INDICATION-SPECIFIC PRICING OF PHARMACEUTICALS IN THE UNITED STATES HEALTH CARE SYSTEM

A Report from the 2015 ICER Membership Policy Summit

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2015 ICER Policy Summit:
Indication-specific Pricing in the United States Health Care System

Purpose

The 2015 ICER Policy Summit convened an influential group of evidence policy leaders from insurers, pharmacy benefit management firms, and life science companies to discuss indication-specific pricing (ISP) of biopharmaceuticals and to explore the opportunities and challenges of ISP in the US health care system.

Participants

Held from December 9-11, 2015 the Policy Summit brought together 44 health care leaders from 22 payer and life sciences organizations. ICER staff developed a background paper on ISP prior to the meeting to provide participants with a common foundation in some of the key conceptual and practical issues. To create an environment of frank, open discussion the Summit was held under the "Chatham House Rule" whereby participants are able to share comments and perspectives heard at the meeting, but commit to not identifying the person or organization making the statement.[1]

Payer Organizations: Aetna, Association of Health Insurance Plans, Anthem, Blue Shield of California, CVS Caremark, Express Scripts, Harvard Pilgrim Healthcare, Kaiser Permanente, OmedaRx, Premera, United Healthcare

Life Sciences Organizations: AstraZeneca, Bristol Myers-Squibb, Eli Lilly, Genentech, GlaxoSmithKline, Johnson & Johnson, Merck, National Pharmaceutical Council, Novartis, Pfizer, Takeda

Report

This report provides a synthesis of insights collected from the literature, pre-meeting conversations with experts, and discussions held during the Policy Summit. It first presents different examples of indication-specific pricing, and then summarizes the potential benefits and risks for both payers and manufacturers. Lessons learned from ISP in international markets are examined. The main focus of the paper, however, is to analyze the barriers and potential solutions for efforts to implement ISP initiatives in the US. This analysis is accompanied by a set of recommendations for future consideration by payers, manufacturers, and policymakers. Importantly, no assertion, judgment, or recommendation included in this report should be viewed as representing the opinion of any participant or their company. In keeping with Chatham House Rules, insights in this paper are not linked to any individual person or company. A manuscript version of this white paper will be developed at a future date and submitted to a peer-reviewed journal.

What is ICER?

The Institute for Clinical and Economic Review (ICER) is a non-profit organization that evaluates evidence on the value of medical tests, treatments and delivery system innovations and moves that evidence into action to improve the health care system. To accomplish this goal ICER performs analyses on effectiveness and costs; develops reports using innovative methods that make it easier to translate evidence into decisions; and, most distinctively, fills a critical gap by creating sustainable initiatives with all health care stakeholders to use evidence to drive improvements in both practice and policy. Through all its work, ICER seeks to play a pivotal role in creating a future in which collaborative efforts to move evidence into action provide a foundation for a more effective, efficient, and just health care system.

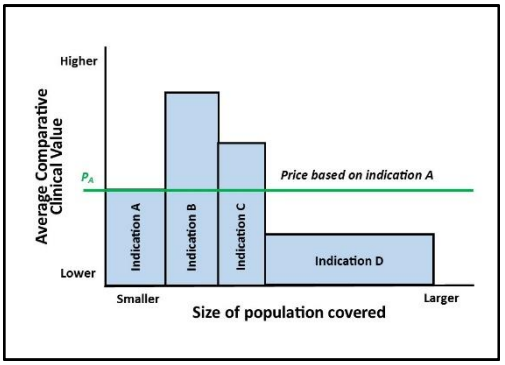
Executive Summary
2015 ICER Policy Summit

Indication-specific Pricing of Pharmaceuticals in the US Health Care System

The Institute for Clinical and Economic Review (ICER) held a Policy Summit on December 9 – 11, 2015 with 44 health care leaders from the 22 payer and life sciences organizations that comprise the ICER membership group. The purpose of the meeting was to explore the potential value of indication-specific pricing (ISP) of pharmaceuticals for both payers and life science companies and to discuss prospects for its implementation in the US health care system.

What is Indication-specific Pricing?

ISP involves setting different prices for different indications or for distinct patient subpopulations eligible for treatment with a medication. The relative clinical benefit of a drug can vary widely between different indications or between different subpopulations within the same indication. However, despite different clinical benefit across indications, the reimbursement system in the United States, rooted in a history of pricing by dosing unit, assigns a single uniform price to a drug, no matter how it is used. As a result, price and clinical value do not necessarily align well across multiple indications. With multi-indication drugs on the rise, it is important for payers and manufacturers to consider the options through which pricing can better reflect differential benefit by indication.



The Potential Benefits and Risks of Indication-specific Pricing

	Potential Benefits	Potential Risks
Payers	• Offers new mechanism to facilitate patient access to medications within a model that seeks to balance payer needs for affordability and manufacturer needs for sustainability • Aligns with value-based drug pricing and benefit designs • Offers potential to save the system money and facilitate patient access to medications • Allows more appropriate pricing for lower value follow-on indications • Provides an opportunity to demonstrate commitment to considering overall health system costs in assigning prices to different indications • Highlights competitive advantage in innovative thinking about value-based pricing mechanisms	• Administrative burden of implementation may be greater than anticipated • Could have minimal impact on overall affordability or even increase costs • Could be difficult to explain to patients and stakeholders and may raise concerns if not tied to lower out of pocket costs for patients

	Potential Benefits	Potential Risks
Manufacturers	• Offers new mechanism to facilitate patient access to medications within a model sensitive to payer needs for affordability and manufacturer needs for sustainability • Provides incentive to develop indications for small populations while protecting existing price in high-value indications • Aids decision-making regarding pipeline prioritization • Supports rationale for higher prices for secondary indications that provide greater clinical benefits • Addresses payer resistance to new indications • Demonstrates commitment to changes that will impact the sustainability of health care and decrease overall health system costs	• Payers may be reluctant to acknowledge added clinical value, may limit access to new, higher-value indications • May support efforts to link drug prices to a standard of clinical value that constrains pricing power • Potential conflict with other pricing policies in including Medicaid Best Price and average sales price (ASP) • Potential risk for arbitrage by purchasers of the drug • Reduces potential return for development of "lower value" secondary indications

Models of Indication-specific Pricing

1.) **Distinct product differentiation, authorized and marketed under different brand names with different prices.** For example, Sildenafil is marketed as two branded products - Viagra® for erectile dysfunction and Revatio® for pulmonary arterial hypertension.[2,3]

2.) **No brand differentiation, distinct, separate discounts are applied for each indication**. For example, Italy uses indication-specific patient registries to track medication usage and collect patient data with different risk sharing agreements for each indication.[4]

3.) **No brand differentiation, a single "weighted-average" price is developed using estimates of indication use across the population, with possible retrospective reconciliation through rebates based upon actual use.** For example, Australia uses a single weighted average price for multi-indication drugs covered under the government-sponsored drug benefit.[5,6]

Implementation Challenges

Despite the intrinsic appeal of a pricing system sensitive to differences in clinical value across indications, and some positive international experience, as noted above there remain many risks for both payers and manufacturers. There are also multiple administrative, legal, and regulatory challenges that currently darken the prospects for ISP in the US.

Complex drug purchasing and delivery systems. The multiple pathways and intermediaries involved in drug purchasing and delivery in the US make linking prices with indications extremely difficult in practice.

Limitations of drug formulary tier structure and difficulty linking ISP to differential patient cost-sharing. Drug formularies may not have the capability to place the same drug in different tiers according to indication (i.e., high value indication in a preferred tier and low value indication in a non-preferred tier). But, in principle, patients prescribed a drug that they need for a "lower" value indication should not always bear greater cost-sharing than patients prescribed the same drug for a "higher" value indication. Administrative challenges of more flexible formulary designs may make it difficult to align patient cost-sharing with value-based pricing in a transparent fashion.

Insufficient data systems and analytic capabilities. Few payers have the data capabilities to implement indication-specific pricing models that require patient-level indication information.

Potential misalignment with Medicare provider reimbursement for office-administered drugs. In certain circumstances, the Medicare reimbursement rate (ASP + add-on percentage) used for physician-administered medications could be lowered to the point where physicians would not be able to bill Medicare enough to offset the cost of acquiring the affected drugs.

Unintended pricing effects related to Medicaid best price provisions. If a rebate linked to one indication creates a price lower than the basic Medicaid rebate (23.1% of AMP) it could trigger a new "best price" that would become the benchmark for all state Medicaid plans, as well as impacting the mandated price to 340B eligible entities.

Restrictions on negotiations related to off-label indications. Manufacturers can only negotiate reimbursement contracts for FDA-approved indications and therefore discussions regarding indication-specific pricing can only consider FDA-approved indications.

Anti-kickback laws creating legal concerns. Both payers and manufacturers should be mindful of laws forbidding certain kinds of contractual promotion of products that are reimbursable by federal health care programs. The Anti-Kickback Statute (AKS) prohibits offering or receiving remuneration (broadly defined) to induce or reward referrals for items or services paid for by federal healthcare programs.[7] For example, if a manufacturer and health plan entered into an ISP arrangement under which the manufacturer accepted risk for "overuse" of a drug for a lower-value indication, this could be viewed as remuneration offered to encourage the health plan to favorably cover the manufacturer's product. Statutory and regulatory safe harbors protect certain arrangements from AKS liability, but it is unclear how enforcement agencies would apply these safe harbors to certain forms of ISP contracts.

Possible Solutions and Policy Recommendations

Payers: Payers could identify drug indications using medical and pharmacy claims data as well as existing drug management capabilities, including prior authorization and specialty pharmacies. Payers could also improve their data systems infrastructure to facilitate improved information capture across platforms. The addition of a field for the ICD diagnosis code in retail pharmacy systems would allow more accurate data collection and claim and rebate processing. Similarly, J-codes could be used to differentiate indications for infused products administered in physicians' offices.

Manufacturers: Manufacturers with a global presence and experience executing indication-specific pricing agreements in countries that support such models can use that expertise to inform and guide implementation in the US health care system.

Payers, Manufacturers, and Policymakers: In early ISP efforts, payers and manufacturers should favor contracts involving oral drugs for which formulary tier placement can be consistent across indications when ISP is implemented. Oral drugs will avoid entanglement with Medicare ASP pricing, and consistent formulary tier placement across indications will help align patient and physician perspectives with a value-based price. ISP efforts in the US should also begin with the weighted-average price approach. Weighted-average pricing can be structured more easily to avoid Medicaid Best Price considerations. The weighted-average price approach also benefits from greater simplicity, which will make it easier to execute and to communicate to involved stakeholders. Lastly, a weighted-average approach to ISP can also be used to avoid explicit negotiation regarding pricing for off-label uses, although it will always be preferable to apply ISP in areas in which off-label use does not represent a substantial part of utilization.

Due to the complexity of the US health care system and the lack of information systems support, payers and manufacturers should consider conducting limited ISP pilots as first steps. In developing such pilots, payers and manufacturers should consider joint efforts to approach senior staff at CMS and the Center for Medicare and Medicaid Innovation (CMMI) to engage them in developing an ISP demonstration project, similar to the demonstration recently launched for value-based insurance design (VBID).[8] As part of these pilots, exemptions can be obtained from regulations such as Medicaid Best Price and Medicare ASP requirements.

Beyond pilots with special exemptions, it will require comprehensive changes to federal regulations for ISP to gain a substantial foothold in the US health care system. To improve the future landscape for ISP and other value-based pricing approaches, payers and manufacturers should collaborate in asking federal policy makers to consider more extensive legislative changes to federal reimbursement policies that obstruct indication-specific pricing agreements.

Summary Table of Challenges and Potential Solutions for Indication-Specific Pricing Programs in the US Market

Challenges	Potential Solutions
Complexity of drug purchasing and delivery systems	Design ISP pilots within less complex drug delivery systems controlled by single entity
Insufficient data systems and analytic capabilities	Use claims data and improve data systems to capture the indication for each prescription use
Limitations of drug formulary tier structure and difficulty linking indication-specific pricing to differential patient cost-sharing	Select drugs for which pricing can vary by indication but formulary tier can remain consistent
Potential misalignment with Medicare provider reimbursement for office-administered drugs	Focus ISP pilots on oral drugs with indications across different conditions and use a single weighted-average price approach Request that federal policy makers include indication-specific pricing in Medicare Demonstration projects
Unintended pricing effects related to Medicaid best price provisions	Focus ISP pilots on oral drugs with indications across different conditions and use a single weighted-average price approach Request that federal policy makers include indication-specific pricing in Medicare Demonstration projects that include exemptions from Medicare and Medicaid pricing provisions Request changes to Medicaid best price provisions so that best prices are linked to specific indications
Restrictions on negotiations related to off-label indications	Select drugs for ISP that have minimal off-label use, apply price adjustments only to labeled indications, and use a weighted-average approach to ISP

Indication-specific Pricing of Pharmaceuticals in the US Health Care System

Introduction

In the continued evolution toward a value-based US health care system, payers, including the federal government, are taking steps to tie health care reimbursement to quality and value measurements.[9] But innovations to create and test value-based reimbursement models for drugs appear to be lagging behind efforts in other parts of the system.[10] One important opportunity lies in developing approaches to reimbursement that reflect differences in the relative clinical effectiveness of the same drugs when they are used for different clinical indications.[11,12] Interest in the idea of indication-specific pricing (ISP) has been catalyzed in the US market in part by the announcement by Express Scripts that in 2016 it will launch an indication-specific pricing initiative for certain cancer drugs as part of its Oncology Care Value program. [13] The purpose of this white paper is to explore the potential value of indication-specific pricing (ISP) of pharmaceuticals for both payers and life science companies and to discuss prospects for its implementation in the US health care system.

I. Background on the Topic

Value-based Pricing and Multi-Indication Medications

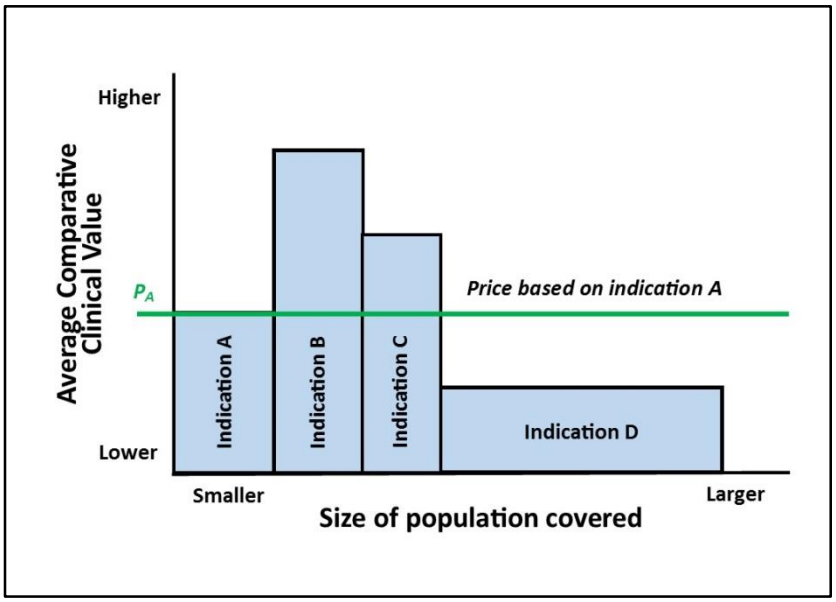
A multi-indication medication is a drug that is approved or prescribed for more than one condition or for a single condition with multiple identifiable patient sub-groups that have important differences in baseline risk and/or treatment outcomes. A recent IMS analysis indicated that the number of multi-indication medications appears to be increasing, accounting for more than 50% of major cancer medicines marketed in 2014 and estimated to grow to at least 75% by 2020.[14] A good example of a multi-indication medicine is Rituxan®, originally developed as a treatment for B-cell non-Hodgkin's lymphoma, but later approved for use in rheumatoid arthritis, another condition in which B-cells play a role in the pathogenesis of disease.[15] Other multi-indication medications vividly demonstrate how widely the clinical benefit can vary across the different indications even when those indications are within the same disease area.[11,14] For example, Abraxane® improves median survival in metastatic breast cancer by 2.2 months over usual care, but the relative improvement in survival for metastatic non–small lung cancer is less than half that.[11] Tarceva®, when used to treat non-small cell lung cancer, provides a median survival gain of 3.4 months, but patients with pancreatic cancer gain only a median survival advantage of 1.4 weeks.[11]

Relative clinical benefits also vary widely, even within a single condition, when there are distinct patient subpopulations defined by genetic subtype, severity of disease, or level of risk. Erbitux®, initially approved for the treatment of all patients with EGFR-expressing colorectal carcinoma after failure with irinotecan-based and oxaliplatin-based chemotherapy, produces substantially better outcomes when used in the sub-population of patients that expresses the wild-type *K-Ras* phenotype.[16] In a genotype analysis of the Erbitux

registry trial, the median overall survival among the entire randomized population was 6.1 months with Erbitux plus best supportive care (BSC) versus 4.6 months for BSC alone. However, the subpopulation expressing the wild-type phenotype of *K-Ras* experienced a median overall survival of 8.6 months with Erbitux plus BSC versus 5.0 months with BSC alone.[5,17] Similarly, Herceptin® provides a median survival gain of almost 2 years among breast cancer patients without metastatic disease, but only 4.8 months among women with distant metastases.

Despite differences in clinical value across indications and patient subpopulations, current pricing and reimbursement systems in the United States assign one single, uniform price to each drug, no matter how it is used. As a result, price and clinical value do not necessarily align across all indications. Consider the example in Figure 1 below that depicts a single drug with four different indications of varying clinical benefit and different associated population sizes. If Indication A is the lead indication and its comparative clinical value is used to justify its initial single price for the compound, the price will be out of alignment with the clinical value for subsequent indications B and C, which have higher clinical benefit. Conversely, the single price linked to Indication A exceeds the clinical value for Indication D and the discrepancy is further exacerbated by the fact that Indication D involves a much larger patient population than Indication A.[18]

Figure 1: The Clinical Benefit of a Compound Can Vary by Indication[18]



Indication-specific Pricing for Multi-Indication Medications

Indication-specific pricing involves some mechanism for paying different amounts depending on the indications or distinct patient populations treated.[4] As some authors have noted, there are different conceptual and practical issues related to indication-specific pricing depending on where a multi-indication drug is in its development lifecycle.[4] Before regulatory approval for a drug's first indication, when the indication profile of a drug is still evolving and can be said to be in a "dynamic context," strategic decisions need to be made by the manufacturer about whether to commit to the development of more than one indication. Conversely, when a drug has already been approved for marketing by the FDA for multiple indications, and the indications for the drug can be considered to be in a relatively "static context" the main focus is on how to price the drug and structure reimbursement contracts. For purposes of this paper we will address some issues related to the dynamic context but focus primarily on the static context in order to emphasize areas of policy most relevant to both manufacturers and payers.

II. Indication-specific Pricing for Multi-Indication Medicines: Potential Risks and Benefits

There is an intuitive appeal to the idea of "reimbursing for value" in the case of multi-indication drugs by developing differential payment for each indication based on how much relative clinical benefit is gained by patients. Payers and manufacturers alike see an important potential benefit for patients who would experience improved access to innovative medicines within a system that balances affordability for payers and sustainability for manufacturers. However, we should first consider in more detail the potential strategic advantages and risks for payers and manufacturers in advancing this approach.

Potential Benefits for Payers

1. **Offers a new mechanism to facilitate patient access to medications within a model that seeks to balance payer needs for affordability and manufacturer needs for sustainability.** Payers recognize that any approach to pharmaceutical pricing needs to find a balance across multiple important goals.
2. **Catalyzes broader efforts to move toward value-based pricing.** Indication-specific pricing can be one facet of a broader strategy to move drug pricing to a value-based model. The basic idea of assigning different prices to drugs when used for different indications presupposes that there is some conceptual basis for arriving at a "value-based" price for each indication. How much lower should the price be for a drug when it is used to treat the indication for which it provides less clinical benefit? Answering this question may pave the road for payers and manufacturers to consider an explicit, consistent value framework to support an indication-specific pricing strategy. This linkage between clinical value and pricing in isolated indication-specific pricing contracts may serve eventually to help move the entire drug pricing system away from current open-ended "market" models and toward one grounded in value-based criteria.
3. **Supports value-based formulary designs.** Being able to reimburse based upon indication is consistent with a value-based approach to benefit design. It allows payers more flexibility to structure their drug benefits in an explicit and more rational link to underlying clinical value. A closer alignment between reimbursement level with indication reduces the need for rigorous formulary restrictions such as step therapy, closed formularies, prescription limits, 'fail-first' policies, and other medical policy measures meant to control utilization, all of which have an administrative burden and implementation cost of their own.
4. **Offers the potential to save money.** In a single price system, payers may be faced with an "orphan price" model for new drugs in which the pricing is based upon an initial small-population and then remains high when the drug is subsequently used for larger populations, whether the clinical value in the larger population is equal or less than that in the original small population. Payers may feel compelled to take unpopular medical policy steps to limit use of high-priced drugs in broad populations, but a lower price, linked to clinical value, could alleviate this pressure, preserve patient access, and provide overall savings to the system.
5. **Offers the potential to demonstrate commitment to innovative payment models.** Indication-specific pricing can be discussed publicly with purchasers and policymakers in a way that highlights how the payer is bringing value and innovation to its members and business partners. However, this may only be germane if the savings are passed along to the patient in some way.

Potential Risks for Payers

1. **Could have minimal impact on affordability or even increase costs.** If indication-specific pricing is used primarily to identify under-valued indications and support price increases over an existing or potential market-based single price, payers could see overall drug costs increase. Without

benchmarking pricing to some independent standard of clinical value (e.g. cost per QALY), negotiations over indication-specific pricing may recapitulate the pricing outcomes that have seen drug prices increase in recent years. Until it is clear what the underlying framework is that will be used to assign a "value-based" price to each indication, it is difficult to anticipate with great confidence whether indication-specific pricing is more likely to lead to cost savings or cost increases. It is important for payers to recognize that indication-specific pricing, by itself, does not address the fundamental concerns about affordability that present great challenges to the health care system.

2. **May raise concern among purchasers, consumers, and patients.** It is conceptually desirable to align indication-specific pricing with formulary tier placement. It can be argued that drugs priced in alignment with clinical value should, in general, face low barriers to use and lower prices for certain indications should translate to lower out-of-pocket payments for patients. But any change in formulary design requires extensive communication risks with purchasers, consumers, and patients. If patients with the same purchaser will have different co-pays for the same drug depending on their condition, or their sub-population within the same condition, it may raise questions about the equity of the formulary design that will be difficult to answer in ways understandable by all.
3. **Administrative burdens may prove greater than anticipated.** As will be discussed at length later in this paper, data systems necessary to administer some models of indication-specific pricing may be difficult to develop and use, raising uncertainty about resources that must be devoted to the successful implementation of indication-specific pricing strategies. The population sizes or financial rewards will need to be large enough to justify the implementation efforts and costs. Payers should also consider how best to communicate indication-specific pricing to their providers and members, especially if it will result in changes in cost share for patients or administrative requirements for providers (e.g., prior authorization). Internal staff and call centers may need to be provided with talking points to facilitate consistent communication. Alternatively, the involved parties may prefer to keep the agreement details confidential.

Potential Benefits for Manufacturers

1. **Offers a new mechanism to facilitate patient access to medications within a model that seeks to balance payer needs for affordability and manufacturer needs for sustainability.** Manufacturers recognize that any approach to pharmaceutical pricing needs to find a balance across multiple important goals.
2. **Provides incentives to develop high-value, secondary indications.** Having indication-specific pricing provides manufacturers with reasonable incentives to develop secondary indications with high clinical benefit for small populations, when the initial price was set in relation to use in an indication that provided lower clinical value. Such follow-on indications might not be profitable in a single-price system if the price of the compound is dominated by an indication with low clinical benefit in a large population.
3. **Protects existing price in high-value indications.** When a new indication with low perceived clinical benefit follows an indication with high clinical benefit, the second indication runs the risk of exclusion or stringent utilization management. Indication-specific pricing provides flexibility for manufacturers to develop additional lower-value indications, knowing that they will be able to negotiate separately by indication and keep/protect a high price for an existing high-value indication.
4. **Helps justify targeted price increases.** Aligning pricing to clinical benefit supports price discussions when the clinical benefit of a drug is demonstrated to be better than expected in one indication or subpopulation. This may be particularly relevant to drugs approved through accelerated approval pathways that may launch with uncertain clinical benefit profiles. As the benefit profile matures, the drug may outperform initial expectations enabling the manufacturer to seek greater reimbursement in line with the drug's performance.

5. **Addresses payer concerns about coverage for large populations.** Payers may fear that a drug with a high price could be used in larger populations for indications with lower clinical benefit. Indication-specific pricing offers the potential to reduce initial payer resistance to coverage since their exposure to costs would be less for indications they determine to have lower clinical benefit. Thus, indication-specific pricing could help ensure that the appropriate patients have access to the medication.
6. **Offers the potential to demonstrate commitment to innovative payment models.** Similar to the potential benefit for payers, indication-specific pricing can be discussed publicly in a way that goes beyond just price and highlights a product's value in multiple conditions or indications. This type of public positioning can help showcase a manufacturer's innovation and willingness to partner with payers to address the longer term issues of sustainability and patient affordability.
7. **Helps align individual product access, value and price, independent of competitors.** Currently, competitive products may be priced similarly despite varying approved uses and indications. This can create pressure to decrease the price for products with more limited uses in small populations to match the price for competitors in the same class whose price is set in accordance with additional approved indications.

Potential Risks for Manufacturers

1. **Payers may become more reluctant to acknowledge added clinical value.** If higher pricing is predicated upon acceptance of evidence that one indication provides "substantially" more clinical value, there may be greater reluctance on the part of payers to acknowledge added clinical benefits across indications and subpopulations.
2. **Indication-specific pricing may support broader efforts to link prices to a standard metric of clinical value that constrains pricing power.** Discussions of how to scale different prices across different indications may raise fundamental questions that are most naturally answered by reliance on a standard measure of "reasonable" added cost per unit of clinical benefit. Indication-specific pricing may therefore support broader efforts to create value-based pricing models linked to incremental cost-effectiveness and budget impact thresholds.
3. **Indication-specific pricing may interact with other pricing policies.** If sufficiently low enough, the price assigned to a drug within an indication-specific framework could interfere with existing reimbursement mechanisms used by Medicaid and Medicare as well as impact the mandated price to 340B eligible entities and lead to unintended market disruption. Manufacturers should be mindful of how a single contract will impact any government-sponsored medication programs in which they participate.
4. **Potential risk for arbitrage by purchasers of the drug.** If two prices are available in the marketplace, purchasers may be incentivized to buy the drug at the lowest price with the intent of using it for the indication that should merit a premium price.[4]

III. Models of Indication-specific Pricing

Although indication-specific pricing is based upon a central principle of setting a different price for each indication (or subpopulation), it can be administered through varying mechanisms. The three major options are described below:

1. Distinct product differentiation, authorized and marketed under different brand names with different prices

Some manufacturers have addressed the challenge of marketing a single drug with widely differing clinical uses by gaining regulatory approval for different brands of the same compound for each indication. For example, sildenafil was initially approved for male erectile dysfunction under the brand name Viagra® in 1998, but was later proven effective for the treatment pulmonary arterial hypertension in 2005, and marketed for this use under a new brand—Revatio®.[2,3] Similarly, liraglutide was initially approved for diabetes as Victoza® but later approved for the treatment of obesity under the brand Saxenda®.[19,20] This approach facilitates separate value assessments, provides distinguishing product codes (i.e., NDC numbers) and thus provides a mechanism for different pricing for each brand of the same compound.

A good example of the ability of distinct branding to support widely differential pricing can be seen with aflibercept. Aflibercept is marketed in the US as two separate products under the brand names Eylea® for ophthalmological indications and Zaltrap® to treat colorectal cancer.[21,22] In the EU this drug also has the same two branded formulations. The average net price per mg of Eylea in the five largest EU countries and Switzerland is approximately $250, whereas the price per mg of Zaltrap in the same countries is approximately $4.[4]

The multiple brand approach has been used selectively in the US where the indications are distinctly different and separate brands are commercially attractive to help define the market for each or when two manufacturers license the same compound for different uses. However, for similar indications or sub-populations within the same indication, such as cancer, multiple brands may be too burdensome or contribute unnecessary confusion.

2. No brand differentiation, distinct, separate discounts are applied for each indication

When the pathway of brand differentiation is not feasible, another option is to establish indication-specific prices for different indications and administer these different prices through a direct linkage to usage of the drug. Data system and other administrative hurdles make this the most challenging approach to consider for most health care systems, and we are unaware of any examples of this approach in the United States. There are, however, a few known international examples. Work by the Office for Health Economics (OHE) in England suggests that Italy has had the most experience with this approach. One example is bevacizumab (Avastin®), which has multiple indications, including treatment of colorectal cancer and other tumor types.[4] In Italy, separate risk-sharing agreements apply on an indication-by-indication basis for Avastin®, and a specific additional 7% discount applies to the product when used in advanced colorectal cancer. Italy also applies a specific discount to a single indication of another cancer drug with multiple indications, cetuximab (Erbitux®). An additional 5% discount applies to Erbitux® when it is used in metastatic colorectal cancer. This approach, though conceptually simple can be difficult to implement, as it requires robust data systems for successful execution.

3. No brand differentiation, a single "weighted-average" price is developed using estimates of indication use across the population, with possible retrospective reconciliation through rebates based upon actual use

Instead of trying to capture indications in order to assign differential pricing, most applications of indication-specific pricing use *ex ante* estimates of population use to establish a single weighted-average price, and then use some mechanism to review retrospectively the use of a drug across all its indications and apply a rebate as needed based on actual use. For example, preliminary analyses might estimate that 50% of a drug's use would be for an indication with an indication-specific price of $100, and 50% would be for a different indication in which the drug's clinical value is higher and therefore merits an indication-specific price of $200. A single weighted average price of $150 could therefore be calculated and used for all indications while awaiting reconciliation. If, after a year, the actual use of the drug turns out to be 75% for the lower-value indication, and only 25% for the higher-value indication, then the contract could require a rebate from the manufacturer to the payer.

Rebates can also be tied to overall budget caps for use of a drug across some or all of its indications. If, for example, a weighted average price is implemented and a budget cap for use in the lower-value indication is made part of the contract, any use that exceeds that budget cap could trigger a rebate from the manufacturer back to the payer. This kind of contract creates a unique incentive for manufacturers to help payers limit overuse of the drug for lower-value indications.

The United States is still virgin territory for this kind of indication-specific pricing and rebate approach, but it appears to be the most common in international markets. In England, among the multiple indications for Erbitux®, only its use for metastatic colorectal cancer triggers a 16% rebate on a per-patient basis. Germany also appears to use a weighted average pricing approach with retrospective reconciliation of some kind, and budget cap rebates are also a part of Italy's pricing approach for a number of drugs.[4]

The weighted average method of ISP appears to be administratively simpler than other approaches that require the indication to be known at the point of service. Additionally, it may be easier to communicate this type of pricing to other stakeholders such as clinicians, patients, and the public. However, robust data are still required for a retrospective review of claims that would determine any reconciliation or "true-up" based upon actual usage by indication. Plans with reliable data capabilities may be best suited for this type of engagement. Although it appears that this method would be easy to implement, it is unclear what the impact of the weighted price would be on existing pricing models used by Medicaid and the 340B program. This is issue is discussed in more detail later in this paper.

IV. The International Experience with Indication-specific Pricing

Health care systems outside of the United States are often dominated by a government sponsored entity that negotiates pricing and reimbursement agreements with pharmaceutical manufacturers. With a dominant single payer, these systems represent a different level of complexity compared to the environment here in the United States, and in some cases may have an easier path to implementing innovative pricing arrangements. Although indication-specific pricing is still not the norm in international health care, some countries have experience with ISP and it may be informative to review these experiences when considering how ISP could work here in the United States.

Australia

In Australia, medications with multiple indications and cost-effectiveness that varies across indications or subgroups within an indication can be subject to a pricing approach that weights different value-based prices across indications to produce a single weighted average price.

Manufacturers can set drug prices with complete freedom in the open market without regulatory intervention. However, if listing under the government-sponsored Pharmaceutical Benefits Scheme (PBS) is sought, manufacturers must submit clinical and pharmacoeconomic data to the Pharmaceutical Benefits Advisory Committee (PBAC) which assesses whether the medication represents "value for money" for the Australian community at the proposed price.[5,6] The manufacturer-provided economic analysis includes proposed pricing, estimates of utilization, and net cost to the system over the first five years of use. For multi-indication medications, this information must be submitted for each major indication. Using the manufacturer submission, PBAC compares the new medication to existing therapy to calculate incremental cost-effectiveness ratios for each major indication. The decision to approve or not approve a medication is based upon the cost-effectiveness analysis and not budget impact. Negotiation for indication-specific pricing occurs only at the levels of utilization and weighting to arrive at a single weighted average price rather than different prices for different indications.[6] Drugs that have received an explicit weighted average price in the PBS include the HIV drug raltegravir and the anti-emetic aprepitant.

United Kingdom

In the U.K., a flexible-pricing scheme was introduced as an option in the 2009 Pharmaceutical Price Regulation Scheme (PPRS). Under the PPRS, manufacturers are allowed a one-time price increase for a major new indication with the provision that the price increase would not come into effect until NICE had approved its use in final guidance or, if NICE did not review the indication, after 12 months from the date of licensing for the new indication. Any medicine can have only one price increase in its commercial lifetime and the company must provide the drug at the old price for the original indication. However, this flexible pricing scheme has not been used often because of the administrative complexity of supporting multiple prices for different indications.[4]

The Office of Health Economics recently evaluated the UKs capabilities to support pricing of multi-indication medicines and found different data capabilities in England, Northern Ireland, Scotland and Wales.[23] In England, a joint venture between the Clinical Practice Research Datalink and IMS Health (called HTI-CRPD GOLD) has the capability to match prescriptions and diagnoses across primary and secondary care according to a patient's NHS number. However, the linked dataset covers only 332,000 individuals across England. The data capture capabilities are not as robust in the other parts of the UK.

Italy

In Italy, some products are subject to indication-specific registries that are owned and maintained by the Italian Medicines Agency (AIFA). The registries ensure appropriate use according to the approved indication, collect data on real world use, and can measure therapeutic effect from baseline to last available follow-up. Registries are maintained for all Avastin® (bevacizumab) indications, except for breast cancer and colorectal cancer, with risk sharing agreements that differ by indication. Similar arrangements exist for Cimzia® (certolizumab pegol), Erbitux ® (cetuximab), and Afinitor® (everolimus).[4]

Switzerland

In Switzerland, an agreement is in place for Avastin in which the manufacturer provides different rebates according to the indication for use – breast cancer or renal cell carcinoma. When Avastin is used in lung cancer, only the low-dose regimen is reimbursed.[4]

For additional examples of indication-specific pricing from the international experience, see Appendix 2. Appendix 2 was taken, with permission, from the report produced by the U.K. Office of Health Economics entitled, "Multi-indication pricing: Pros, Cons, and Applicability to the U.K."[4]

V. Implementation Challenges in the United States

For manufacturers and payers interested in developing an indication-specific pricing strategy, a number of specific challenges must be considered.

Complexity of drug purchasing and delivery systems

One fundamental challenge is that the multiple pathways and intermediaries involved in drug purchasing and delivery in the U.S. are so complex that linking drug prices with indications is extremely difficult. Drugs are distributed from manufacturers through various channels, including wholesalers, pharmacies, hospitals, and/or providers. Through all the different pathways by which drugs reach individual patients, the point at which payment is made is far removed from the point at which a drug is delivered to an individual patient for a specific indication.[24] As a result, the current system of payment and distribution of drugs in the US has been unable to support distinct prices for drugs depending on the indication for which it is prescribed.

The complexity of purchasing and delivering cancer drugs serves as a useful example. Oral cancer drugs are commonly distributed through pharmacies to patients. But the parties that buy and distribute these medications to pharmacies do so in bulk without knowing which patients are receiving their drugs for which indications. Pharmacies do not necessarily know or record the indication for which the drug is prescribed, even if the prior authorization process required by the insurer requires the information. Even when the indication is known at the point of dispensing, it may need to be verified for accuracy if it is the subject of a manufacturer rebate agreement. For cancer drugs infused in the physician's office, prescribing physicians and hospitals sign contracts to purchase the drug from the manufacturer (or an intermediary) at a set price per milligram in a process not linked with the intended indication. This challenge is discussed further later in this paper.

Limitations of drug formulary tier structure.

Drug formularies may not have the capability to place the same drug in different tiers (i.e., high value indication in a preferred tier and low value indication in a non-preferred tier), absent changes to the way in which drugs are identified during billing. Indication-specific pricing models that link reimbursement to indication may require modifications to formulary structure to accommodate differential tier placement and, when patient copays are different, communication materials may be needed to educate providers and members in order to avoid confusion.

Insufficient data systems and analytic capabilities

Indication-specific pricing through brand differentiation is relatively independent of the challenges presented by complex drug delivery and payment mechanisms, but is dependent on the FDA new drug approval process. However, the other two models – differential pricing administered through adjudication of indications, and single weighted-average pricing with retrospective reconciliation – require payers to exercise robust data capabilities that few currently have. Capturing indication information in a precise and

reliable manner is not a standard part of current data systems. Clinicians are not always required to provide the indication when prescribing a drug, and therefore standard pharmacy claims data for indication-specific pricing are not useful. Medical benefit claims for drugs are generally associated with a 3-month time lag. Even electronic medical records (EMRs) rarely contain indication information in a format that links through to the pharmacy benefit.

Potential misalignment with Medicare provider reimbursement for office-administered drugs

Medicare Part B covers a limited number of outpatient drugs that are administered by a physician, typically injectable drugs. Physician offices buy these drugs upfront, store them in the office and then bill Medicare after administration to patients. Current physician reimbursement for this "buy and bill" system utilizes a J code and is based upon the average sales price (ASP) plus a 4.3% administrative fee.[25] ASP is a volume-weighted average sales price issued quarterly by CMS that is based upon data submitted by manufacturers six months earlier, and does not reflect subsequent price increases.[25] If indication-specific pricing were applied to physician-administered drugs under the current buy and bill model, the reimbursement levels might not be sufficient to cover the acquisition cost of the drug for some indications. For example, consider a situation in which the average sales price of a drug with two indications is $750, and therefore the physician reimbursement for use of this drug for either indication would be ASP + 4.3%, or $782.25. However, if indication-specific pricing were being applied, the physician acquisition cost for the drug could be set at $500 for indication A and $1,000 for indication B. Under such a scenario the Medicare reimbursement of ASP + 4.3% ($782.25) easily covers the acquisition cost for the drug when used for indication A, but the physician would lose money when using the drug for indication B, even though use for indication B represents a higher clinical value (thus the higher price).

The same conundrum arises with oral drugs dispensed by a retail or specialty pharmacy. A pharmacy is unaware of the patient's diagnosis at the time a drug is ordered, especially if the drug is one that is kept on the shelf. A low reimbursement of the retail pharmacy for Indication A (lower value) would be insufficient to cover the pharmacy's purchase cost if the drug was purchased for the same amount as that paid for Indication B (higher clinical value and higher reimbursement). Under current practices, wholesalers are unable to distinguish different lots of the same drug as having different costs, so wholesalers cannot pass different costs through to the purchasing pharmacy.

Unintended pricing effects related to Medicaid best price provisions.

The Medicaid Drug Rebate Program was created to help the state and federal governments provide a more affordable outpatient drug benefit. In exchange for coverage in state Medicaid programs, manufacturers enter into an agreement with the Department of Health and Human Services that requires a manufacturer to provide a quarterly rebate to state Medicaid programs based upon a statutory formula: for "innovator" products, the base rebate amount per each unit is 23.1% of the average manufacturer price (AMP), the price that manufacturers charge retail pharmacies before any negotiated discounts. However, if the manufacturer offers a rebate to any qualified purchaser in excess of 23.1%, Medicaid must also receive that "best price" rebate.[26,27] Indication-specific pricing agreements with commercial payers could interfere with the Medicaid Drug Rebate Program if one of the indications for a drug is linked to a rebate that exceeds the basic Medicaid rebate (23.1% of AMP); this would trigger a new "best price" that would be applied to all uses of the drug in all state Medicaid programs. A single weighted-average pricing approach is less likely to create a price more than 23.1% below the AMP, but manufacturers will need to assess carefully the potential impact of any indication-specific pricing contract on Medicaid best-price provisions and discuss the situation with CMS. Since the best price penalty applies regardless of whether the lower price is deliberately negotiated as lower or is unintentionally calculated as less than the best price in the market as a result of a weighted price or other agreement, absent an explicit exemption to the best price provision from CMS, manufacturers may be unwilling to enter into a contract for indication specific pricing.

Restrictions on negotiations related to off-label indications

Manufacturers can only negotiate reimbursement contracts for FDA approved indications. Drugs that have significant off-label uses, including ones that may be supported by research, guidelines and compendia, are unlikely to be suitable candidates for indication-specific pricing since a decision must be made regarding which price will be used for off-label uses, and manufacturers cannot enter into contract negotiations that in any way give the perception of promoting off-label use. Indication-specific pricing discussions should therefore focus on drugs that have a low risk for off-label use beyond existing indications.

Difficulty linking indication-specific pricing differential to patient cost-sharing

In principle, patients prescribed a drug that they need for a "lower" value indication should not always bear greater cost-sharing than patients prescribed the same drug for a "higher" value indication. But administrative challenges in formulary management may make it difficult to align patient cost-sharing with value-based pricing in a transparent fashion.

Anti-kickback laws may create legal concerns

Both payers and manufacturers should be mindful of laws forbidding certain kinds of contractual promotion of products that are reimbursable by federal health care programs. The Anti-Kickback Statute (AKS) prohibits offering or receiving remuneration (broadly defined) to induce or reward referrals for items or services paid for by federal healthcare programs.[7] For example, if a manufacturer and health plan entered into an ISP arrangement under which the manufacturer accepted risk for "overuse" of a drug for a lower-value indication, this could be viewed as remuneration offered to encourage the health plan to favorably cover the manufacturer's product. Statutory and regulatory safe harbors protect certain arrangements from AKS liability, but it is unclear how enforcement agencies would apply these safe harbors to certain forms of ISP contracts. Safe harbors may be particularly important for indication-specific pricing agreements since specific legal requirements exist for discounts and price reductions provided to health plans or managed care organizations.[28,29]

Table 1 below presents a cumulative list of the statutes and regulations that may impinge on indication-specific pricing agreements.

Table 1. Legal and regulatory challenges for indication-specific pricing

Regulatory and Legal Issues Affecting Indication-specific Pricing	Corresponding Statutes/Regulations
Medicare Average Sales Price (ASP)[30]	42 U.S.C. § 1395w-3a 42 C.F.R. § 414.804
Medicaid Best Price Rebate Program[9,30]	42 U.S.C. § 1396r-8 42 C.F.R § 447.505
Office of Inspector General, Federal Anti-kickback Statue[28,29]	42 U.S.C. 1320a-7b(b)
Health Resources and Services Administration, 340B Drug Pricing Program[26]	42 U.S.C. § 256b
Off-label Promotion of Drugs[30]	21 C.F.R. § 312.7

VI. Possible Solutions and Policy Recommendations

Despite the implementation challenges that any indication-specific pricing program would face, feasible approaches do exist, as has been demonstrated in some of the successful international examples of indication-specific pricing. But the market and regulatory landscape in the US make swift adoption of international models impossible. Provided here are additional suggestions for addressing these implementation challenges.

Payers can use claims data and improve data systems infrastructure to capture the indication for each prescription use

Whether using a single weighted-average price or separate, differential discounts by indication, indication-specific pricing requires robust data capabilities that are not available system-wide today. Medical claims data are associated with a significant lag time that prevents real-time adjudication and pharmacy claims are often disassociated from medical claims, yielding an incomplete picture of the patient health status or history. Nonetheless, some payers already have the data capture capabilities and cross-platform integration to support innovative reimbursement models that depend upon claims information. Other payers can seek to improve these capabilities. In both situations, various other segments will need to be modified in order to support these data capabilities to make indication specific pricing a reality.

Drug markers or ICD-10 codes from claims data could be used as surrogates to help identify indication, but this would be limited to situations where the drug is used for distinctly different indications that can be clearly identified and are easy to differentiate from each other, such as rheumatoid arthritis and cancer. Prescribing physicians, either through prior authorization, as part of a new prescription format, or both, could be required to report the indication for each patient receiving a particular drug. Specialty pharmacies that serve as intermediaries between manufacturers and patients have extensive data tracking capabilities that could be adapted to capture drug-indication pairings.

Medication indication is part of protected health information and is subject to patient privacy laws. Therefore, although indication data may be needed to support indication-specific pricing agreements, any patient-level information will need to be de-identified before it can be shared as part of the indication data analysis. This is not an insurmountable problem, and payers should be able to administer an indication-specific pricing program using processes that protect patients from potential breeches of confidentiality.[31]

In the U.S., the issuance of different billing codes for physician administered drugs (usually referred to as J codes and issued by CMS) for different indications could be a simple way to address the differentiation issue for infused products. For oral products, National Drug Codes (NDCs) are the universal product identifier assigned post-FDA approval and used to bill payers. An NDC code is a standardized 10 digit number with 3 distinct segments for the labeler, product, and trade package size.[32] Creation of additional NDCs for billing purposes would be more difficult and is less realistic than the assignment of different J codes.

Payers and manufacturers can minimize the challenge presented by off-label use within ISP agreements by selecting drugs with minimal off-label use and by using the weighted-average ISP model

Communication between payers and manufacturers regarding off-label use of pharmaceuticals is an ongoing area of debate with policies that are unclear and challenging to interpret.[33] However, off-label use should not be an insurmountable barrier to indication-specific pricing. Recognizing that limitations exist on promotion of off-label indications, and that some utilization will fall outside of the FDA approved drug label, payers and manufacturers can address these concerns by selecting drugs for ISP that have minimal off-label use, by applying indication-specific price adjustments only to labeled indications, and by using a weighted-average approach to ISP.

Manufacturers can leverage their international experience with indication-specific pricing

Manufacturers with a global presence and experience executing indication-specific pricing agreements in countries that support such models should use that expertise to inform and guide implementation in the US health care system. Manufacturers with such experience may be particularly attractive as partners in innovative reimbursement programs.

The long-term prospects for indication-specific pricing will be improved if payers and manufacturers collaborate to ask federal policymakers to create exemptions from federal reimbursement policies that obstruct indication-specific pricing pilots.

Payers and manufacturers should work together to present to CMS and other relevant agencies formal requests to create exemptions to Medicaid best price, ASP + 4.3%, and other federal policies that create significant barriers for indication-specific pricing. The Medicaid best price policy could be modified to accommodate indication-specific pricing models by specifying that there can be different best prices for different indications, and that any new, lower best price created by an ISP agreement will affect only the best price for that indication and not require that prices for use in all indications be set to the lowest price for any single indication. The consequence of this modification would allow ISP contracts to have no effect on Medicaid best price for prices in the market that are undifferentiated by indication.

Both payers and manufacturers should ask federal policy makers to include indication-specific pricing in Medicare Demonstration Projects

The Center for Medicare and Medicaid Innovation (CMMI) should consider indication-specific pricing for inclusion in its initiatives to accelerate the development and testing of new payment and service delivery models. CMMI recently announced a program to test value-based insurance design Medicare Advantage plans in seven states over a five-year period. To facilitate the test of the V-BID model, CMS exercised its Section 115A authority to grant a limited waiver of certain regulatory requirements that provided the necessary flexibility to design and execute the test.[8] A similar demonstration project could be conducted for the indication-specific pricing model.

In the short term, manufacturers and payers can best address challenges presented by claims databases and federal reimbursement policies by focusing indication-specific pricing programs on oral drugs with indications across different conditions and by using a single weighted-average price approach

Although oral drugs are not entirely unaffected by indication-specific pricing (a pharmacy could purchase a product at higher price, store it on the shelf, and then dispense it at a later date when the reimbursement level is lower than the acquisition price), oral drugs are more likely to avoid entanglement with infusion-based ASP + 4.3% pricing policies that might create financial losses for practitioners using the drug for its lower value indication. To address concerns about ASP, infused drugs could be distributed and coded based on their separate indications to accommodate the process of physicians and hospitals buying and then billing after the drug is administered. But this approach would require extensive administrative work.

It is highly advisable to consider indication-specific pricing only for drugs that have indications in different conditions, such as different cancers or cancer and rheumatological conditions. Very distinct indications make it easier to use existing data systems to identify the different indications for which a single drug is used.

Lastly, using a single weighted-average price is far more feasible in the current environment than trying to track indication-specific use and applying different discounts to each indication. The latter approach, although a more "pure" form of indication-specific pricing, is more likely to create a price that triggers Medicaid best price provisions; it also presents the greatest potential challenges for sorting out and describing to stakeholders how patients and providers are affected by different prices for different indications.

Table 2 below summarizes the potential challenges facing indication-specific pricing models in the US market and the potential solutions presented in this paper.

Table 2. Challenges and Potential Solutions for Indication-Specific Pricing in the United States

Challenges	Potential Solutions
Complexity of drug purchasing and delivery systems	Design ISP pilots within less complex drug delivery systems controlled by single entity
Insufficient data systems and analytic capabilities	Use claims data and improve data systems to capture the indication for each prescription use
Limitations of drug formulary tier structure and difficulty linking indication-specific pricing to differential patient cost-sharing	Select drugs for which pricing can vary by indication but formulary tier can remain consistent
Potential misalignment with Medicare provider reimbursement for office-administered drugs	Focus ISP pilots on oral drugs with indications across different conditions and use a single weighted-average price approach Request that federal policy makers include indication-specific pricing in Medicare Demonstration projects
Unintended pricing effects related to Medicaid best price provisions	Focus ISP pilots on oral drugs with indications across different conditions and use a single weighted-average price approach Request that federal policy makers include indication-specific pricing in Medicare Demonstration projects that include exemptions from Medicare and Medicaid pricing provisions Request changes to Medicaid best price provisions so that best prices are linked to specific indications
Restrictions on negotiations related to off-label indications	Select drugs for ISP that have minimal off-label use, apply price adjustments only to labeled indications, and use a weighted-average approach to ISP

VII. Conclusion

The 2015 ICER Policy Summit set out to explore the potential benefits and risks of indication-specific pricing for pharmaceuticals in the US health care system, understand the barriers to its implementation, and explore potential solutions and policy recommendations. Payers and manufacturers both saw the potential of indication-specific pricing to align their efforts to achieve better patient access to innovative medicines at prices that can help achieve the twin goals of an affordable health care system and a sustainable business model for pharmaceutical manufacturers. That being said, indication-specific pricing is but one of many possible policy tools available to payers and manufacturers. Some payers feel that they may be able to achieve the broader goals of indication-specific pricing through the application of existing medical policy tools, such as step therapy policies, tiered formularies, and vigorous price negotiation using some form of value-based benchmark. And payers were clear that indication-specific pricing, by itself, is no panacea for the challenges to affordability.

Manufacturers, for their part, although encouraged by successful indication-specific pricing contracts in international markets, were also realistic in acknowledging the many barriers to this approach in the US. It is not easy to find a payer partner with the database capabilities and willingness to take on the risks involved in a pricing pilot program that would be required for an indication-specific pricing contract. In addition, Medicaid best price provisions and ASP-based reimbursement create significant challenges for manufacturers interested in developing differential prices by indication. Regardless of the logistical and reimbursement hurdles experienced by manufacturers, their desire to ensure any savings achieved within an indication-specific pricing model reach the patient remain to be seen. Manufactures would not support a system in which savings generated were only captured by payers, employers, and PBMs.

However, despite awareness of the limitations and risks of indication-specific pricing, there remained much support for its general goals and interest in its possibilities. Prominent in the Policy Summit discussion was consideration of the publicly announced initiative by Express Scripts to collaborate with drug makers in indication-specific pricing for some cancer medications. Many will be watching this initiative as a sentinel of the prospects for further development of indication-specific pricing in the US.

As manufacturers, payers, and policy makers contemplate the potential merits of indication-specific pricing and approaches to it, it is clear that individual pilots, like that of Express Scripts, will be the most likely next steps forward. Organizational cultures vary widely in their level of tolerance for risk or willingness to be innovative in reimbursement practices. Some organizations will take a “wait and see approach” while others will see merit in attempting implementation earlier and setting the foundation for future reimbursement practices. For those willing to test this innovative reimbursement model, success will require selecting the right situation and identifying a business partner with a shared view of the benefit of collaborating. However, it behooves all to understand the potential risks and benefits of indication-specific pricing, to understand some of the lessons learned from international examples, to be aware of specific challenges this approach faces in the US, and to have a firm grasp of the basic models through which indication-specific pricing can be implemented.

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Appendix 1: Organizations Participating in the 2015 ICER Policy Summit

Used with permission. Originally published in: Mestre-Ferrandiz J, Towse A, Dellamano R, Pistollato M. Multi-indication pricing: Pros, cons, and applicability to the UK. 2015. https://www.ohe.org/news/multi-indication-pricing-pros-cons-and-applicability-uk. Accessed October 29, 2015.

Appendix 2: Analysis of "real-world" international experiences of multi-indication pricing (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: 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 on a compassionate-use, free-goods basis. Finally, in September 2013 alemtuzumab received a marketing authorization for multiple sclerosis from the EC, as Lemtrada.

[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]

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

Source: MME elaboration based on the approved SmPCs of the products published on the EMA website: Avastin: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.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 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 methotrexate 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.

[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).

[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 m^2 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)

[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
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
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 January2015];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.

[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 seems 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 weighted average 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 weighted average 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/
    - SMChttp://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)

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