of the drug in question (in relation to an appropriate comparator) is a key criterion for making such recommendations. NICE, for example, is likely to reject drugs⁹⁸ costing more than about £30,000 per incremental Quality Adjusted Life Year (QALY) compared to a next-best comparator, although it will take into account factors such as the type of drug assessed, the uncertainty of clinical evidence on its efficacy, the severity of the disease treated and so on.

The ICERs for some of the treatments rejected by NICE discussed above ranged from about £35,000 per QALY. In this annexe, however, we review a number of drugs for which the ICER may well be higher than for rejected products, but which are currently being prescribed in large volumes.⁹⁹ This does not represent value for money and is not in patients' interests. The money spent on these drugs could be used to provide access to the treatments listed above – those for which clinical evidence is sufficiently clear – which patients are currently being denied. In other words, it is quite conceivable that cost-effectiveness thresholds could be higher for the same level of pharmaceutical expenditure if the remit of NICE, SMC and AWMSG were extended to include all drugs under a value-based pricing system. Under higher thresholds, some treatments that are rejected on cost grounds under present arrangements might become acceptable.

Under current arrangements, NICE and AWMSG are only passed (by government) a short list of products each year and SMC, whilst it has assessed all drugs at launch since 2002, does not conduct reviews of older products. Moreover, while NICE does conduct some ex-post reviews, these sometimes focus on therapeutic groups rather than individual products. For example, the focus of NICE's review of statins published in 2006 was on the cost effectiveness of statins as a group (that is, relative to non-statin therapy) rather than on the cost effectiveness of individual statins relative to others. It did note, however, that "therapy should normally be initiated with a drug with a low acquisition cost. Furthermore, NICE used prices from 2004 (during analysis undertaken in 2005) since when the relative cost effectiveness of the statins will have changed significantly due to large falls in the generic price of simvastatin.

While the guidance of NICE, SMC and AWMSG is not always followed it can lead to real restrictions in patients' access to drugs.¹⁰⁰ These difficult choices are, we repeat, inevitable given the limited resources the NHS has at its disposal. But the existence of rationing underlines the need for the NHS to eliminate any inefficiencies in current expenditure.

⁹⁸ In practice, decisions are made by indication and patient subgroup. For more details see Annexe B.

⁹⁹ At the limit, if two drugs have entirely equivalent benefits for patients, then the ICER of the more expensive over the cheaper is, in effect, infinite. In practice the more expensive product is said to be 'dominated' by the cheaper and, under the processes of bodies such as NICE, would be rejected. See Annexe B for more details.

¹⁰⁰ See Annexe B for an account of the implementation of guidance issued by NICE, SMC and AWMSG.

The themes discussed in this box are assessed in greater detail in Annexe B of this report which discusses the role of the UK cost-effectiveness bodies in the NHS.

Promising new research

- 10.18 As discussed in Chapter 2 of this annexe, the application of value-based prices should give better signals to companies to invest in the areas of greatest clinical need in the future. Such signals could help influence the development of drugs by the global pharmaceutical industry, in the light of the influence of UK prices on prices in other countries evaluated in Annexe D of this report.
- 10.19 A few promising areas of research that are already ongoing where this consideration could be relevant are detailed in the box below.

Box 10.3: Promising new research of likely but uncertain value to the NHS

This discussion has been somewhat sceptical of the clinical benefits of certain technologies that can be used to refine the effects of existing drugs, such as chiral switching and modified-release formulations. But it is vital to recognise that, in principle, developments in the way existing drugs are delivered can be as important for patient welfare as the discovery of entirely new medicines. Indeed, in some cases chiral switching and modified-release formulations can deliver such benefits (as is the case with one of the MR formulations considered above).

The delivery of a drug can be improved by altering its chemistry, as with chiral switching, but also by combining it with a device or biological agents. New delivery systems can be expensive but affording them is more difficult if the prices of some less innovative products are inefficiently high.

One area where much valuable research into new drug delivery technologies is ongoing is in the treatment of cancer. Interventions for cancer, such as radiotherapy and chemotherapy, are often cytotoxic: although intended to kill the cells of a malignant tumour they usually also damage healthy cells, leading to unpleasant or harmful side effects. Technologies ensuring that anticancer agents are delivered only to tumour sites and do not reach systemic circulation are important for patient welfare. Emerging technologies include:

- Biodegradable wafers, infused with a chemotherapy agent, for implantation into the cavity created when a tumour is surgically removed. As a wafer erodes, a (toxic) chemotherapy agent can be released directly into a tumour site at high concentrations without reaching systemic circulation.
- New catheters to enhance chemotherapeutic delivery to tumours without blocking or destroying blood vessels.
- Technologies to introduce drugs inside tumours – cleanly and without wastage – once accessed via a catheter or other means, including radiofrequency ablation, ultrasound and UV light.
- Immunoconjugates in which a cancer drug is combined with a natural antibody so as to bind selectively to tumour cells expressing specific antigens.

Treatments such as these are often experimental and can sometimes only be developed through clinical use with small available numbers of patients. As a result, it is difficult to predict when a line of research will provide little benefit or when it will revolutionise care.

Such uncertainty is costly but it is useful for the NHS to be able to bear it – and therefore not to waste resources in areas where clinical benefits are more clear-cut.

Another area of active research is in the development of convenient delivery systems for a broad range of drugs. When drugs are difficult or unpleasant to take patients may not comply with prescriptions and may consequently waste NHS funds spent on them. New drug delivery systems currently being taken forward include:

- Carrier molecules enabling complex chemicals that would otherwise need to be administered by invasive means (such as a drip) to be formulated as an oral capsule.
- Inhalable formulations of medicines that do not act specifically on the lungs. In some cases it is possible to improve the bioavailability of a drug by avoiding metabolism in the liver or the gut. Not all inhalable formulations have this advantage, however, and some may cause particular side effects. Nonetheless there can be benefits of convenience and wellbeing, such as with inhalable insulin for patients who are needle-phobic or who suffer from skin conditions.
- Trans-dermal delivery systems as an alternative to injections. Developers are looking at ways to safely disrupt the layers of the skin including iontophoresis (the use of an electric current to introduce ions of a drug into bodily tissues) and ultrasound energy.
- Nanotechnology to open up new ways of administering drugs. Nano-formulations can allow chemicals that would otherwise be insoluble to be manufactured as an injection, benefiting patients with difficulties swallowing. In another development, devices may become available that allow for several drugs to be administered in the same oral capsule but released at different points in the body.