Office of Health Economics Research

Seminar Briefing 18

Multi-indication Pricing: Pros, Cons and Applicability to the UK.

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Executive summary

What is the problem?

Many medicines currently available, and many more in pharmaceutical industry pipelines, are likely to be effective in multiple indications. More than 50 per cent of major cancer medicines marketed in 2014 were for multiple indications. By 2020, this share is estimated at 75 per cent. Value is likely to be different across these indications. If prices paid for on-patent medicines are to reflect their value then multi-indication medicines should have different prices across indications, reflecting the different values. Yet current pricing and reimbursement systems are not equipped to handle this. There tends to be one single (uniform) price across all indications. As a result, price and clinical value will rarely match up across multiple indications.

A single, uniform, price across indications has negative consequences. First, if the single price is based on the higher-valued indications, that price might be higher than optimal for one or more lower-value uses/indications, leading to restricted access, as use in such indications might not be deemed cost-effective and hence not reimbursed. Second, if the single price is based on the lower-value indications, it might discourage companies to develop further, valuable, indications under the threat that potentially higher-value indications will be reimbursed at the price set for other lower-value indications.

Some current pricing models do allow for what is termed "blended" pricing – still a "uniform-price" approach, but price is based upon an average of the value of all of the indications, weighted by expected patient volumes. The challenge with such an approach is whether budget holders are clear which is the correct price to use when deciding about patient access to a particular indication.

A potential solution?

Alternative pricing strategies that allow separate and distinct prices to be paid for major patient subgroups and indications, based upon the value demonstrated in clinical trials and real-world settings, may be preferred by the different stakeholders, including payers, health technology assessment (HTA) bodies and manufacturers. Multi-indication pricing (MIP) involves setting a different price for each indication approved for the medicine. This could ensure that medicines are priced according to value per indication, in line with standard economic theory when arbitrage does not prevent differential pricing. Patients may then have the opportunity to access a medicine if priced in line with the expected value for the potential outcomes achieved in that particular indication (usually expressed as a cost-effectiveness threshold in the UK) as payers will make all uses of the product available to patients. Companies will have the incentive to develop follow-on high-value, low-volume, indications that are not profitable at the price of the main indication. Conversely, they will have an incentive to develop additional lower-value indications to sell at lower prices, knowing that they can keep a high price for an existing high-value indication.

MIP could take various forms, depending on how it is administered, applying at "list" or "net" price. "List" prices are the official ex-factory prices published in the relevant national databases. Different selling prices by indication could apply at the "visible" (i.e. official ex-factory) price level. "Net" prices are actual prices paid after any discounts and/or rebates provided by the manufacturer.

Applying MIP to "net" prices could involve varying net selling prices by indication by either (i) applying differential discounts or (ii) using retrospective manufacturer rebates after monitoring use of the drug by indication. Such discounts are typically "invisible" (i.e. confidential).

There are examples of MIP in some countries administered through different brands of the same molecule for very different conditions. This experience is of little relevance for medicines with various oncology indications – which is the greater, short- and longer-term challenge. One country that has tackled the oncology challenge is Italy, through the Agencia Italiana del Farmaco (AIFA), responsible for monitoring drug usage across indications with patient registries for multi-indication, single-brand medicines.

Is MIP possible in the UK?

A workshop with health care system stakeholders was organised to explore (i) the attractiveness of MIP as a potential solution to the challenge of providing optimal pricing for, and reimbursement of, multi-indication drugs and (ii) the feasibility of implementing MIP in the UK's National Health Service (NHS). The workshop agreed that relative prices should reflect relative value, but prices should not exceed value, and thus MIP might be a way forward.

However, a number of operational challenges need to be overcome. These fall under two general headings:

1. Whether the NHS can handle MIP schemes involving variable net selling prices by indication, requiring monitoring of volume usage per patient per indication, and undertake any financial reconciliation ex post to ensure that the correct funds flow across the necessary stakeholders, be it at national or local level. Evidence from early patient access schemes suggested that the NHS seems to be bad at pursuing rebates. Stakeholders need to collaborate to resolve those issues that ensure sustainable access to oncology medicines with agreed clinical benefit. Without this consensus the ability to implement long-term solutions such as a MIP-type scheme are limited.

2. Data availability: are there data sets which allow such monitoring of volume usage per patient per indication, and is the necessary data being generated routinely or requiring ad hoc intervention? There is a UK collaboration to pilot, in oncology, the feasibility of MIP in the UK setting, based on the NHS's Systemic Anti-cancer Therapy (SACT) data set. SACT is a mandatory chemotherapy dataset covering treatment for all solid tumours and haematological malignancies within organisations providing cancer services funded by the NHS in England. Although SACT is unique to England, the types of data collected in the dataset are routinely captured in oncology electronic prescribing systems.

The feedback from the workshop regarding this pilot, and any future use of SACT data to help implement MIP, could be differentiated between those decision makers at national level and those working with NHS providers on current data systems. Broadly speaking, those working at the centre see this as a potentially effective mechanism to monitor drug volume usage per indication for oncology and potentially support MIP when desirable; those working with providers were more sceptical as to what was being added by SACT data.

Reflections and conclusions

Handling pricing for drugs with multiple indications within the same disease area – including different potential lines of treatment and/or combination regimens – is a challenge, and will increasingly be so. A necessary condition for the implementation of MIP-type schemes explored in this briefing (with the possible exception of ex ante "blended" simple discounts) is the potential to track the specific utilisation of the drug in different indications, regimens and patient sub-populations. The UK collaboration referred to above suggests to us that this is achievable.

Overall, our final reflections are as follows.

- All stakeholders present at the workshop were interested in the potential use of MIP but many were sceptical of the ability of the NHS to get good value from its use.

- There was general support on the notion of relative prices reflecting relative value, but it was important that price did not exceed value in any indication.

- There is a need to ensure collaboration across all stakeholders (NHS, industry, patients, doctors, nurses and other health care professionals) if the NHS were to benefit from any future pricing scheme(s) that allow different prices across indications.

- If MIP were pursued, there was interest in using either (i) "blended" pricing (at list level) or (ii) schemes that might generate variable "net" selling prices.

- SACT data can in principle support the implementation of MIP, albeit with challenges. The current UK collaboration will help us understand whether the SACT dataset could in practice underpin such pricing systems.

1. Introduction

1.1. What is the problem?

Many medicines currently available, and many more in the pipelines of the pharmaceutical industry, are likely to show effectiveness in multiple indications. The value might be different across the different indications. Figure 1 shows the current and future pipeline for oncology medicines in particular and the growing important of multi-indication cancer medicines.

Figure 1. Multiple indications for oncology medicines
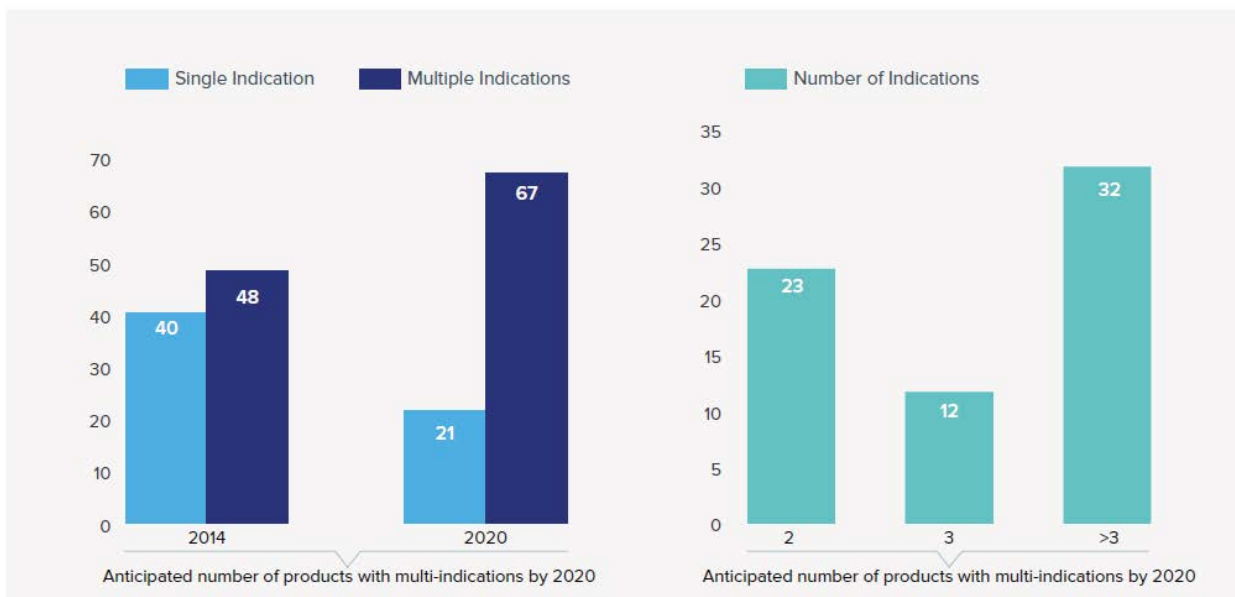
Source: Aitken, Blansett and Mawrie, 2015

Figure 1 shows that for the 88 cancer drugs identified in the report as marketed in 2014, 40 were for single indications and 48 for multiple indications. By 2020, the authors estimated that most oncology drugs will carry multiple indications – out of a total number of 89 medicines, 67 will have multiple indications approved, and within those, nearly 50 per cent will have more than three indications approved. Having multiple indications makes the assessment of value for oncology products more complex.

In an OHE consulting report on the value footprint of oncology drugs (Rejon-Parilla et al., 2014), the authors found that four out of the ten oncology drugs assessed were for multiple indications.[1] A white paper produced by the Boston Consulting Group (Said, Brouwers and Tollman, 2007) demonstrated that in the US a biologic that has been on the market for six years is expected to have on average two additional indications approved. Contrary research, showing that the average number of indications indicated for a given drug is decreasing over time (Dayoub, Jena and Lakdawalla, 2014), was conducted only up to 2008 and represented an overall "average" rather than the situation for biologics or oncology.

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[1] These are the ten cancer drugs approved by the European Medicines Agency (EMA) during the 2003–2005 period.

Prices of on-patent medicines should aim to reflect their value – thus, for multi-indication medicines, prices across indications should be different where this reflects different value. However, current pricing and reimbursement systems are not equipped to handle the complexity of multi-indication medicines and flexible pricing. The reality is that there tends to be one single (uniform) price across all indications, and price and clinical value rarely match up across multiple indications. Aitken, Blansett and Mawrie (2015) showed that in England there is no correlation between list price and the Cancer Drugs Fund (CDF) score of effectiveness.

Bach (2014) offers hypothetical analyses on how current treatment costs for four oncology drugs in the US (Abraxane, Tarceva, Erbitux and Herceptin) would change if: (1) prices for all indications were anchored to the price of the indication that provides the largest median survival gain, and (2) all prices for all indications are set to achieve a value of $150,000 per year of life gained. Table 1 shows this analysis.

Table 1. Bach (2014) analysis on "indication-specific pricing" for cancer drugs in the US

Table. Comparison of Incremental Survival Improvement and Cost of Treatment for Several Cancer Drugs Across Different Approved Indications, Plus a Hypothetical Scenario in Which Price Is Set per Indication to Yield the Same Total Treatment Cost per Median Benefit (Indication-Specific Pricing)[a]

Drug and Indication	Median Survival Gain, y[b]	Typical Treatment Duration, mo	2014 US$				
			Typical Treatment Cost[c]	Cost per Year of Life Gained (Median)	Current Monthly Price	Monthly Price Based on Indication With Most Value[d]	Monthly Price Based on Achieving Value of $150 000 per Year of Life Gained
nab-Paclitaxel (Abraxane)							
Metastatic breast cancer	0.18[5]	4.16[7]	25 990	145 288	6255	6255	6458
Non–small-cell lung cancer	0.08	4.16	29 988	399 840	7217	2622	2708
Pancreatic cancer	0.15	4.00	27 065	180 433	6766	5448	5625
Erlotinib (Tarceva)							
First line treatment of metastatic non small-cell lung cancer	0.28	8.20	51 596	182 104	6292	6292	5183
Pancreatic cancer	0.03	3.90[6]	21 696	650 885	5563	1556	1282
Cetuximab (Erbitux)							
Locally advanced squamous cell carcinoma of the head and neck	1.64	1.39[7]	14 292	8706	10 319	10 319	177 798
First-line treatment of recurrent or metastatic squamous cell carcinoma of the head and neck	0.23	4.16	42 875	190 556	10 319	471	8123
Trastuzumab (Herceptin)							
Adjuvant treatment of breast cancer	1.99[8]	12.0	64 941	32 645	5412	5412	24 867
Metastatic breast cancer	0.40	10.0	54 118	135 294	5412	905	6000

[a] Data on survival gain and median treatment duration from the FDA label[9] and publications accompanying those studies.

[b] As per FDA package inserts or studies summarized therein (unless otherwise noted). Package inserts are available via drugs@FDA.[9]

[c] Only includes direct cost of the drug, as per http://www.mskcc.org/research/health-policy-outcomes/cost-drugs.

[d] Assumes the price of the drug in its most effective setting is the appropriate reference price.

Source: Bach (2014)

Table 1 shows that the current monthly prices across indications are very similar, if not identical, for each of the four oncology drugs studied. However, when relative prices by indication are assumed to reflect median survival or a value per life year, prices by indication can very different. Prices for some indications would increase, others would be lowered. Bach (2014) argues that current mechanisms in the US do not and cannot accommodate what he terms "indication-based pricing". The author does, however, offer suggestions on how the system (both for drugs bought and distributed from pharmacies to patients and for drugs infused in the physician's office) could be modified to accommodate flexible pricing. We pick up these suggestions in our Conclusions section.

A single, uniform, price across indications can have negative consequences. First, if the single price is based on the higher-valued indications, that price might be higher than optimal for one or more uses/ indications with lower values, leading to restricted access for indications deemed not cost-effective. Second, if the single price is based on a relatively low-value current indication, it might discourage companies from developing further, higher-value indications with smaller expected volumes, as the higher-value indication will be reimbursed at the price set for the lower-value indication.

Some current pricing models do allow for what is termed "blended" pricing. This is still a "uniform-price" approach, but the price is based upon an average of the (different) value of indications, weighted by expected patient volumes. The challenge with such an approach is whether budget holders are clear which is the correct price for a particular indication when deciding access.

1.2. Objectives, methods and the structure of this briefing

This briefing addresses two fundamental questions:

1. Would MIP be useful in the UK's National Health Service (NHS)?

2. If it would, in principle, could MIP be implemented in the UK?

To this end, we carried out desk research on MIP and modelled the effects of MIP versus uniform or flat pricing (i.e. same price across all indications). We held a workshop (on 26 January 2015 at the Royal Society, London) with health care system stakeholders to discuss the pros and cons of MIP and the practicalities of implementing MIP in the UK.

This OHE briefing reports on these two tasks, and, where relevant, we combine our original analyses with feedback received at the workshop. It is structured as follows:

- Section 2 outlines what MIP is and how it could be implemented, followed by workshop reflections on the desirability of using MIP in the UK.

- Section 3 discusses some of the operational challenges of implementing MIP in the UK. It includes discussion of a UK collaboration between several NHS trusts and one oncology company (Roche Products Ltd), with Deloitte MCS Ltd providing the health care analytics technology platform. This collaboration is based on the NHS's Systemic Anti-cancer Therapy (SACT) data set and aims to show MIP can be feasible in the UK.

- Section 4 sets out our conclusions.

- Appendix 1 is a conceptual description of MIP, setting different case scenarios to explore the impact of having different prices across indications, as compared to uniform or flat pricing, on manufacturers, patients and payers.

- Appendix 2 is a review of international examples of medicines approved for multiple indications, to explore how they have been priced in a number of countries.

- Appendix 3 lists the 26 January 2015 Workshop attendees.

2. Multi-indication pricing as a potential solution

2.1. The theoretical case for MIP

Multi-indication pricing (MIP) involves setting a different price for each indication which is approved for the medicine. In principle, such an approach could involve a different price for each subgroup of patients within an indication, and for each additional indication, however small the difference in effectiveness between the new indication and an existing one. In reality, we are discussing the context in which there is a significant difference in value that matters to the health system or to the company, and will therefore impact either on reimbursement decisions for that indication, or on research and development (R & D) decisions about future indications, or on both.

The case for price differentiation in pharmaceuticals is prima facie strong, as R & D costs are recovered by companies during the patent period by charging prices above manufacturing and distribution costs. Differential pricing by indication will lead to companies recovering more of this R & D cost from higher-value (greater incremental health effect) uses of a product than from lower-value indications.[2] This is likely to increase overall use of the drug in the short run (achieving static efficiency) and send the right signals for future R & D investment to get more health gain in the future from additional indications from this drug or from other new products (dynamic efficiency). It increases static efficiency because prices for each indication can be set at levels that are cost-effective for the payer, thus all of the patients who can benefit from the treatment get access to it. Each indication for the product will be reimbursed. It increases dynamic efficiency because all of the indications that can profitably be developed (i.e. R & D costs can be recovered) when reimbursed at a price at which they are cost effective for the payer will be developed, delivering health gain for patients.

In some circumstances, static efficiency (maximising patient use of the drug) can be achieved by payers seeking to impose the lowest price per indication across the board. This reduces their expected expenditure. However, in others, the company will choose not to market one or more of the indications. Likewise, in a dynamic setting, there are circumstances in which a company will still develop all indications under a uniform price. This again will reduce payer expenditure whilst giving patients access to all possible indications. However, there are other circumstances in which, for example, companies will not develop a new high-value small-population indication because they cannot recover costs at the current uniform price because it is too low. They may decide to withdraw the lower-value indication from the market if only one price is permitted so they can market the higher-value indication, depriving patients of the lower-value product access to health gain.[3] New lower-value indications may not be developed under uniform pricing as they will not be deemed cost-effective by payers at the current (uniform) high price, and the company does not want to opt for a low uniform price as it will lose profits on the high-value indication. There is also the more general point that, whilst payers are keen to save on expenditure in the short run, paying prices below the value of the health gain during the patent period reduces the incentives for companies

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[2] We are at this point of the argument assuming that the volumes of patients treated are similar.
[3] Claxton et al. (2008) have argued that uniform pricing should be preferred as payers will get a greater share of the social surplus during the patent period, and companies should choose their uniform price. For a discussion of this and other pricing issues see Danzon, Towse and Mestre-Ferrandiz, (2013).

to invest in R & D in the longer run. Examples of the circumstances in which MIP produces losses or gains to payers, patients and manufactures are set out in Appendix 1.

We are making a number of simplifying assumptions at this stage. We are ignoring the costs of implementing differential pricing. These have to be taken into account. We are also assuming that drugs are used in each reimbursed indication in line with the clinical guidance set out in the approval. We are also ignoring issues around uncertainty about the exact value of the indication and how this should be dealt with. We return to these implementation issues in section 2.3 below.

2.2. Different forms of MIP

MIP could take various forms, depending how it is administered. Figure 2 illustrates one way to assess at what level and in what form a MIP scheme could be implemented for medicines with multiple indications.

Figure 2. Framework to outline possible MIP schemes for medicines with multiple indications depending on the indication.
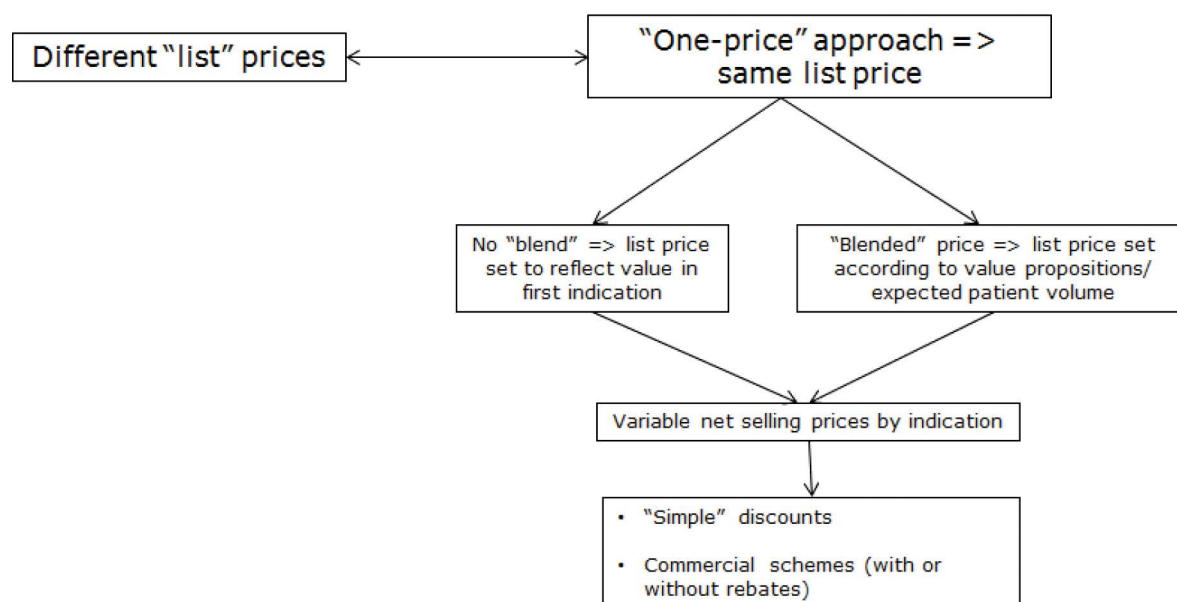
First, MIP can apply at "list" or "net" level. "List" prices refer to the official ex-factory prices as published in the relevant national databases and/or official journals/gazettes. "Net" prices refer to the actual prices paid by the relevant payer, which would take into account any discounts and/or rebates provided by the manufacturer. If "list" prices are different across indications, we would automatically have a MIP system. At the workshop it was argued that, for MIP to apply to list prices (i.e. different list prices across indications), full transparency on prices and use across indications would be required – which might be challenging because of the incentive for arbitrage, i.e. for users in a high-price setting to seek to acquire the drug at the price relevant to a low-price indication.

Alternatively, MIP could be implemented across "net" prices. This alternative was regarded as more practical during the workshop discussion. In this scenario, there could be a uniform list price across indications, but we would have variable net selling prices. This option could result by applying either (simple) financial (differential) discounts or commercial schemes involving rebates (from the manufacturer) after monitoring the use of the drug at indication level. A related issue is whether the

list price is "blended" or not. This refers to a "uniform-price" approach where the (list) price is based upon a weighted average of the (different) values of the various indications and expected patient volumes. A further issue to consider is whether the variable net selling prices by indication are "visible" (i.e. disclosed) or "invisible" (i.e. confidential).

Simple ex ante discounts can vary depending on the indication.[4] Commercial schemes can allow different net prices per indication through agreed ex post rebates (from the manufacturer) after monitoring the use of such drug at indication level. The rebates can be defined in terms of relevant parameters, such as when a particular number of patients/doses or expenditure has been reached, or in terms of agreed health outcomes.[5]

2.3. The desirability of MIP as a potential solution in the UK

The workshop agreed that relative prices should reflect relative value, and thus MIP might be a way forward for multi-indication medicines. However, it was important that prices did not exceed value and that use of the product was in line with the clinical guidance linked to the reimbursement decision. While MIP is particularly relevant for oncology drugs, it was also noted that it may also apply to treatments for rare diseases where a product may have more than one indication, including one indication with much larger patient numbers.

There was a discussion in the workshop as to what is the "optimal" price. In our theoretical analysis (see Appendix 1) prices were set for illustrative purposes at the upper end of the cost-effectiveness threshold range referred to in NICE Methods Guidelines, i.e. £30,000 per quality-adjusted life year (QALY). If all indications are set at the cost-effectiveness threshold, the social surplus would go to the manufacturer during the patent period. This sends the right signals for future innovation and might be acceptable to UK HTA agencies: the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG). It was argued, however, that the payer or budget holder, represented by NHS England for England, and the pricing agency, represented by the Department of Health, might prefer prices below the threshold, i.e. relative prices reflective of value but not equal to value.

There was a debate on how any form of pricing scheme, be it MIP or not, could address the challenge of uncertainty of health outcomes (i.e. whether outcomes post-launch confirm data from clinical trials) and indication use (i.e. for which indication the medicine will be used) at the time of launch. This point was related to discussion about more adaptive pathways/adaptive licensing to tackle emerging evidence.[6] If prices are set at the threshold level and there is also uncertainty about the outcomes of the medicine, then that would impose a further barrier to implementing MIP. Moreover, what would happen to the different prices if the anticipated value was not realised ex post? The payer/government would want lower prices in a context of high uncertainty. Linked to the point about uncertainty in outcomes, there was a discussion on the challenges of comparing the effectiveness of

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[4] Having different simple discounts per indication was referred to as "multi-indication discounting" during the workshop.
[5] There are many options to such commercial schemes. In the UK, the term used is Patient Access Schemes, which include both financial-based schemes and outcomes-based schemes. For a good overview of performance-based risk sharing agreements, see Garrison et al. (2013).
[6] Broadly speaking, the idea underpinning adaptive licensing is that when there might be something really promising that offers clinical potential, access is granted to a defined subset of a patient population, and expanded where relevant as more evidence is collected.

a medicine (based on real-world data or SACT data) with its efficacy (which would be based on clinical trials) and reassess funding decisions based on such comparison. While the discussion at this stage focused on cancer, it was argued that patient populations might be very different between those in clinical trials and those included in existing datasets in the UK, such as SACT data. Of course, how to handle uncertainty is an issue in any setting, whether uniform pricing or MIP is being considered. However, any introduction of MIP would require explicit consideration of how any uncertainty about clinical value was being addressed.

A further issue was the general agreement that MIP would be easier with completely different indications/treatment strategies, where there are de facto two different brands of the same molecule treating very different indications. We set out in Table 2 two examples taken from Appendix 2.

Table 2. Potential examples of multi-indication pricing: international case studies

Product	Therapy area	Rationale
Aflibercept	Multiple indications in oncology, ophthalmology	In the EU aflibercept is available as two distinct products, authorised and marketed under two different brand names, Zaltrap and Eylea. Separation is also helped by dosage form. Oncology use is an infusion and the ophthalmology use is pre-filled syringes.
Alemtuzumab	Onco-haematology, multiple sclerosis	In this case the manufacturer did not feel comfortable leaving the older product (MabCampath in onco-haematology) on the market and withdrew it to protect pricing of the second one (Lemtrada in MS), which they had judged to be commercially more promising. Both are liquid, injectable formulations, for IV infusions, and therefore there is opportunity for arbitrage.

In the case of aflibercept, despite being based on the same active substance, and being both liquid, injectable formulations, the price per mg of Eylea is almost 59 times higher than the price of Zaltrap if official ex-factory prices are considered. Separate branding works. In the case of alemtuzumab, if official ex-factory prices are considered, the price per mg of Lemtrada is 162 times higher than the latest price of MabCampath was before it was withdrawn. The size of the price gap and/or the ease of substituting one injectable form for another may lie behind the decision to withdraw the brand with the lower-priced indication.

However, this experience was deemed of little relevance for medicines with various oncology indications. The greater short- and longer-term challenge is multi-indications in oncology with one single brand for an on-patent product. We can distinguish here between different cancers and different stages in the treatment of the same cancer. Both are likely to be of growing importance.

Finally, there was discussion of the assumptions on the sequencing of launching follow-on indications on the need for MIP. It was argued that if the first indication was of higher value, then it would be easier to negotiate the price for the second indication, as ultimately prices could be lowered to accommodate the second, lower-valued, indication. However, if the second indication was of higher

value, then pricing negotiations could be more complex. For instance, under the assumption that MIP is not feasible and that some form of a "blended" price is the resulting outcome, in theory, this "blended" price could increase to reflect the higher value of the second indication. But as mentioned during the Workshop, price increases for branded medicines seldom happen. In the case of oncology, one typical scenario is first marketing of a lower-value use in a metastatic setting, with a subsequent higher-value indication for use in an adjuvant setting when the disease is less progressed. The case for MIP would therefore be greater. Likewise there is an element of serendipity about the development of new indications in other disease areas (for example a different cancer), and so companies may well be in situations in which development decisions have to be made about higher- or lower-value indications as compared with those currently on the market.

3. Making MIP a reality in the UK?

Workshop participants identified a number of operational challenges that would need to be addressed before there was likely to be widespread acceptance of the implementation of MIP-type schemes by any part of the NHS in the UK.

The challenges have been grouped across two main themes.

1. Systemic issues in the UK NHS that, while unrelated to the appropriateness of MIP to address the current (and future) challenges outlined above, will nevertheless affect the willingness to implement MIP.

2. Current data sets and how they support implementation of MIP. We looked at a UK oncology collaboration to pilot the feasibility of MIP, based on the Systemic Anti-cancer Therapy (SACT) data set.

3.1. Systemic issues in the UK NHS

A key challenge is whether the UK NHS can deal with MIP schemes involving variable net selling prices by indication requiring monitoring of volume usage per patient per indication, and undertake any financial reconciliation ex post to ensure that funds flow across the necessary stakeholders, be it at national or local level. It was argued during the workshop that an important driver towards schemes with different "net" prices across indications (however realised) would be ensuring that mechanisms were in place to feed back any potential discounts (which would need to be different across indications to resemble a MIP scheme [7]) or more complex rebates. There is a need to explore how much distortion in decision making would occur if rebates from commercial schemes did not accurately go back to the individual, budget holding, trust. Evidence from early patient access schemes suggested that the NHS seems to be bad at pursuing rebates and there was general agreement that, currently, it is very difficult to track rebates in the system.

On the possibility of financial reconciliation ex post to calculate necessary rebates, two uncertainties need to be addressed: (1) What is the data showing in terms of volume use per patient per indication? (2) How well does it link in with the existing guidance (issued by HTA bodies) on what is deemed to be cost-effective? It maybe that any form of MIP will have to be through some sort of rebate

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[7] Noting that any scheme based on simple, uniform discounts across indications could not be treated as a MIP scheme.

scheme, because at the time a medicine with multiple indications is purchased, it will not be known which indication it will be used for. The NHS does not have sufficiently sophisticated financial systems to facilitate reconciliation in terms of following drug usage across indications – with the possible exception of the oncology pilot study discussed in the next section. Any such tracking will require additional data collection and analysing resources, which are lacking. Moreover, prescribing systems and pharmacy systems (used to manage drug expenditure) are doing different things and they are not always connected to each other.

Hospitals buying medicines receive any negotiated simple discounts. It is less clear that hospitals get back rebates from more complex schemes through, for example, patient access schemes, and at the workshop it was said that some do not. Handling rebates is particularly challenging when they are attached to an outcome. Patient access schemes with free stock (e.g. the first four batches are paid for, and any extra come for free) are easier to manage, but only slightly, because there is still a need to distinguish between those doses which are free for some patients and those which come at a charge for other patients. It was argued that this is not how NHS systems are geared up to supply medicines.

In Scotland, as well as England, there has been a desire to negotiate patient access schemes with straightforward discounts at point of invoice. There is a system in place whereby the Scottish NHS can get discounts in primary care. Handling rebates when attached to an outcome is difficult. Indeed, tracking outcome for a patient, then tracking the rebate back to that patient and linking to the cost centre is currently impossible in Scotland.

The option of using "flexible pricing schemes" through the Pharmaceutical Price Regulation Scheme (PPRS) as a means to achieve MIP was discussed. Flexible-pricing schemes, introduced as an option in the 2009 PPRS agreement, allow companies to introduce a different price for a major new indication. If it is an increase in price, "there will be no limit on the price increase". Three restrictions apply, however (DH, 2013, pg 26). First,

The price increase would not come into effect unless the relevant indication was selected for appraisal and [either] NICE final guidance had been issued; [or] after twelve months from the date of licensing of the relevant indication (or twelve months after the scheme member proposed the price change if the proposal is made post licensing of the relevant indication); whichever date is reached first.

Second, "to limit the number of applications to a manageable level and to facilitate implementation in the NHS for any medicine it will normally only be expected to have one price change per active substance during its lifetime (DH, 2013, pg 26)." Third, "in the event of a price increase, a [company] must make arrangements to provide the product at the old price for the original indication . . . through the application of a straightforward discount, introduced on the day that any new price commences (DH, 2013, pg 26)." This means that companies have to operate two prices for the NHS.

As highlighted during the workshop, "flexible pricing schemes" have never been used. Attendees were puzzled as to why. One view was that the Department of Health had discouraged manufacturers from coming forward with such proposals, implying that it did not want (on behalf of the four nations) different prices per indication. It is also important to note that the 2014 Pharmaceutical

Price Regulation Scheme (DH, 2013, p.29), states,

> *However, a Patient Access Scheme (PAS) should only modify the cost of a single product. Further, the Department is unlikely to agree to more than one PAS for a single medicine, because of the complexity this would introduce for the NHS. In view of this, PAS proposals should be designed so that the same PAS could apply across all relevant indications.*

The relation between flexible pricing schemes and PAS for multi-indication medicines is arguably therefore uncertain.

There was also a discussion on where risk lies when implementing MIP. If the NHS needs to track a price offered by the industry and then go back to companies to renegotiate a simple discount or monitor usage relative to original predictions, then the risk would fall on the NHS. This could put extra pressure on the NHS, and currently there are no resources to undertake such validation analyses within the NHS. It was also argued that perhaps the risk lies with non-oncology patients – focusing on oncology medicines could increase access for cancer patients at the expense of non-oncology patients given the pressures on NHS budgets.

3.2. Current data capabilities to support MIP in the UK

Critical to any implementation of MIP is data availability on the use of medicines across different groups of patients/indications. A possible solution discussed was to obtain this information in the first instance from a limited but reliable sample of hospitals, which could generate high-quality, specific data which could then be extrapolated to the country as a whole. Data needs depend on whether any ex post payments and/or ex ante discounts need to be reflected back to the trust or the supplier. It was also pointed out that the quality of the data can increase when new incentives are implemented; for example, once hospitals in England were coded and paid according to healthcare resources groups (HRG),[8] the coding improved.

There is an ongoing UK collaboration supported by healthcare analytics from Deloitte MCS Ltd, between Roche and several NHS Trusts, to pilot, in oncology, the feasibility of MIP based on the Systemic Anti-cancer Therapy (SACT) dataset. This "SACT Reporting Solution" pilot illustrates that it is currently possible to implement a MIP-based scheme.

In the next sections we outline the workshop feedback on this pilot and on SACT data generally.[9]

3.3. Background to the SACT data set and the SACT Reporting Solution

The Systemic Anti-cancer Therapy (SACT) data set covers chemotherapy treatment for all solid-tumour and haematological malignancies.[10] It supports both the Department of Health's National Cancer Strategy and NHS England's agenda for broader UK data transparency. Clinician-led implementation of the SACT programme ran between April 2012 and April 2014, and since 1 April 2014 completion of this 43-field data set has been a mandated requirement for all 147 NHS providers

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[8] For more information on HRGs, see: http://www.hscic.gov.uk/hrg.
[9] For more information on current capabilities for linking data on medicine use and patient diagnosis across the four countries of the UK, including SACT, see Chapman and Karslberg Schaffer (2015).
[10] See http://www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/data_sets/systemic_anti-cancer_therapy_data_set_fr.asp?shownav=1 [accessed January 2015].

of chemotherapy agents in England.[11] The data collected by hospitals and trusts is submitted to a central body, the Chemotherapy Intelligence Unit (CIU) at Public Health England.[12] Although SACT is unique to England, the types of data captured are also available in electronic prescribing systems covering oncology products.

Roche Products Ltd and Deloitte MCS Ltd, with specific NHS trusts,[13] have designed and built a "SACT Reporting Solution" to demonstrate how the existing SACT dataset can be used to (i) provide operational reporting for the NHS and (ii) support future potential novel commercial pricing models and real-world evidence generation. The project is designed to explore whether SACT data can be of good quality (see Figure 3), securely anonymised/pseudonymised, aggregated, reported, and subsequently accessed by the NHS to manage chemotherapy services more efficiently, to drive improvements in patient safety and treatment outcomes.[14]

Figure 3: Continuous data quality overview of SACT data field entry (example only)

Data quality overview

Field	Current status	Prior status	Diff
Demographics and consultant			
1 - NHS Number *	100.00%	100.00%	0.00%
2 - Date of birth *	100.00%	100.00%	0.00%
3 - Gender - current	100.00%	100.00%	0.00%
4 - Ethnicity	50.25%	93.33%	-43.08%
5 - Patient Postcode *	100.00%	100.00%	0.00%
6 - Registered GP Practice Code	100.00%	80.74%	19.26%
7 - Consultant GMC Code *	100.00%	80.74%	19.26%
8 - Consultant specialty code	100.00%	80.74%	19.26%
9 - Organisation code of provider	100.00%	80.74%	19.26%
Clinical status			
10 - Primary diagnosis (ICD-10)	100.00%	80.74%	19.26%
11 - Morphology	0.00%	80.74%	-80.74%
12 - Stage of disease	100.00%	80.74%	19.26%
Cycle			
26 - Cycle Number	100.00%	100.00%	0.00%
27 - Start date of cycle	100.00%	100.00%	0.00%
28 - Weight at start of cycle	100.00%	100.00%	0.00%
29 - Performance status at start of cycle	0.46%	12.59%	-12.13%
30 - OPCS procurement code	0.00%	0.00%	0.00%
Drug details			
31 - Drug name	100.00%	100.00%	0.00%
32 - Actual dose per administration	100.00%	100.00%	0.00%
33 - Administration route	100.00%	100.00%	0.00%
34 - Administration date	100.00%	100.00%	0.00%
35 - Organisation code of provider (administration)	100.00%	100.00%	0.00%
36 - OPCS delivery code	100.00%	100.00%	0.00%

Field	Current status	Prior status	Diff
Programme and regimen			
13 - Programme Number	0.00%	7.70%	-7.70%
14 - Regimen Number	0.00%	70.37%	-70.37%
15 - Intent of treatment	99.76%	0.74%	99.02%
16 - Regimen	100.00%	14.88%	85.12%
17 - Height at start of regimen	100.00%	100.00%	0.00%
18 - Weight at start of regimen	100.00%	100.00%	0.00%
19 - Peformance status at start of regimen	81.46%	10.00%	71.46%
20 - Co-morbidity adjustment	0.00%	0.00%	0.00%
21 - Date decision to treat	100.00%	100.00%	0.00%
22 - Start date of regimen	100.00%	100.00%	0.00%
23 - Clinical trial	0.00%	0.00%	0.00%
24 - Chemo-radiation	100.00%	100.00%	0.00%
25 - Number of cycles planned	0.00%	0.00%	0.00%
Outcomes			
37 - Date of final treatment	0.00%	0.00%	0.00%
38 - Regimen modification - dose reduction	100.00%	100.00%	0.00%
39 - Regimen modification - time delay	100.00%	100.00%	0.00%
40 - Regimen modification - stopped early	100.00%	100.00%	0.00%
41 - Regimen outcome summary	0.00%	0.00%	0.00%
42 - Date of death *	100.00%	100.00%	0.00%
Demographics and consultant			
43 - NHS Number status indicator code	100.00%	100.00%	0.00%
Total			
Total records	29,490		

* This denotes fields that have been transformed from the original SACT feed by the Pseudonymisation process.

Roche is using the project to test a proof of concept for MIP for one brand of its medicine (see Figure 4). To date the learnings of this work on SACT have been shared with various NHS and governmental agencies.

[11] See http://www.isb.nhs.uk/library/standard/91 [accessed January 2015].
[12] See http://www.chemodataset.nhs.uk/home [accessed January 2015].
[13] See http://www.roche.co.uk/home/corporate-responsibility/patients/joint-working.html [accessed January 2015].
[14] More information on this pilot can be found in McNamara and McNamara (2014).

Figure 4. Prototype MIP reports: volumes and number of patients by commercial scheme (example only)

Reasons for usage	Volume (mg)	Number of Patients
CA_GB_6	8,265	13
CA_GB_7	19,670	23
CA_GB_8	1,613	
CA_GB_9	7,725	7
No Scheme	4,965	8
SACT Total	**42,238**	**51**
Redistributed Sales Total	**9,400**	**N/A**

Key: CA_GB stands for "commercial agreement in Great Britain". The numbers 6 to 9 for each of the "commercial agreements" denote different agreements for the brand across multiple indications.

Deloitte aims to explore whether, subject to the appropriate NHS, HTA and government approval and support, a sustainable UK business model can be built that provides the required health care data to NHS and industry stakeholders to support commercial agreements. One option would be to fund it through an industry subscription model.

The programme is also seeking to help realise the potential of the NHS's real-world data. The UK has several features that should make it an attractive place to invest in clinical research, but these natural advantages have not been fully capitalised upon. If harnessed properly, the breadth and depth of health care data captured by the NHS is one the UK's biggest assets.

The SACT Reporting Solution allows specific NHS trusts and Roche to perform a wide variety of analyses. These include:

- Data quality: assess the completeness of SACT fields

- Reconciliation: analyse the difference between month-on-month volumes of drugs administered and supplied; this uses aggregated volumes from SACT data and the manufacturer's supply-chain data

- NHS analysis: create example reports to measure the trusts activity, regimen usage, case mix, demographics and compliance

- Industry reports: analyse the completeness of SACT data to support patient access schemes and MIP.

National data access is also being sought to further support the value and utility of the SACT data set.

3.4. Feedback from the workshop: collecting the data

There was a division of opinion between those decision makers at national level and those working with NHS providers. Broadly speaking, the two views were:

1. Those working at the centre see SACT data as a potentially effective mechanism to monitor drug volume usage per indication for oncology and support one or more of the different approaches described in Figure 2 above.

2. Those working with providers were more sceptical as to what value was being added by the SACT data – with the caveat that SACT data was not originally created to support flexible pricing schemes.

With a simple price–volume agreement, the number of patients for each indication could be predicted in advance. The actual numbers of patients using the product for each indication could then be compared with the predictions and any necessary payments (from companies to the Department of Health, but also from the Department of Health to companies) could be made if the prediction was wrong. Before the advent of the SACT data set, the general view expressed at the workshop (and as reiterated above) was that it is currently not feasible to do this ex post validation exercise, let alone track down any rebates arising from more complex schemes across the system.

In addition, some of the challenges with SACT data and the material presented above were discussed. We have grouped them across key themes:

- There is variation in the quality of data across different trusts and source data verification can be limited. Not all is extracted from an electronic prescribing system. Information already included in the electronic prescription databases will automatically be uploaded (which refers to the cells shaded in green in Figure 3) and information not included will not be uploaded to SACT data (cells shaded in red in Figure 3). Oral presentations for cancer medicines are not captured very effectively in English SACT data. For instance, if a patient was given a pack but only one tablet was administered in the clinic and they took the rest home, SACT data would only capture the one tablet. Further, data from community pharmacies is not currently included, but may be needed. For instance, some outpatient prescriptions may go through an outsourced pharmacy.

- It was mentioned at the workshop that NHS trusts receiving the SACT Reporting Solution were finding it useful – for example, to show whether they are submitting data according to the templates from the SACT data set. Whether that is of intrinsic clinical value is a different issue. We can also see that the outcomes data section is currently very limited, and physicians have little incentive to report any decision to stop treatment (for whatever reason). Moreover, SACT data, due to data quality, does not easily provide details of line of treatment, i.e. whether the medicine is being used as first, second or further lines of treatment (in Figure 3, SACT data field 13, "Programme number",[15] which is highlighted in red).

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[15] It was argued in the workshop that the "Programme number" field has no data uploaded (appears as 0 per cent) because with multiple lines of treatment it is sometimes difficult to know the exact line of treatment of any therapy, and finding that level of detail might require a non-negligible amount of time.

- It was mentioned that any of the pricing schemes outlined in Figure 2 implemented at a national level would need to mechanise the data collection system (as per Figure 4 above) to make it sustainable – and this is a first step towards that. Perhaps for each individual hospital, the costs of running complex pricing schemes would not be that significant – so any "simple" discount or more complex commercial scheme (that might need some form of monitoring and validation) offered would be welcomed. The bigger challenge lies when these schemes are scaled up and need to be tracked. SACT data provides levers to track the usage of medicines in the CDF – recognising that there might be other sources of information but that currently the only workflow where a national data set is being generated around this information is SACT data.

There was also discussion about the Scottish experience with data collection. ChemoCare®, the new electronic chemotherapy prescribing and patient scheduling system known in NHS Scotland as CEPAS, is being rolled out. It was announced in July 2012 that ChemoCare had successfully gone live across all three of the Scottish Cancer networks.[16] It provides support for safe prescribing and administration, giving each patient a single electronic chemotherapy treatment record that is accessible to designated members of the multi-professional team across the pathways of care and from multiple geographical points of service delivery.[17] However, it was argued that ChemoCare requires further development to track patients for MIP. Moreover, there has been a push to move chemotherapy treatments from hospital to primary care, especially for well-tolerated treatments. This means that any future patient–treatment tracking scheme cannot be only hospital-based.

Databases in Italy were also discussed. Separate registries are created by indication, and sometimes even by line of treatment, depending on the nature of the pricing agreement. These registries apply to oncology, orphan drugs and a number of other indications. Each company has to pay □30,000 per year for each registry relevant to its products.[18] Under this system, hospitals need to send the data to AIFA (Agencia Italiana del Farmaco).[19] AIFA verifies the quality of the data, as well as verifying that the use has been appropriate according to the deal, after which AIFA confirms to the hospital that it can reclaim the credit. This credit is then applied in the form of either free goods or a credit note on the next purchase. This means that rebates in the system go back to the individual hospital and pharmacy purchasing the medicine. AIFA had to engage with individual regions to improve the response rate;[20] at the same time regional authorities had to convince the hospitals to submit the data, even though it is ultimately in the hospitals' own interest to submit the data to benefit from any discounts.[21]

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[16] See http://www.cis-healthcare.com/latest/chemocare_goes_live_across_nhs_scotland/.

[17] For more information on ChemoCare, please see http://www.cis-healthcare.com/products_services/chemocare/.

[18] Also, several companies help hospitals to complete these records manually by providing support staff, such as nurses. AIFA (Agencia Italiana del Farmaco).

[19] AIFA is the national authority responsible for drugs regulation in Italy.

[20] Note that in Italy health care responsibilities are devolved to the regions.

[21] Navarria et al. (2015) analyse current performance-based schemes in Italy, which are mostly for oncology medicines. They comment on the complexity of the system due to the high number of registries and the heterogeneity of the mechanisms through which regions/companies/pharmacies/hospitals are actually refunded. They suggest a "success-fee" strategy instead, which consists of an ex post payment to the manufacturer, applied only for those patients receiving a real benefit from therapy. The drug is provided by the company at no initial cost to the NHS. This "success-fee" scheme has been used for the first time for a drug indicated for mild to moderate idiopathic pulmonary fibrosis, pirfenidone. Still, such mechanisms require data sets to monitor use and outcomes at indication/patient level.

4. Reflections and conclusions

Handling multiple indications within the same disease area – including different potential lines of treatment and/or combination regimens – is a challenge. A condition that is necessary for the implementation of most of the pricing schemes considered in this briefing (with the possible exception of simple discounts) in the case of multiple indications approved for the same medicine is the potential to track the specific utilisation of the drug in its different indications, regimens and patient sub-populations. This requires the implementation of multiple patient registries or other methods to track who is treated, for what specific indication, with what quantities of a given drug, in the context of each specific approved therapeutic regimen.

The (limited) international experience explored in this briefing shows that certain health systems – e.g. Italy – have already accumulated significant experience in the form of indication-specific net selling-price arrangements, both at the national and at the sub-national levels. Other health systems, like France, thus far seem to have preferred a different approach, adjusting prices – at the "visible" (or list) and/or the "invisible" (or net) level – to reflect the "blended" value proposition emerging for the various indications approved for the same medicine and the expected patient volumes.

What option is desired, and implementable, depends on the problems/challenges we need to address. Broadly speaking, we are trying to: (1) ensure sustainable access to and uptake of (cost-effective) cancer medicines, in England and elsewhere; (2) ensure that relative prices reflect relative value and, from an NHS perspective, do not exceed value; (3) share appropriately the gains (surplus) across manufacturers and payers to generate long-run incentives for R & D; (4) balance payers' affordability issues; and (5) avoid too much complexity or bureaucracy. Of course, what is optimal to implement also depends on data capabilities.

There is also a need to consider the dynamic-pricing case, given the interest in adaptive pathways.[22] What is not yet clear is how pricing schemes, in general, link to adaptive pathways, but, by implication, the number of indications will increase over time and/or the assessment of value of a given indication will change over time as more evidence of relative effectiveness becomes available. There was an appetite to explore further the link between adaptive licensing and pricing schemes which could ultimately allow for prices to be modulated according to additional evidence and an adaptive license that can change over time. Along these lines, further solutions could be explored, such as a UK pharmaceutical price regulation scheme (PPRS) or flexible pricing schemes (with the proviso that the current arrangements for such pricing schemes, and PAS, limit the way MIP schemes could be implemented).

Overall, our final reflections are as follows:

- Stakeholders present at the workshop recognised the challenge of paying for multi-indication drugs and were interested in the potential use of MIP. MIP is a potential solution that makes sense for companies, and theoretically MIP can improve overall social welfare, but there is a need to ascertain more clearly the benefits for the NHS.

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[22] The key principle of adaptive pathways is a "trade-off between earlier access for some patients versus an increased level of acceptable uncertainty about benefits and risks, although the degree of uncertainty is expected to diminish with additional evidence generation" (Eichler et al. 2012, pg. 428).

- There was general support for the notion of relative prices reflecting relative value, albeit whilst ensuring they did not exceed value. Greater clarity is therefore required in terms of how to operationalise MIP and any form of variable net selling prices, to ensure that both payers and companies benefit.

- There was an interest in using "blended" pricing (at list level) coupled with schemes that might generate variable "net" selling prices. This is because it seems that any form of MIP is more realistically achievable at the "invisible", net selling price level rather than through different list prices. This could be achieved by indication-based discounts and/or rebates (via more complex commercial schemes). Ultimately, an important driver towards such systems would be the existence of mechanisms to ensure that any potential discounts or rebates to the system, with a certain degree of accuracy, go back to the trusts.

- One solution addressing the complexities of any form of MIP (particularly at net level) could be to do this at central level, where effectively we have a "blended" single list price, with simple discounts worked out retrospectively at the centre based on the volumes of different indications and the different values in the different indications. NHS England could pay back additional rebates to the Trusts based on that data.

- SACT data can support the implementation of MIP, notwithstanding some of the inherent data issues that come as a result of SACT original intent. The NHS's unique SACT data set is seen as a helpful route to understanding whether it is feasible to implement such pricing systems in the UK. There would be, as suggested by Bach (2014), some secondary benefits from investment in improved electronic documentation and richer data sets monitoring usage of medicines to achieve more sophisticated pricing mechanisms. There would be more transparency in the use of medicines and such investment would help create an infrastructure for generating real-world evidence of the outcomes achieved from treatment.

Appendix 1: Conceptual analysis of MIP versus uniform pricing

Price discrimination (or price differentiation) is a pricing strategy where customers with different willingness to pay are charged different prices for the same good (or very similar goods with identical production costs). This is not per se a good or bad practice and its consequences should be assessed on a case-by-case basis, balancing anti-competitive and efficiency arguments. As a result of this exercise, price discrimination may either be beneficial or cause detriment in terms of total welfare. [23]

In the context of pharmaceuticals, the case for price discrimination across indications – here "multi-indication pricing" (MIP) – can arise when the same medicine has different indications, which provide different therapeutic benefits to patients with different health conditions.[24] A MIP approach could ensure that medicines are appropriately priced for each of their indications. The purpose of this work is to explore under which circumstances MIP is feasible and desirable for all stakeholders.

This Appendix is based on a theoretical analysis to explore the impact of price differentiation (versus uniform or flat pricing) on manufacturers, patients and payers.

Scenarios to explore the impact of MIP

We analyse different scenarios to show under which circumstances the introduction of MIP can be beneficial from the manufacturer's, payer's and patients' perspectives. It is important to distinguish between two different setups:

- Static context. In this case, the manufacturer's decision to invest in the development of an indication is not considered. It is assumed that the drug has already been authorised for marketing (i.e. the research and development (R & D) costs of each indication are sunk) and that the problem of the manufacturer is to decide the price(s) of the drug.

- Dynamic context. In this case, the manufacturer has not yet incurred the R & D costs to develop all of the different potential indications. It has first to make the strategic decision about whether to invest in the development of an indication (this decision depends on the possibility of recovering the R & D costs). Once the drug has been developed for a specific indication, the manufacturer has to decide the price(s).

The general framework is the same in both cases: a new drug, which can have two different indications (X and Y), is considered for launch in a new market. Indication X provides a higher therapeutic value and four quality-adjusted life years (QALYs) per patient,[25] and the patient population is 2,000 patients. Indication Y provides a lower therapeutic value and one QALY per patient, and has a different (i.e. non-overlapping) population of 5,000 patients. Our analysis assumes a fixed demand within an indication, rather than a downward-sloping demand curve; i.e. we do not model the situation where demand can increase if you decrease the price. Such modelling becomes more complex and is outside the scope of this briefing.

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[23] A necessary but not sufficient condition for total welfare to increase is that price discrimination leads to an increased consumption of the good compared to the case of uniform pricing.

[24] Pharmaceutical companies are also known to implement price discrimination across countries, charging higher prices in regions where customers have more purchasing power (Danzon and Chao, 2000; Rojas, 2005). Price discrimination for branded pharmaceuticals is a widely debated topic. For more information, please see Danzon and Towse, 2003; Danzon, Towse and Mestre-Ferrandiz, 2013). In this case, price discrimination is seen by many as justifiable on the grounds that (1) the companies could not recover their R & D expenses if they sold their products to everyone at or near marginal costs (dynamic efficiency), and (2) price differentiation increases access, which ultimately is linked to welfare (static efficiency).

[25] For our purposes, we assume that health gains are measured by QALYs.

If the manufacturer can freely choose two different prices for the two indications, we assume that the prices that maximise the manufacturer's revenue are: £120,000 for indication X and £30,000 for indication Y.[26] For both indications, the price per QALY is £30,000. We assume for simplicity that at this cost-per-QALY the drug is regarded as cost-effective for both indications by HTA bodies and payers. When MIP is not feasible, there can only be one price for both indications – but we also assume that this price would be such that the price per QALY is £30,000.

As mentioned above, the key difference between the static and the dynamic analysis is that, in the latter, companies have to make a decision as to whether or not to incur development costs of either indication. For the purposes of our analysis, we assume that these costs are £100m for each of the indications.[27] We also consider two possible sub-scenarios:

- The manufacturer knows all the possible indications for which the medicine can work before developing any of the indications

- The manufacturer discovers that the medicine can work for a second indication only after the first indication has been developed and the medicine marketed.

We now take in turn the static and dynamic context.

Static context (i.e. indications already approved)

In this case, both indications are already approved for marketing and the manufacturer does not need to consider how to recover the R & D costs. We first consider the case where MIP is feasible. If the drug is introduced in the market, in this scenario the total revenue for the manufacturer is £390m (£240m for indication X plus £150m for indication Y), which also coincides with the payer's expenditure. The total amount of QALYs generated is 13,000 (8,000 from indication X and 5,000 from indication Y; see Table A1.1).

Table A1.1: multi-indication pricing in a static context

	Indication X	**Indication Y**
(A) QALYs per patient	4	1
(B) Price per treatment	£120,000	£30,000
(C) Patient population	2,000	5,000
(D = B × C) Cost for the payer/ revenue for the manufacturer	£240,000,000	£150,000,000
(E = A × C) Total QALYs generated	8,000	5,000

If the payer uses its market power to impose a uniform pricing structure (i.e. the same price for both indications) and/or arbitrage cannot be prevented, the manufacturer cannot charge two different prices. In this case, the options are to set the price at either £30,000 or £120,000.[28]

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[26] For ease of explanation, we assume that the variable cost to manufacture the drug is zero, so the price that maximises the revenue is the same as that which maximises profits. If variable costs were introduced, the analysis would be more complex but the qualitative results would not change.

[27] We also abstract from the economies of scope that could arise when both indications are developed. It can be the case that research for one indication has positive spillovers into the research for the other indication, implying that the overall R & D costs are lower if both indications are researched. This point was raised at the workshop.

[28] No other price would be optimal from the manufacturer's perspective.

If the manufacturer sets the price at £120,000, only indication X is cost-effective. In this case, 2,000 patients will benefit from the drug and the total amount of QALYs produced will be 8,000. The revenue for the manufacturer/bill for the payer will be £240m (see Table A1.2).

Table A1.2: uniform pricing where only indication X is cost-effective

	Indication X	Indication Y
(A) QALYs per patient	4	1
(B) Price per treatment	£120,000	£120,000
(C) Patient population	2,000	-
(D = B × C) Cost for the payer/ revenue for the manufacturer	£240,000,000	-
(E = A × C) Total QALYs generated	8,000	-

If the manufacturer sets the price at £30,000, both indications are cost-effective. In this case, the population covered and the total amount of QALYs generated is the same as in the multi-indication pricing scenario (7,000 patients and 13,000 QALYs). However, the manufacturer's revenue and, consequently, the payer's expenditure are lower: £210m (see Table A1.3).

Table A1.3: uniform pricing where both indications are cost-effective and the manufacturer prefers to supply the medicine for the high-value indication only

	Indication X	Indication Y
(A) QALYs per patient	4	1
(B) Price per treatment	£30,000	£30,000
(C) Patient population	2,000	5,000
(D = B × C) Cost for the payer/ revenue for the manufacturer	£60,000,000	£150,000,000
(E = A × C) Total QALYs generated	8,000	5,000

If MIP is not feasible, in this example the manufacturer prefers to set the price at the highest level, making the lowest-value indication non-cost-effective, as this provides the highest total revenue (£240m versus £210m).[29] The implication of not having MIP is that some patients (those of indication Y) do not have access to the drug. However, if the payer can use its power to impose the price of £30,000 for both indications, the manufacturer would face a take-it-or-leave-it situation:[30] supplying the medicine at £30,000 for both indications or not supplying it at all. In the static framework, given that all the costs are sunk, the manufacturer will decide to supply the medicine and the outcome will be the one in Table A1.3. The payer will end up paying the lowest-possible medicine bill and all the patients will have access to the medicine. This outcome can change considerably in a dynamic context, when the manufacturer can decide whether to develop an indication or not (see next section).

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[29] The scenario where the manufacturer finds it more profitable to set the lower price is also a possible outcome.
[30] In this example we abstract from international issues and assume that there is only one country.

Dynamic context (i.e. the manufacturer needs to decide for which indications to invest in R & D for marketing approval)

The setup of this scenario is similar to the one in the previous section. The only difference is that the manufacturer has not yet incurred the development costs of either indication. We assume that these costs are £100m for each of the indications.[31] This can represent the share of R & D that is reasonably attributed to the hypothetical country considered in this scenario analysis. This is calculated by the manufacturer depending on the size and ability to pay of a market.[32]

We consider two possible sub-scenarios:

- The manufacturer knows all the possible indications for which the medicine can work before developing any of the indications

- The manufacturer discovers that the medicine can work for a second indication only after the first indication has been developed and the medicine marketed.

We analyse both sub-scenarios in the following sections.

The manufacturer knows possible indications before development begins

In this case, the manufacturer will develop an indication only if it is possible to recover the associated costs. The case where the manufacturer is allowed to apply MIP is presented in Table A1.4. In this case, the manufacturer chooses to develop both indications. In total, 7,000 patients benefit from the drug and 13,000 QALYs are generated. The total expenditure for the payer is £390m whilst the margin for the manufacturer is £190m.

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[31] We also abstract from the economies of scope that could arise when both indications are developed. It can be the case that research for one indication has positive spill overs on the research for the other indication, implying that the overall R & D costs are lower if both indications are researched.

[32] We abstract from the "free-riding" issue, where a country/payer may decide not to contribute to R & D costs. We also assume that the market in this example is crucial for the manufacturer: if the share of R & D costs imputed to this market cannot be recovered, the correspondent indication is not researched.

Table A1.4: multi-indication pricing in a dynamic context

	Indication X	Indication Y
(A) QALYs per patient	4	1
(B) Price per treatment	£120,000	£30,000
(C) Patient population	2,000	5,000
(D = B × C) Cost for the payer/ revenue for the manufacturer	£240,000,000	£150,000,000
(E = A × C) Total QALYs generated	8,000	5,000
(F) Development cost	£100,000,000	£100,000,000
(G = D – F) Margin for the manufacturer	£140,000,000	£50,000,000

If MIP is not feasible, the manufacturer can decide whether to:

a. Develop indication X and price it at £120,000

b. Develop indication Y and price it at £30,000

c. Develop both indications and price them at £30,000.

The alternative where both indications are developed and priced at £120,000 is not considered, as indication Y would not be cost-effective at £120,000 and the manufacturer would not invest in its development given it will not be approved for reimbursement.

The outcome in case a is presented in Table A1.5. The total number of QALYs generated is 8,000 and 2,000 patients benefit from the drug. The cost for the payer is £240m and the margin for the manufacturer is £140m.

Table A1.5: indication X is developed in a dynamic context

	Indication X
(A) QALYs per patient	4
(B) Price per treatment	£120,000
(C) Patient population	2,000
(D = B × C) Cost for the payer/revenue for the manufacturer	£240,000,000
(E = A × C) Total QALYs generated	8,000
(F) Development cost	£100,000,000
(G = D – F) Margin for the manufacturer	£140,000,000

The outcome of case b is presented in Table A1.6. The total number of QALYs generated is 5,000 and 5,000 patients benefit from the drug. The cost for the payer is £150m and the margin for the manufacturer is £50m.

Table A1.6: indication Y is developed in a dynamic context

	Indication Y
(A) QALYs per patient	1
(B) Price per treatment	£30,000
(C) Patient population	5,000
(D = B × C) Cost for the payer/revenue for the manufacturer	£150,000,000
(E = A × C) Total QALYs generated	5,000
(F) Development cost	£100,000,000
(G = D − F) Margin for the manufacturer	£50,000,000

The outcome of case c is presented in Table A1.7. The total number of QALYs generated and the number of patients who benefit from the drug is the same as in the MIP scenario (13,000 QALYs and 7,000 patients). The total bill for the payer is £210m and the margin for the manufacturer is £10m.

Table A1.7: both indications X and Y are developed and marketed at the same price

	Indication X	Indication Y
(A) QALYs per patient	4	1
(B) Price per treatment	£30,000	£30,000
(C) Patient population	2,000	5,000
(D = B × C) Cost for the payer/ revenue for the manufacturer	£60,000,000	£150,000,000
(E = A × C) Total QALYs generated	8,000	5,000
(F) Development cost	£100,000,000	£100,000,000
(G = D − F) Margin for the manufacturer	£−40,000,000	£50,000,000

Because the manufacturer can anticipate the outcome in each of the scenarios before investing in the development of either indication, it will consider the most profitable outcome. In this case, the manufacturer would prefer scenario a as this is providing the highest margin. Only indication X would be developed and 2,000 patients would have access to it. The total number of QALYs generated would be 8,000.

However, the other scenarios could also have been chosen if:

1. The patient population of the lower-value indication (Y) is large enough or if the value of indication Y (and, consequently, the price that makes it cost-effective for the payer) is high enough. In this case the outcome can be scenario b above

2. in addition to 1, the development cost of X can be recovered even if its price is the same as that of Y (i.e. £30,000). In this case the outcome can be scenario c above.

If the payer is able, and chooses, to use its power to impose the £30,000 price for both indications, in the dynamic case the manufacturer would anticipate it and develop indication X only (as in Table A1.5), given it provides the highest margin. Therefore indication Y would not be available and the payer would not be able to use its market power to impose the lowest price.

However, if the revenue from indication X allowed recovering the R & D costs (either because the patient population is large enough or because the development cost is low enough), the manufacturer would prefer developing also that indication (see Table A1.8, where the population for indication X is now assumed to be 4,000 patients). However, in general, the payer power to impose a single price is weaker in the dynamic context, as the manufacturer can counteract it by anticipating it in making its R & D decisions about which indications to develop.

Table A1.8: both indications are developed and marketed at the same price when the payer imposes the lower-value indication price

	Indication X	Indication Y
(A) QALYs per patient	4	1
(B) Price per treatment	£30,000	£30,000
(C) Patient population	2,000	5,000
(D = B × C) Cost for the payer/ revenue for the manufacturer	£120,000,000	£150,000,000
(E = A × C) Total QALYs generated	8,000	5,000
(F) Development cost	£100,000,000	£100,000,000
(G = D – F) Margin for the manufacturer	£20,000,000	£50,000,000

Dynamic context with sequential discovery: the manufacturer only discovers the second indication after the first has been developed and marketed

In this case, the manufacturer develops one indication first and discovers the second indication only after the first indication has already been marketed (and a price has been attached to it). This case is more complex than the previous, as it introduces more variables. Unfortunately, this limits the possibility of representing the different outcomes through examples as there are too many possible scenarios to deal with.[33] It is, however, possible to describe the different scenarios and provide the circumstances under which they are likely to happen.

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[33] One solution would be to develop a (simple) model to represent this case and analyse the different outcomes. However, this is out of the purpose of this short note and, in case it is necessary, it could be addressed in future analysis.

The outcome if MIP is feasible would be the same as in Table A1.4: even if the indications are developed and marketed in sequence, the optimal pricing strategy would be the same from the manufacturer's perspective. The intuitive argument for this is that MIP would allow the manufacturer to treat separately the two markets for the two indications.

The outcome when MIP is not feasible depends on whether the high-value (versus low-value) indication is discovered first.[34]

If the manufacturer markets indication X first (at £120,000), then researching and marketing indication Y would imply that the price for X will need to decrease to £30,000 (otherwise it would not be possible to market indication Y once it is available). The manufacturer will decide to research and market the second indication if:

- The combined revenue from X and Y minus the development cost for Y will exceed the revenue from X only (the indication already marketed)

- The development cost of X has already been recovered or the additional revenue generated by marketing X and Y at £30,000 will allow recovering profitably the part of the development cost of X not yet recovered.

If either of these two conditions were not verified, then the manufacturer would decide not to develop indication Y. In this case, it would also not be possible for the payer to impose the £30,000 price, as indication Y would not be available.

If the manufacturer markets indication Y first (at £30,000), then three different outcomes are possible.

- Indication X is not developed. This would be the outcome if the development cost of X were not be recoverable if it is marketed at £30,000

- Indication X is developed and marketed with Y at £30,000. This would be the outcome if the development cost of X were recoverable if it is marketed at £30,000 and this solution is not more profitable than that in the following point

- Indication X is developed and marketed at £120,000 whilst indication Y is withdrawn from the market. If the profit from this decision is larger than the profit from marketing both indications at £30,000, and if it is possible to withdrawn indication Y from the market, this will be the outcome.

Also in this case it would be impossible (or very difficult) for the payer to impose the £30,000 price as the manufacturer would be able to counteract it by withdrawing the lower-value indication.

If the patient population of the lower-value indication (Y) is large enough or if the value of indication Y "is not so low", then the manufacturer will find it more profitable to set the price at the lowest level.[35] For instance, if the population for indication Y is 7,000 patients rather than 5000, the outcome will be the one presented in Table A1.9. The total revenue for the manufacturer would be £270m and the manufacturer would prefer to set the lower price and serve the market for both indications rather than supplying the market for the higher-value indication only.

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[34] In the following analysis, we abstract from uncertainty, i.e. we assume that if an indication is researched, it will also be successfully developed and marketed.
[35] This result abstracts from the issues of international reference pricing or parallel trade. In reality, in a wider context it can happen that a manufacturer cannot set the lowest price in a market even if this is the most profitable option from its perspective. This is the case when other countries reference their price to that in that market or when parallel trade between that market and other countries is allowed.

Table A1.9: uniform pricing where both indications are cost-effective and the manufacturer prefers to supply the medicine for both indications

	Indication X	**Indication Y**
(A) QALYs per patient	4	1
(B) Price per treatment	£30,000	£30,000
(C) Patient population	2,000	7,000
(D = B × C) Cost for the payer/ revenue for the manufacturer	£60,000,000	£210,000,000
(E = A × C) Total QALYs generated	8,000	7,000

In this case, patient access and total QALYs gained would be the same as in the MIP scenario; however, the payer's expenditure would be lower compared with the MIP case.

Summary on conceptual analysis

This analysis illustrates different stakeholder perspectives.

From the patients' perspective:

- With MIP all the possible indications can be reimbursed (if deemed cost-effective)
- If MIP is not feasible, all the possible indications can be reimbursed, but only under some circumstances
- Under different circumstances, some indications might not be available, because either their price is not cost-effective (static context) or the manufacturer has not developed them (dynamic context).

From the payer's perspective:

- MIP implies the highest expenditure even if the prices for all the indications are cost-effective – because in some cases this could have been achieved at lower cost (i.e. when the price of the high-value indication is linked to the price of the low-value indication)

- In some circumstances, if uniform pricing is the only option (either because the payer uses its purchasing power to impose it and/or arbitrage cannot be prevented), the payer can reimburse all indications at a (low) cost-effective price such that expenditure is smaller than in the MIP case (again, because the price of the high-value indication is linked to the price of the low-value indication)

- Under other circumstances, if uniform pricing is the only option, the disbursement is lower than MIP because one of the indications is not available, to the detriment of patients

- However, under our assumptions, the number of patients treated and QALYs gained are maximised using MIP, both under the static and the dynamic framework, as well as in the situation of a "static, single, low-indication price".

The different outcomes from the payer's perspective under the different scenarios are illustrated in Table A1.10.[36]

[36] The outcomes represented in this table assume the values used to describe the baseline scenarios in this note: high-value indication: price £120,000, four QALYs per patient, 2,000 patients, development cost £100m; low-value indication: price

Table A1.10: outcomes under the different scenarios from the payer's perspective

	No. of patients treated	No. of QALYs gained	Cost
Static framework			
MIP	7,000	13,000	£390m
Single price, the manufacturer prefers to market the high-value indication	2,000	8,000	£240m
Single price, and the payer imposes the low-indication price	7,000	13,000	£210m
Dynamic framework – "no sequencing"			
MIP	7,000	13,000	£390m

From the manufacturer's perspective:

- MIP is the option that generates the highest revenue/margin, and is therefore the preferred one

- If MIP is not feasible and the R & D costs for the different indications are sunk (i.e. it is not considered how to recover the R & D costs), the manufacturer still sets the price at the level that maximises its revenue. However, if the chosen price is that of the higher-value indication, the lower-value indication will not be cost-effective and that market will be foreclosed, even if that indication has already obtained marketing authorisation

- If MIP is not feasible and the manufacturer has to decide which indications to develop (dynamic context), it will develop the indication that provides the highest margin. Three outcomes are possible when "sequencing" is not considered:
    - the higher-value indication is developed and priced at the higher price
    - the lower-value indication is developed and priced at the lower price
    - both indications are developed and priced at the lower price.

If the "sequencing" problem is considered, different outcomes are possible depending on which indication is developed first.

The necessary conditions for the different outcomes to arise in these contexts when MIP is not feasible are summarised in Table A1.11.

£30,000, one QALY per patient, 5,000 patients, development cost £100m.

Table A1.11: possible outcomes when MIP is not feasible

Outcomes	Static context	Dynamic context	
		"no-sequencing"	"sequencing"
High-value indication is marketed	The value of the lower-value indication is relatively small and the patient population is relatively small	The value of the lower-value indication is relatively small and the patient population is relatively small 13,000 £390m	1. The high-value indication is developed first and it is not profitable to develop the low-value indication and market both at the low-value price 2. The low-value indication is developed first but it is profitable to withdraw it from the market and launch the high-value indication at a higher price
Low-value indication is marketed	The patient population for the lower-value indication is large	The value of the lower-value indication is large enough and/or the patient population is large enough 8,000 £240m	The low-value indication is developed first and the cost to develop the high-value indication cannot be recovered at the low-value price
Both indications are marketed	The value of the lower-value indication is large enough and/or the patient population is large enough	1. The value of the lower-value indication is large enough and/or the patient population is large enough and 2. The development cost of the higher-value indication is small enough	1. The high-value indication is developed first and: a. The combined revenue from the two indications minus the development cost for the low-value indication will exceed the revenue from the high-value indication only, and b. The development cost of the high-value indication has already been recovered or the additional revenue generated by marketing both indications at the low-value price will allow recovering profitably the part of the development cost of the high-value indication not yet recovered 2. the low-value indication is developed first and: a. It is profitable to develop the high-value indication and market it at the low-value price. b. This is more profitable than withdrawing the low-value indication and supplying the high-value indication at a higher price

Third-degree price discrimination

The type of price discrimination by which different groups of customers are charged different prices for the same good is called third-degree price discrimination (Tirole, 1988; Varian, 1989). The conditions for a firm to be able to engage in third-degree price discrimination are:

1. The existence of some market power, i.e. a non-perfectly elastic demand curve for the product

2. The existence of market segments comprising groups of potential customers that differ in their willingness to pay (which may depend on purchasing power and/or tastes/preferences). In this case, the different markets of "customers" are represented by the markets for the different indications. In each market/indication, the willingness to pay will depend on the therapeutic value provided by the medicine for the specific indication

3. The firm's ability to tell which individual belongs in which group

4. The infeasibility of arbitrage.

In the market for pharmaceuticals, the satisfaction of the first condition is not trivial. On the one hand, the manufacturer has the monopolistic market power provided by patent protection and is the only supplier of a given medicine with different indications. On the other hand, in countries with a national payer, the payer has monopsonistic power. The payer can use this power to countervail the manufacturer power and require a single price across different indications.

The second condition is generally satisfied. Although in the case of pharmaceuticals it is often the case that the payer does not coincide with the user of a medicine, there exist different markets for different indications. And if the value provided to the different groups of patients is different for each indication, then the willingness to pay will also be different.

The third condition is not satisfied because of the nature of the supply chain of pharmaceuticals. Usually, manufacturers supply the medicines to wholesalers, who then provide the medicines to hospitals and pharmacies. If a medicine has multiple indications, it is unknown for which indication it will be used until a patient has consumed it. Therefore it is not possible for the manufacturers to identify for which group of patients (and for which indication) a medicine is used.

Because of the nature of the supply chain, also arbitrage cannot be prevented. A direct-to-consumer supply system (e.g. using wholesalers as agents) would allow the manufacturer to charge different prices for different indications. However, and in addition, international arbitrage (or parallel trade) is also likely to happen if price discrimination for different indications is not applied in a consistent way across different countries. Another form of (informational) arbitrage is international reference pricing, which limits the potentiality of price discrimination across indications.

Appendix 2: Analysis of "real-world" international experiences of MIP

Objectives and methods

While there can be a clear theoretical rationale supporting the implementation of MIP, little is known about the practical implementation of this approach in the real world.

In order to shed some light on how – if at all – MIP has been applied, we reviewed several potentially promising examples of medicines which are known to be approved for multiple indications, to verify how they have been priced in a number of countries.

At this stage, our geographic focus was primarily on health systems in which pharmaceutical prices are regulated; in particular, in our analysis we covered the five largest EU countries – France, Germany, Italy, Spain and the UK – and, outside the EU, Switzerland.

In the EU and Switzerland a drug manufacturer has two regulatory routes for a medicine which has the potential to be approved for multiple indications.

- They can file separate, sequential, multiple marketing authorisation applications, possibly under different brand names for separate groups of indications

- They can file just one marketing authorisation application for the initial indication(s) and then expand the range of approved indications, filing subsequent variations to the initially approved label.

In our analysis, we reviewed examples of both categories.

Also, in order to capture the latest trends and changes to pricing regulations (e.g. the introduction of the AMNOG (Arzneimittelmarkt-Neuordnungsgesetz or Pharmaceuticals Market Reorganisation Act) reform in Germany), we focused our analysis on relatively recent examples.

The list of products included in the analysis is presented in Table A2.1.

Table A2.1: Potential Examples of Multi-Indication Pricing – International Case Studies

Product	Therapy area	Rationale
Aflibercept	Multiple indications in oncology, ophthalmology	In the EU aflibercept is available as two distinct products, authorised and marketed under two different brand names Potential price differentiation possibly supported by differential branding in the two distinct therapeutic areas; further price differentiation theoretically possible within the individual disease areas
Alemtuzumab	Onco-haematology, multiple sclerosis	In this case the manufacturer did not feel comfortable leaving the older product (Mab-Campath in onco-haematology) on the market and withdrew it to protect pricing of the second one (Lemtrada in MS), which they had judged to be commercially more promising This might provide a manufacturer's perspective on the size of a price differential judged "unmanageable"
Bevacizumab	Multiple indications in oncology	Potential differential pricing in this case is within the same therapeutic area (oncology) for different cancer types/lines of therapy, all treated with the same product (no brand differentiation)
Certolizumab pegol	Multiple indications in rheumatology	Potential differential pricing in this case is within the same therapeutic area (rheumatology) for different indications/patient populations, all treated with the same product (no brand differentiation)
Cetuximab	Multiple indications in oncology	Potential differential pricing in this case is within the same therapeutic area (oncology) for different cancer types/lines of therapy, all treated with the same product (no brand differentiation)
Everolimus	Multiple indications in solid organ transplants, oncology and rare diseases	In the EU everolimus is available as three distinct products, authorised and marketed under three different brand names Potential price differentiation possibly supported by differential branding in each distinct therapeutic area; further price differentiation theoretically possible within the oncology disease area

Source: authors' analyses from publicly available information.

For all case studies the analysis was based on information available in the public domain as of December 2014 (for pricing information) and January 2015 (for other key product information). All sources used for the pricing information and exchange rates are reported at the end of Appendix 2.

Concerning the pricing information, for France, Germany, Italy, Spain and Switzerland the focus was on official ex-factory prices as published in the relevant national databases and/or official journals/gazettes. For the UK, estimated ex-factory prices were calculated on the basis of the NHS/list prices published on the MIMS UK, based on the following formula, generally used to convert NHS prices to ex-factory prices in the context of international reference pricing schemes broadly applied in the majority of the EU, in Switzerland and in other countries (e.g. Canada): NHS price × 0.875.

Where possible, also official net selling prices (i.e. official ex-factory prices minus mandatory discounts as published in sources available in the public domain) were reviewed and analysed. For all price levels, prices per mg of active substance in the different indications/for the different medicinal products were compared.

All prices expressed in local currencies were converted in GBP applying the average exchange rates of the 90 days from 6 September–4 December 2014 as published in OANDA (http://www.oanda.com/ [accessed 5 December 2014]).

Key findings

We now present the key findings for each of the medicines in Table A2.1

Aflibercept

Aflibercept is marketed in the EU and Switzerland as two separate products, under the brand names Eylea in the ophthalmological indications and Zaltrap in the oncological indications. The two medicinal products were developed almost simultaneously for their respective indications. Eylea and Zaltrap were approved by the EMA on 22 November 2012 and 1 February 2013 respectively. Interestingly, they are also marketed by different pharmaceutical companies: Eylea is commercialised by Bayer, while Zaltrap is commercialised by Sanofi-Aventis.

Characteristic	Eylea	Zaltrap
Manufacturer	Bayer Pharma	Sanofi-Aventis
EMA approval date	22 November 2012	1 February 2013
Approved indications	Eylea is indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) and visual impairment due to diabetic macular oedema (DME)	Zaltrap in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy is indicated in adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen
Dose	2 mg aflibercept per injection, equivalent to 50 μl Wet AMD: 1 injection per month for 3 consecutive doses, followed by 1 injection every 2 months Macular oedema due to CRVO: After the initial injection, treatment is given monthly DME: one injection per month for five consecutive doses, followed by one injection every two months	4 mg/kg of body weight IV infusion over 1 hour, followed by the FOLFIRI regimen The treatment cycle is repeated every 2 weeks
Authorised presentations	Solution for intravitreal injection in 40 mg/ml pre-filled syringes and 40 mg/ml solution in vials	Solution for IV infusion in 100 mg in 4 ml vial (25 mg/ml) per vial (pack size 1 and 3) and 200 mg in 8 ml vial (25 mg/ml) per vial
Nature of the active substance	Aflibercept is a fusion protein consisting of portions of human VEGF (vascular endothelial growth factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology	

Source: MME elaboration based on the approved SmPCs of the products published on the EMA website: Eylea: http://www. ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002392/WC500135815.pdf [accessed January 2015]; Zaltrap: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/ human/002532/WC500139484.pdf [accessed January 2015]

The average official ex-factory price per milligram of Eylea in the five largest EU countries and Switzerland is GBP 176.66. The average official ex-factory price per mg of Zaltrap in the same countries is GBP 2.95.

Taking into account mandatory price discounts, the average net ex-factory price per mg of Eylea in the five largest EU countries and Switzerland is GBP 167.04. The average net ex-factory price per mg of Zaltrap in the same countries is GBP 2.67.

Despite being based on the same active substance, and being both liquid, injectable formulations, the price per milligram of Eylea is almost 59 times higher than the price of Zaltrap if official ex-factory prices are considered, and almost 62 times higher if net ex-factory prices are considered.

Concerning the available evidence of confidential discounts and other arrangements influencing the pricing of Eylea and Zaltrap for specific countries, we found that:

- For Eylea:
  - The visible ex-factory price in Italy is subject to a confidential additional discount (on top of the mandatory price cuts) for sales to institutions belonging to the Italian NHS
  - In the UK, the product is recommended for use under the NHS in England and Wales (for the treatment of wet AMD and macular oedema due to CRVO) and in Scotland (for all approved indications), only on condition that a confidential discount under a patient access scheme (PAS) is granted to the NHS
  - No relevant evidence could be found with regard to possible confidential discounts in France, Germany, Spain and Switzerland

- For Zaltrap:
  - In Italy, the product is subject to both a confidential cost-sharing agreement and a confidential discount (on top of the mandatory price cuts) for sales to institutions belonging to the Italian NHS
  - In the UK, the product was available in England with funding from the Cancer Drug Fund (CDF)[37] and with a PAS; in Scotland, use on the NHS is recommended only with a PAS. Finally, Wales announced that its appraisal was scheduled for December 2014, but no decision had been published at the time of preparing this paper
  - No relevant evidence could be found with regard to possible confidential discounts in France, Germany, Spain and Switzerland

Alemtuzumab

The first medicinal product based on alemtuzumab was licensed and marketed (initial EMA approval in July 2001) under the brand name MabCampath; the marketing authorisation holder was Genzyme. Following this initial approval, Genzyme initiated the development of alemtuzumab for the treatment of multiple sclerosis. In February 2011, Genzyme was acquired by Sanofi-Aventis.[38] In August 2012 MabCampath was withdrawn from all markets, remaining exclusively available for individual patients

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[37] Zaltrap as a second line treatment for metastatic colorectal cancer was available under the CDF. However, on 12 January 2015, NHS England delisted the drug from the CDF, so it will no longer be funded by the NHS. The change, which came into effect on 12 March 2015, does not apply to patients already receiving treatment via the CDF, which was set up in 2010, to provide patients access to a number of cancer drugs not routinely available on the NHS.

[38] Source: Wall Street Journal, at http://www.wsj.com/articles/SB10001424052748703373404576147483489656732 [accessed December 2014].

on a compassionate-use, free-goods basis. Finally, in September 2013 alemtuzumab received a marketing authorization for multiple sclerosis from the EC, as Lemtrada.

Characteristic	Lemtrada	MabCampath
Manufacturer	Genzyme (now part of Sanofi-Aventis)	Genzyme (now part of Sanofi-Aventis)
EMA approval date	12 September 2013	6 July 2001; withdrawn August 2012
Approved indications	Treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features	Treatment of patients with B-cell chronic lymphocytic leukaemia (BCLL) for whom fludarabine combination chemotherapy is not appropriate
Dose	Initial treatment course: 12 mg/day for 5 consecutive days (60 mg total dose) Second treatment course: 12 mg/day for 3 consecutive days (36 mg total dose) administered 12 months after the initial treatment course	Initial dose escalation: 3 mg on day 1, 10 mg on day 2 and 30 mg on day 3 assuming each dose is well tolerated Thereafter, the recommended dose is 30 mg daily administered 3 times weekly on alternate days up to a maximum of 12 weeks
Authorised presentations	12 mg alemtuzumab in 1.2 ml (10 mg/ml) per vial for IV infusion	30 mg alemtuzumab in 1 ml vial (30 mg/ml) for IV infusion 30 mg alemtuzumab in 3 ml ampoule (10 mg/ml) for IV infusion
Nature of the active substance	Alemtuzumab is a monoclonal antibody produced in mammalian cell (Chinese hamster ovary) suspension culture in a nutrient medium by recombinant DNA technology	

Source: MME elaboration based on the approved SmPCs of the products published on the EMA website: Lemtrada: http://www. ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003718/WC500150521.pdf [accessed January 2015]; MabCampath: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000353/WC500025270.pdf [accessed January 2015]

At the time of its withdrawal, the average official ex-factory price per mg of MabCampath in the five largest EU countries and Switzerland was GBP 3.54. The average official ex-factory price per mg of Lemtrada in the same countries is GBP 578.00.[39]

Taking into account mandatory price discounts, the average net ex-factory price per mg of MabCampath in the five largest EU countries and Switzerland was GBP 3.49. The average net ex-factory price per mg of Lemtrada in the same countries is GBP 578.00.[40]

39   As of December 2014, Lemtrada had only completed initial pricing procedures in Germany and in the UK.
40   Given the current pricing status of Lemtrada, no visibly quantifiable mandatory discounts are at the moment applicable in the countries in which a price has been set.

MabCampath and Lemtrada are both liquid, injectable formulations, for IV infusions. If official ex-factory prices are considered, the price per mg of Lemtrada is 162 times higher than the latest price of MabCampath and 166 times higher if net ex-factory prices are considered.

Concerning the available evidence of confidential discounts and other arrangements influencing the pricing of Lemtrada and MabCampath for specific countries, we found that:

- For MabCampath:
  - In Italy the product was subject to an annual budget cap, with mandatory paybacks in case of "excessive" sales
  - No relevant evidence could be found with regard to possible confidential discounts in the other countries covered in the analysis

- For Lemtrada:
  - No relevant evidence could be found with regard to possible confidential discounts in any of the countries reviewed.

Bevacizumab

Bevacizumab is globally licensed and commercialised under the brand name Avastin for all its approved indications.

It received its initial EMA approval on 12 January 2005, for use in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan for the first-line treatment of patients with metastatic carcinoma of the colon or rectum.

The product received subsequent licenses for multiple additional indications in other tumour types, in combination with other agents and in additional lines of treatment. The latest approved indication, granted by the EC in July 2014, was: in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin, for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor–targeted agents.

Characteristic	Avastin
Manufacturer	Roche
EMA approval date	12 January 2005
Approved indications	In combination with fluoropyrimidine-based chemotherapy indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum (mCRC) In combination with paclitaxel indicated for first-line treatment of adult patients with metastatic breast cancer (mBC) In combination with capecitabine indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not appropriate In addition to platinum-based chemotherapy, indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology In combination with interferon alfa-2a indicated for first-line treatment of adult patients with advanced and/or metastatic renal cell cancer (mRCC) In combination with carboplatin and paclitaxel indicated for the front-line treatment of adult patients with advanced FIGO stages III B, III C and IV epithelial ovarian, fallopian tube or primary peritoneal cancer In combination with carboplatin and gemcitabine, indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents In combination with paclitaxel, topotecan or pegylated liposomal doxorubicin indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents
Dose	mCRC: 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks mBC: 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion NSCLC: 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion mRCC: 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion Epithelial ovarian, fallopian tube and primary peritoneal cancer: ● Front line: Avastin is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. Dose is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion ● Platinum-sensitive recurrent disease: In combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of Avastin as single agent until disease progression. Dose is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion ● Platinum-resistant recurrent disease: in combination with one of the following agents: paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. Dose is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion. When Avastin is administered in combination with topotecan (given on days 1–5, every 3 weeks), the recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks
Authorised presentations	100 mg/4 ml (25 mg/ml) vial and 400 mg/16 ml (25 mg/ml) vial, for IV infusion
Nature of the active substance	Bevacizumab is a recombinant humanised monoclonal antibody produced by DNA technology in Chinese hamster ovary cells

No differential pricing by indication exists at the official ex-factory price level.

Concerning the available evidence of confidential discounts and other arrangements influencing the net pricing of Avastin for specific countries, we found that:

- In France, after an initial phase in which visible ex-factory prices remained stable, several price cuts occurred in September 2011, January 2012, October 2013 and June 2014; interestingly, the first series of price cuts (2011–2012) was published in the Journal officiel only four months after the Transparency Committee had published its final assessment of Avastin in the breast cancer indication, stating that the product was bringing no additional benefit in that indication (ASMR V;[41] an earlier, 2007, assessment in the same indication had concluded that there was a moderate additional benefit, with an ASMR III)

- In Italy the product is subject to mandatory inclusion of patients in indication-specific registries maintained by the AIFA (Italian medicines agency) for all its approved indications except for breast and colorectal cancer (CRC); risk-sharing agreements apply on an indication-by-indication basis for all indications; a specific additional 7 per cent discount applies to the product when used in advanced CRC; also, an annual budget cap, with mandatory paybacks in case of "excessive" sales, applies in the latter indication; no reimbursement is as yet applicable in the case of use in platinum-resistant ovarian cancer

- In the UK, in England Avastin was only available, under certain conditions, in breast cancer, ovarian cancer (first-line and recurrent, platinum-sensitive) and advanced CRC, with funding from the Cancer Drug Fund;[42] apart from the above, the product is not recommended by either NICE or the SMC for routine use under the NHS

- In Switzerland, a cost-sharing agreement is in place for use of Avastin in breast cancer and in renal cell carcinoma, with Roche rebating different amounts on a per-mg basis in the two indications; in lung cancer, the product is only reimbursed if the low dose regimen (7.5 mg/kg) is used; no special conditions are publicly known regarding the other approved indications of the product

- No relevant evidence could be found with regard to possible confidential discounts in the other countries covered in the analysis.

Certolizumab pegol

Certolizumab pegol is licensed and commercialised under the brand name Cimzia. Cimzia received its initial EMA approval in October 2009, in combination with methotrexate, for the treatment of moderate to severe active rheumatoid arthritis (RA), in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate. Also monotherapy with Cimzia is allowed in case of intolerance to methrotrexate or when continued treatment with The product received subsequent licenses for the additional indications of axial spondyloarthritis (with and without ankylosing spondylitis) and psoriatic arthritis.

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[41] ASMR: amélioration du service médical rendu, improvement of medical benefit.
[42] Avastin as a first-line treatment for advanced bowel cancer and as a second-line treatment for advanced epithelial, ovarian, fallopian tube or primary peritoneal cancers was available under the CDF. However, on 12 January 2015, NHS England delisted the drug from the CDF, so it will no longer be funded by the NHS. The change, which came into effect on 12 March 2015, does not apply to patients already receiving treatment via the CDF.

Characteristic	Cimzia
Manufacturer	Merck KGaA
EMA approval date	1 October 2009
Approved indications	Rheumatoid Arthritis:
	Cimzia, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate
	Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate
	Axial spondyloarthritis:
	Cimzia is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:
	Ankylosing spondylitis (AS):
	Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSAIDs)
	Axial spondyloarthritis without radiographic evidence of AS:
	Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs
	Psoriatic arthritis:
	Cimzia, in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate
	Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate
Dose	Loading dose (all indications):
	The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4
	Maintenance dose:
	Rheumatoid arthritis:
	After the starting dose, the recommended maintenance dose of Cimzia for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia where appropriate
	Axial spondyloarthritis:
	After the starting dose, the recommended maintenance dose of Cimzia for adult patients with axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks
	Psoriatic arthritis:
	After the starting dose, the recommended maintenance dose of Cimzia for adult patients with psoriatic arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia where appropriate
Authorised presentations	200 mg per ml solution for injection, in pre-filled syringes; for subcutaneous use
Nature of the active substance	Certolizumab pegol is a recombinant, humanised antibody Fab' fragment against tumour necrosis factor alpha (TNFα) expressed in Escherichia coli and conjugated to polyethylene glycol (PEG)

Source: MME elaboration based on the approved SmPCs of the products published on the EMA website: Cimzia: http://www. ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001037/WC500069763.pdf [accessed January 2015]

No differential pricing by indication exists at the official ex-factory price level.

Concerning the available evidence of confidential discounts and other arrangements influencing the net pricing of Cimzia for specific countries, we found that:

- In Italy the product is subject to mandatory inclusion of patients in indication-specific registries maintained by the AIFA (Italian medicines agency) for its initial indication in active RA; confidential discounts are in place in case of sales to institutions belonging to the Italian National Health Service. At the moment, pricing and reimbursement procedures for the two additional indications in axial spondyloarthritis and psoriatic arthritis are still ongoing

- In the UK:
  - In England, the product is recommended as an option in active RA, if used in line with the use of other TNF inhibitors approved in RA (NICE technology appraisal guidance (TA130)); in this context, the product is subject to a patient access scheme (PAS), whereby the first twelve weeks of treatment are provided for free to all new patients. NICE guidance on the use of the product in axial spondyloarthritis is expected to be published in July 2015, while use in psoriatic arthritis was not considered appropriate for a NICE technology appraisal
  - In Scotland, the product is recommended for restricted use in all its approved indications, subject to the application of a PAS (conditions remain confidential)

No relevant evidence could be found with regard to possible confidential discounts in the other countries covered in the analysis.

Cetuximab

Cetuximab is licensed and commercialized under the brand name Erbitux. Erbitux received its initial EMA approval in June 2004, in combination with irinotecan, for the treatment of patients with EGFR[43] -expressing metastatic CRC, who had failed an irinotecan-including cytotoxic therapy.

The product received subsequent licenses for additional regimens and lines of treatment in CRC and for the treatment of patients with squamous cell cancer of the head and neck (see Appendix 3 for full details).

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[43] EGFR: epidermal growth factor receptor.

Characteristic	Erbitux
Manufacturer	Merck KGaA
EMA approval date	29 June 2004
Approved indications	Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer - in combination with irinotecan-based chemotherapy - in first line in combination with FOLFOX - as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck - in combination with radiation therapy for locally advanced disease - in combination with platinum-based chemotherapy for recurrent and/or metastatic disease
Dose	In all indications, Erbitux is administered once a week. The initial dose is 400 mg cetuximab per m2 body surface area. All subsequent weekly doses are 250 mg cetuximab per m2 each
Authorised presentations	100 mg cetuximab in 20 ml (5 mg/ml) per vial and 500 mg cetuximab in 100 ml (5 mg/ml) per vial, for IV infusion
Nature of the active substance	Cetuximab is a chimeric monoclonal IgG1 antibody produced in a mammalian cell line (Sp2/0) by recombinant DNA technology

Source: MME elaboration based on the approved SmPCs of the products published on the EMA website: Erbitux: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000558/WC500029119.pdf [accessed January 2015]

No differential pricing by indication exists at the official ex-factory price level.

Concerning the available evidence of confidential discounts and other arrangements influencing the net pricing of Erbitux for specific countries, we found that:

- In Italy the product is subject to mandatory inclusion of patients in indication-specific registries maintained by the AIFA (Italian medicines agency) for its three most recent indications (metastatic CRC in combination with FOLFOX, first-line and in monotherapy in irinotecan failures; head and neck cancer, in combination with platinum-based chemotherapy); payment by results and/or cost-sharing agreements apply for all indications except head and neck cancer, in combination with radiotherapy; a specific additional 5 per cent discount applies to the product when used in metastatic CRC, in combination with irinotecan; also, an annual budget cap, with mandatory paybacks in case of "excessive" sales, applies in the latter indication

- In the UK, only two indications are recommended for use on the NHS:
    - In England, the product is recommended in combination with FOLFOX, for the first-line treatment of metastatic CRC, subject to a 16 per cent rebate on a per-patient basis and other conditions;[44] for the same indication, a similar recommendation is in place in Scotland (although only a generic PAS is mentioned there)

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[44] Erbitux as a second- or third-line treatment for metastatic colorectal cancer was also available under the CDF. However, on 12 January 2015, NHS England delisted the drug from the CDF, so it will no longer be funded by the NHS. The change, which came into effect on 12 March 2015, does not apply to patients already receiving treatment via the CDF.

- The second indication recommended on the NHS in both England and Scotland is for use in head and neck cancer, in combination with radiotherapy: no mention is made of PAS or other price arrangements with regard to this indication in either England or Scotland

No relevant evidence could be found with regard to possible confidential discounts in the other countries covered in the analysis.

Everolimus

Everolimus is marketed in the EU and Switzerland as three separate products, under the brand names Certican, for the management of rejection in solid-organ transplants; Afinitor, for several oncological indications; and Votubia, for two rare disease conditions, for which the product also obtained orphan drug designations.

Certican was developed in the late 1990s–early 2000s and was registered using the Mutual Recognition Procedure (first approval in Sweden dates back to 2003), while Afinitor and Votubia were approved by the EMA on 3 August 2009 and 2 September 2011 respectively (both were centralised procedures). All three brands of everolimus are commercialised by the same company, Novartis, which presumably implies a coordinated approach to the pricing of these products.

Characteristic	Certican	Afinitor	Votubia
Manufacturer	Novartis		
EMA approval date	Certican received its first approval in the EU from the Swedish Medical Products Agency in July 2003; in December 2003 approval was extended to fourteen more countries via the MRP. In December 2004, approval was extended to the ten "new accession countries" that had joined the EU on 1 May 2004	3 August 2009	2 September 2011
Approved indications	Kidney and heart transplant: Certican is approved for the prevention of rejection episodes in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. Certican should be used in combination with ciclosporin for microemulsion and corticosteroids Liver transplant: Certican is approved for the prevention of rejection episodes in adult receiving an allogeneic liver transplant. Certican should be used in combination with tacrolimus and corticosteroids	Hormone receptor-positive advanced breast cancer: for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in post-menopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor Neuroendocrine tumours of pancreatic origin: for the treatment of unresectable or metastatic, well-differentiated or moderately differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease Renal cell carcinoma: for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy	Renal angiomyolipoma associated with tuberous sclerosis complex (TSC): for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications, but who do not require immediate surgery Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC): for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention, but are not amenable to surgery
Dose	Starting dose: Kidney and heart transplant in adults: 0.75 mg twice daily Liver transplant: 1 mg twice daily The dose should be adjusted based on target blood concentrations, tolerability, individual response and clinical situation	10 mg once daily; if dose reduction is required, the recommended dose is 5 mg daily	Renal angiomyolipoma associated with tuberous sclerosis complex (TSC): 10 mg once daily Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC): Starting dose: 4.5 mg/m2; dose titration based on target trough concentrations of everolimus
Authorised presentations	Tablets: 0.25 mg, 0.5 mg and 0.75 mg Dispersible tablets: 0.1 mg and 0.25 mg	Tablets: 2.5 mg, 5 mg and 10 mg	Tablets: 2.5 mg, 5 mg and 10 mg Dispersible tablets: 2 mg, 3 mg and 5 mg
Nature of the active substance	Everolimus is a proliferation signal inhibitor	Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor	Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor

Source: MME elaboration based on the approved SmPCs of the products published on the EMA website (Afinitor and Votubia)

and on the website of the Swedish Medicines Compendium-FASS (Certican). Afinitor: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001038/WC500022814.pdf [accessed January 2015]; Votubia: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002311/WC500112238.pdf [accessed January 2015]; Certican: http://www.fass.se/LIF/product?4&docType=3&specId&userType&nplId=20030718000430 [accessed March 2015]

The average official ex-factory price per mg of Certican in the five largest EU countries and Switzerland is GBP 6.98.[45] In the same countries, the average official ex-factory price per mg of Afinitor is GBP 9.26, while the average official ex-factory price per mg of Votubia is GBP 13.77.

Taking into account mandatory price discounts, the average net ex-factory price per mg of Certican in the five largest EU countries and Switzerland is GBP 6.39. In the same countries, the average net ex-factory price per mg of Afinitor is GBP 8.87 while the average net ex-factory price per mg of Votubia is GBP 13.47.[46]

Therefore, the price per mg of Votubia is almost twice the price of Certican if official ex-factory prices are considered and is more than twice the price of Certican if net ex-factory prices are considered.

Concerning the available evidence of confidential discounts and other arrangements influencing the pricing of Certican, Afinitor and Votubia for specific countries, we found that:

- For Certican:
    - No relevant evidence could be found with regard to possible confidential discounts in any country
- For Afinitor:
    - In Italy, the product is subject to both a confidential payment-by-results agreement and a confidential discount (on top of the mandatory price cuts) for sales to institutions belonging to the Italian NHS, for the two indications of hormone receptor-positive advanced breast cancer and neuroendocrine tumours of pancreatic origin; no such arrangements exist instead for the renal cell carcinoma indication
    - In the UK, the product was available in England with funding from the Cancer Drug Fund for all approved indications and with a PAS;[47] in Scotland, use on the NHS is recommended only for the two indications of renal cell carcinoma and neuroendocrine tumours of pancreatic origin, with no mention of a PAS
    - No relevant evidence could be found with regard to possible confidential discounts in France, Germany, Spain and Switzerland
- For Votubia:
    - In the UK, the product has not been appraised by NICE in England; in Scotland, the manufacturer did not submit any reimbursement applications to the SMC, thus receiving negative reimbursement recommendations for both approved indications
    - No relevant evidence could be found with regard to possible confidential discounts in France, Germany, Spain and Switzerland; at the time this report was prepared (6 March 2015) the product has yet to complete pricing and reimbursement procedures in Italy.

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[45] Certican is not approved in the UK.
[46] Votubia is not yet priced and reimbursed in Italy.
[47] However, on 12 January 2015, NHS England delisted the drug from the CDF in the renal cell carcinoma and advanced breast cancer indications, so it will no longer be funded by the NHS for these uses. The change, which came into effect on 12 March 2015, does not apply to patients already receiving treatment via the CDF.

Discussion

Our examples suggest that MIP seems practically applicable, at least in certain countries and subject to a number of conditions.

Especially in the case of drugs approved as differently branded medicines in different disease areas, a large price difference seem to be achievable at the official ex-factory price level as well as at the net ex-factory price level and this has been verified in all of the countries included in the analysis.

However, a possible limitation to the practicability of MIP is related to the formulation of the different medicines based on the same active substance.

- In the case of aflibercept, not only were the two products formulated in different concentrations, but also the route of administration was different, thus creating better conditions for the implementation of MIP.

- In the case of alemtuzumab, one of the two formulations available for the older product had exactly the same concentration as the second product supposed to be used (and priced) in the "higher-value" (on a per mg basis) indication, thus posing a significant challenge to MIP and, possibly, determining the company's decision to withdraw the older product from the market in order not to endanger the pricing of the second, commercially more attractive, one.

- In the case of multiple indications approved for the same branded medicine, MIP (in some form) seems to be possible in some countries, including Italy and the UK.

- Other countries, such as France, seem to prefer a "blended" pricing approach, with across-the-board price adjustments applied when the composite value and volume of patients of the product – considering the full range of its approved indications and uses – changes over time as a consequence of the availability of new clinical evidence and new indications.

- Also in Germany a "blended" pricing approach seems to have been consistently applied in the context of the national pricing negotiations that have been introduced with the 2010 reform known as AMNOG; however, theoretically, potential for the application of differential net pricing at the individual indication level may exist in the context of sub-national pricing negotiations with individual statutory health insurances, which may ensue following the completion of the national pricing procedure.

Sources of pricing and HTA information used for the international case studies and currency exchange rates

1. France:
   - Thériaque www.theriaque.org
   - HAS http://www.has-sante.fr/portail/jcms/fc_1249588/en/accueil

2. Germany:
   - ABDA Datenbank, accessed through Pharmazie.com www.pharmazie.com

3. Italy:
   - AIFA reimbursement drug lists www.agenziafarmaco.gov.it
   - Farmadati Database www.farmadati.it

4. Spain:
   - Portalfarma Drug database www.portalfarma.com

5. UK:
   - MIMS UK www.mims.co.uk
   - NICE http://www.nice.org.uk/
   - SMC http://www.scottishmedicines.org.uk/Home

6. Switzerland
   - Spezialitätenliste http://bag.e-mediat.net/SL2007.Web.External/

Exchange rates used for the analysis: 90 days average, 6 Sept.–4 Dec. 2014	
EUR/GBP	0.7897
CHF/GBP	0.6547

Source: OANDA (http://www.oanda.com/ accessed 5 December 2014)t

Appendix 3: Workshop attendees

Allan Wailoo, Professor of Health Economics, University of Sheffield; Director of NICE Decision Support Unit
Anne Lee, Chief Pharmacist, Scottish Medicines Consortium
Christine Gilmour, Co-chair of the Scottish Patient Access Scheme Assessment Group and Chief Pharmacist at NHS Lanarkshire
James Raftery, Professor of Health Technology Assessment, University of Southampton
Jane Page, Regional Specialist Pharmacist (Procurement), East Midlands; PASLU
Leela Barham, Independent Consultant
Mark Verrill, Consultant Medical Oncologist, Head of the Department of Medical Oncology, Freeman Hospital, Newcastle upon Tyne
Martin Buxton, Emeritus Professor of Health Economics, Brunel University
Meindert Boysen, Programme Director Technology Appraisals, PASLU and HST, NICE
Mike Drummond, Managing Director, Drummond Health Economics Ltd; Professor of Health Economics, University of York
Pedro Pita-Barros, Professor of Economics, Universidade Nova de Lisboa
Adrian Towse, Director, OHE (Workshop Chair)
Jorge Mestre-Ferrandiz, Director of Consulting, OHE
Renato Dellamano, President, MME Europe

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About the Office of Health Economics

Founded in 1962, the OHE's terms of reference are to:

- commission and undertake research on the economics of health and health care

- collect and analyse health and health care data for the UK and other countries, and

- disseminate the results of this work and stimulate discussion of them and their policy implications.

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The views expressed in this publication are those of the author and do not necessarily represent those of the OHE.