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SYSTEMATIC REVIEW

Price Models for Multi-indication Drugs: A Systematic Review

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Abstract

Background Marketing of new and existing drugs with new indications used alone or in combination is increasing.

Objective To identify the advantages and disadvantages of indication-based pricing (IBP) systems for such drugs from the standpoint of economic theory, practical applications and international experiences.

Methods We conducted a systematic review of published articles and reports using six bibliographic databases: PubMed, ASCO, Scopus, DARE, HTA and NHS EED. We also conducted a search of gray literature in Google Scholar. The same search terms were used as in Towse et al. (The debate on indication-based pricing in the U.S. and five major European countries. OHE Consulting Report, London, 2018). Articles and reports published from 1 January 2000 to 30 September 2018 were included.

Results A total of 26 studies met the inclusion criteria. There are three main types of IBP: different brands with different prices for each indication, an averaged single price for all indications and a single price with differential discounts. The studies indicate that IBP systems are premised on the idea that charging a different price for different indications reflects the differences in their value and in social willingness to pay for each one and for the investment in R&D based on the indication's incremental clinical benefit. Some argue that a uniform price reduces access and increases the price for lower-value indications, while others contend that if IBP sets prices at the maximum threshold of social willingness to pay for each indication, all surplus is transferred to the producer and consumer surplus is reduced to zero. No practical applications of pure IBP were found. Single pricing for drugs is the most prevalent approach. The system that most closely approximates an IBP model consists of agreements that are generally confidential and linked to risk-sharing agreements.

Conclusions There are no applications of pure IBP systems and their practical consequences are therefore unknown. More economic theory-based assessments of the pros and cons of IBP and studies different from reviews are needed to capture their intricacies and specificities.

Key Points for Decision Makers

There are three types of IBP: different brands with different prices for each indication, an averaged single price for all indications and a single price with differential discounts.

No practical applications of pure IBP were found, and their practical consequences are therefore unknown.

Single pricing for drugs is the most prevalent approach.

The system that most closely approximates IBP consists of agreements that are generally confidential and linked to risk-sharing agreements.

More economic theory-based assessments of the pros and cons of IBP are needed.

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1 Introduction

The authorization and marketing of new or existing drugs with new indications used alone or in combination has increased markedly in recent years, and it is highly likely that this trend will continue in the future, especially in oncology and hematology [1–3].

One of the challenges in regulating a drug with more than one indication, administered alone or in combination, is determining the most appropriate way of setting its price. If the therapeutic value of each indication is different, its price should reflect these differences and the social or individual willingness to pay for each of them, taking into account the type of health system in question. This principle is called indication-based pricing (IBP), which can be considered a variant of value-based pricing. In recent years, this type of pricing has been referred to in a variety of ways: "indication-based pricing", "indication-specific pricing", "indication value-based pricing", "multi-indication pricing", and "multi-indication and combination pricing". The abbreviation "IBP" encompasses all of the above.

According to the published literature, to improve the process of pricing and reimbursing of new or existing drugs with new indications, used alone or in combination, several requirements should ideally be met from the social welfare perspective. First, the price should be related to the therapeutic value of each indication, although this is not the only factor that should be taken into account in determining price. Second, the evolution of prices should be sufficiently variable and dynamic to allow for periodic fluctuations in the relative value of the medicine and in the volume of sales for each new indication authorized in the course of the medicine's life cycle. Third, pricing decisions should take account of criteria of efficiency, equity, sustainability and solvency of the health system, without neglecting the promotion of therapeutic competition when possible. Lastly, the prices set should adequately encourage research and development (R&D) on new indications while upholding the objective of contributing to better health and greater social welfare [4–7].

The general objective of this systematic review is to describe and assess the information available internationally on IBP systems for multi-indication drugs used alone or in combination. This general objective is addressed through three specific objectives: to identify and evaluate (1) the advantages and drawbacks of IBP systems from the standpoint of economic theory, (2) the IBP approaches used in practice and (3) experiences in using IBP systems.

2 Materials and Methods

We conducted a systematic review of published articles and reports following the PRISMA recommendations (http://www.equator-network.org/reporting-guidelines/prisma/). We searched papers in four bibliographic databases: PubMed, ASCO, Scopus, DARE, HTA and NHS EED. We also conducted a search of gray literature in Google Scholar. In addition, the bibliographic references included in all identified articles and reports were examined. This review builds on an earlier one by Towse et al, which examined articles published up to an unspecified date in 2017 and included only English-language articles listed in the PubMed and ASCO bibliographic databases. In our systematic search we used the same key words as Towse et al: (indication-specific OR indication-based OR multi-indication) AND ("value" OR "cost*" OR "analysis*" OR "pricing" OR "commerce" OR "price" OR "economic*" OR ("cost-benefit" OR "cost-benefit analysis" OR ("cost" AND "effectiveness") OR "cost effectiveness"). Articles and reports on IBP published from January 1, 2000, to September 30, 2018, were included. Additionally, as we knew in advance that the "risk-sharing agreements" ("managed-entry agreements", MEA) are an approximation to IBP, we searched for published examples of these schemes in order to know their practical applications in more detail. Details of the full electronic search strategy for all databases can be found in Annex 1

The review includes original and review articles, commentaries, editorials and opinion articles, as well as any type of report published in print or online in English or in Spanish, including so-called gray literature. Abstracts from conference proceedings were excluded. The criterion for inclusion was that the studies reviewed or analyzed IBP methods for drugs, whether used alone or in combination. This review was conducted from a societal perspective.

3 Results

The sequence of searches in the bibliographic databases and their results are described in the flow chart in Fig. 1. Initially, 89 studies of potential interest were identified, of which 59 were excluded after their titles and abstracts were reviewed. Of the 59 excluded studies, 10 were duplicates and 49 did not meet the inclusion criteria because they did not deal with IBP systems.

Of the 30 studies that met the initial inclusion criteria, 4 were excluded because they were conference abstracts. Ultimately, 26 studies that met the inclusion criteria (objectives 1, 2 and 3) were selected [1, 4–28]. Of these 26, 11 had been included in the review by Towse et al. [1, 4, 6, 9, 10, 20, 22, 24, 29–31], and 15 provided new

information regarding multi-indication drugs used alone or in combination presented in this review [5, 7, 11–19, 21, 23, 26]. Of the latter 15 studies, 7 were published prior to the end of 2017 and 8 prior to 30 September 2018. In the additional search (to further elaborate objective 2 and 3) we found 11 articles describing practical application of risk-sharing agreements [29–39].

3.1 Theoretical Rationale

The theoretical rationale for IBP systems stems from the need to apply differential pricing if it is intended that the value of the medicine for each indication is reflected [4–7]. The literature reviewed describes the concept of IBP as a variant of value-based pricing (VBP) because the expected health benefits of each indication may be fundamentally different and therefore the social or individual willingness to pay and the price should reflect such differences [5, 12]. From this theoretical perspective, IBP models would be nothing more than an application of VBP models to medicines with more than one indication when the incremental benefits of the various indications are different and it is accepted that the application of a single price would be inadvisable because of its potential negative effects on social welfare [7, 12, 16].

The aim in IBP systems is to set different prices and differentially cover the R&D investment of pharmaceutical companies based on the incremental clinical benefit or the cost-effectiveness ratio of each indication. The ultimate aim is for the price of the medicine for each indication to reflect the social willingness to pay for a therapeutic innovation (public health systems), expressed in a practical manner—for example, by means of thresholds that represent the maximum cost that the payer is willing to pay for one quality-adjusted life year (QALY) [5, 12].

Excluding Chandra and Garthwaite [4], the majority of the articles reviewed share, explicitly or implicitly, the premise that a single uniform price for the same drug, used alone or in combination, across all indications can have various negative social and economic consequences [8, 11, 12]. For example, uniform pricing could have a negative impact on access, since some lower-value indications may not be reimbursed. At the same time, uniform pricing could discourage the development of additional high-value indications if the uniform price is based on a low-value indication [11].

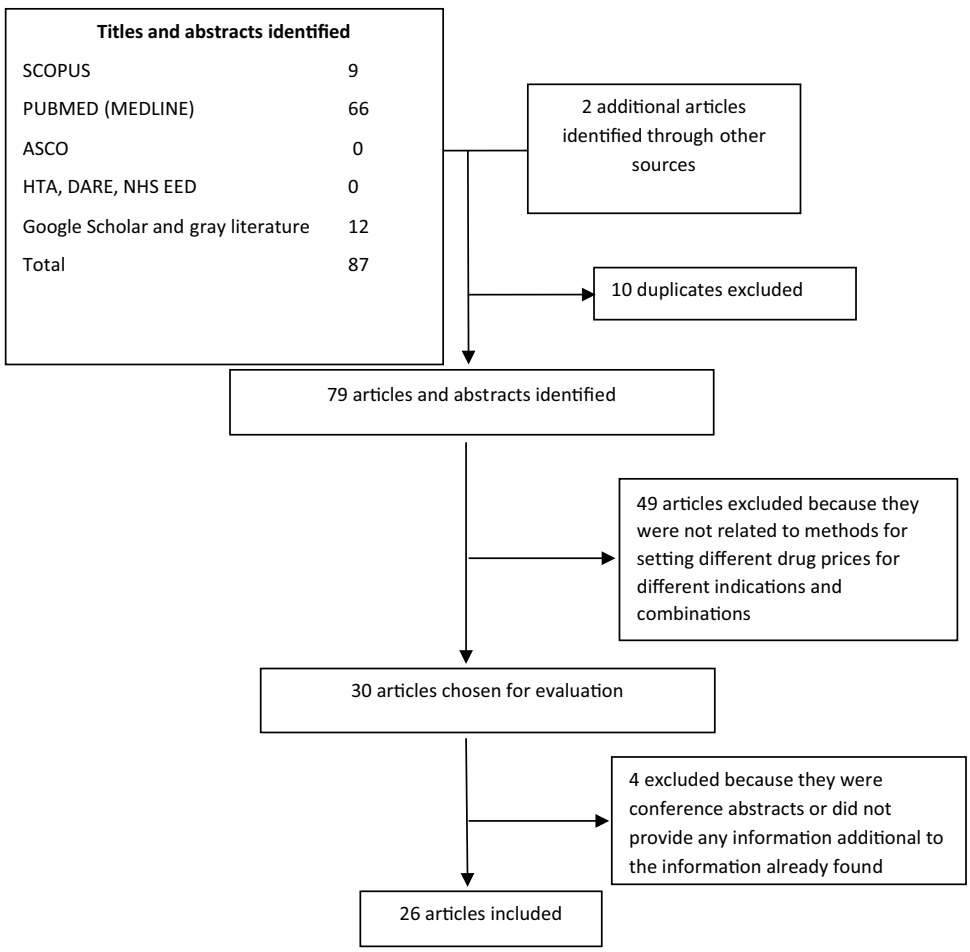

Fig. 1 Flow chart of literature search and article selection following the PRISMA recommendations

From the perspective of economic theory, Cole et al. note that an IBP model can improve social welfare in the sense that more patients may have access to a drug, irrespective of surplus distribution between consumer and producer [11]. From a static perspective, in the short term—always bearing in mind that single or multiple prices are set by identifying the value of an innovation and establishing thresholds of social willingness to pay—the impact of an IBP system will depend on the level at which the single price was previously set, the value of the new indication and the additional R&D cost of the new indication.

Economic theory also suggests that there are two longer-term dynamic effects of IBP that affect R&D and pricing [11]. First, if prices reflect the value of particular indications, the investment in R&D will be optimal from a social point of view. With a single price, some indications (of lesser value) may not be developed, even though the incremental value of the drug to patients exceeds R&D and supply costs. Second, scientific progress stimulates R&D competition and often leads to several drugs of the same therapy class coming to the market. Cole et al. point out that IBP models make it more likely that competitive products will be developed, and that competition will occur in any given indication [11].

Regarding the effect of IBP on price level, it has been described how IBP models could result in lower prices for indications with lower therapeutic and social value, based on the assumption that the uniform price is anchored to the indication that provides the most value [9]. On the other hand, Chandra and Garthwaite argue that IBP models, when they are based on a uniform price that maximizes profit to a monopoly, can cause the prices of higher-value indications to rise and increase producer surplus while reducing consumer surplus [4]. Accordingly, an IBP system, in the view of these authors, is nothing more than a form of price discrimination that allows the monopolist to extract the maximum that the consumer is willing to pay if the price for each indication is set at the willingness-to-pay threshold [4].

3.2 Approaches to the Application of IBP

The approaches for practical application of the IBP model described in the 26 studies included in this review are summarized in Table 1. In short, we identified three IBP approaches: (1) different brands with different prices for the same drug, (2) a single price calculated as an average for the various indications and (3) a single price with differential discounts. The creation of separate brands, which approximates a pure case of IBP, could complicate the application of the model if the price difference between brands is significant and the dosages are similar [6–8, 12, 14, 16, 17, 20–28, 36–39].

Possible solutions proposed to address the potential complexity of IBP systems include "blended single price" approaches, ranging from the simplest, with a single price calculated as an average across indications and weighted solely by expected volumes of use for each indication, to the most complex, in which the added therapeutic value of each indication (leaving aside the question of how "value" is defined and calculated, which is beyond the scope of this article) also enters into the weighting [6–8, 12, 14, 16, 17, 20, 30, 32]. The first case, where the price is weighted only on the basis of expected prevalence of use, is widely used, but does not really constitute a standard IBP model because it does not incorporate value in the weighting, although it does take into account a dimension of indication, namely the potential number of patients, for the purposes of determining budgetary impact and economies of scale in a production process with high fixed R&D costs [7, 8, 12, 14, 20, 30, 32].

In contrast, in the second case the differential value of each indication is also used to weight the average price, which is a single price for all indications that is not differentiated by indication [7, 8, 21, 26]. A risk associated with this approach is that decisions taken by local decision-makers about the use of medicines in specific patients do not—due to lack of adequate information or incentives—take into account the correct differential price for each indication. An additional difficulty is that frequent dynamic adjustments

Table 1 Approaches to the application of indication-based pricing (IBP)

1. Different brands of the same medicine for different indications, with different prices for each indication (pure IBP)
2. Blended single price calculated for the various indications as an average, with two main variants according to the chosen weighting factor:
2.1 Single price calculated as an average across the various indications and weighted only by expected volumes of use for each indication (prices not based on value)
2.2 Single price calculated as an average that reflects volumes of use and the value of each indication (prices partially reflect value)
3. Single price that reflects the indication with the greatest value (for example), with differential discounts for indications that provide less added value, which in some cases may be provided through financial or outcome-based risk-sharing agreements (blended IBP partially reflecting value)

Source: Prepared by the authors

may be required if the weighting factors change over time [6–8, 12, 16, 17, 20, 30, 32].

The confidential discount approach, applied in many cases through risk-sharing agreements of a financial nature or based on health outcomes, makes it possible to reconcile an apparently single price with the theory of IBP. This approach is also known as managed entry agreements. In sum, the practical application of a pricing system such as IBP may prove difficult for reasons that vary according to the approach used [6–8, 16, 17, 20–28, 36–39].

3.3 International Experiences in the Application of IBP Systems

The information provided by the studies included in our review does not allow us to present a complete picture of the various IBP systems in use around the world. We can only describe how the pricing of medicines with multiple indications is being approached in some countries. Although the studies reviewed do not provide exhaustive information and only cover European Union countries, Australia and the USA, there does not appear to be any instance of a pure IBP model being applied at the national level in these countries. The pricing approaches identified in this review that approximate an IBP system and the countries where they are being applied at the national or local level are summarized in Table 2 [6–8, 16, 17, 20–28, 36–39].

In general, the most prevalent approach is a single list price for a given drug, which may or may not be set on the basis of weighting across multiple indications. The most common approach to an IBP-type system are agreements with regional buyers, insurers and hospitals, which are generally confidential and linked in most cases to risk-sharing agreements [6–8, 20–28, 36–39].

Italy is the only country with a national model that comes close to being a de facto mixed or "blended" IBP system that is partially based on value [7, 8, 21, 26]. Created in 2006 and centralized under the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), the model is based on risk-sharing agreements (financial or clinical) with varying features, in which a differential price by indication is established for medications with multiple indications, especially in oncology. This model is supported by an infrastructure for registering information from prescribers and hospitals that would, in theory, lend dynamism to the model and make it possible to obtain information on outcomes by indication and follow up on the agreements [8].

The models used in the other countries do not approach a pure IBP system. In all cases, weighting methods are used to set the prices of medicines with different indications, which results in a single price that can vary over time only if the expected volume of use changes or if elements that reflect the differential value of the medicine in each indication are added as weighting factors. Volume-based price is the most widespread; the second average single price weighted by use and value is applied in only a few countries, such as Australia and Germany [7, 8, 20, 21, 26].

Although the patient access schemes in the UK could be considered close, at least in part, to the Italian model, in the majority of cases in recent years the UK has opted for financial or low-complexity agreements that offer, at most, discounts by indication [7, 8]. In other countries, such as Spain, a single maximum price per drug is established at the central level, but it is almost invariably revised downward each time a new indication is approved. Pricing agreements can then be reached for each indication at a decentralized level (either by regions or individual hospitals) in the form of differential discounts or risk-sharing agreements [7, 8, 20].

The USA is a different case because of the singularities of its health system. Some experiences with differential pricing for different indications are beginning to emerge in this country. For example, some insurers and pharmacy benefit managers (PBMs), such as Express Scripts Holding Company, are implementing an IBP model in certain therapeutic areas through schemes that provide for discounts linked to the differential value of each indication for the same medicine [8, 17].

Our review found no documented examples of pure IBP models to drugs with more than one indication. The model used in Italy has been described as the closest to an IBP system because it sets different prices for each indication. However, it lacks information and transparency concerning the weighting criteria applied to the financial or clinical risk-sharing agreements that it includes. The same applies to the patient access schemes in the UK, the approaches described in the USA, the decentralized approaches that require information registries as a prerequisite to price discrimination (UK and Spain), the risk-sharing agreements with regional buyers or hospitals (UK, Spain, Australia, Belgium, Sweden), the variable payments to the central level (France), and to the pricing models used in the Netherlands, Poland and Norway. Moreover, as the agreements are confidential, there is a lack of information on the extent of their scope, the degree of implementation and outcomes [6–8, 16–18, 25, 26, 32].

3.4 Difficulties of Applying IBP in Practice

Regardless of all the advantages and drawbacks of such pricing systems, a large part of the literature reviewed highlights the difficulties of applying IBP in practice, including the following six, which should be taken into account when establishing an IBP system [7, 8, 11, 16, 18]:

Table 2 Description and applications of indication-based pricing (IBP)-type approaches around the world Source: Prepared by the authors

Price-setting scheme	Description	Countries where applied at the national level	Countries where applied at the micro level	Drug examples	References
Different prices for different brands of the same product	Basically, the same product is marketed under different brand names for different indications, resulting in differentiated prices	This is a classic scheme that has been and is being *used in most countries*; it is more of a marketing strategy than a regulatory one (i.e. *USA*)	Not necessary since differential prices are set at the national level. However, when the dosages in the different indications are very similar, there can easily be inadequate incentives for local purchase and use	*Sildenafil* (marketed as Viagra for erectile dysfunction but Revatio for pulmonary arterial hypertension)	[4, 18, 19, 21, 22]
Average single price weighted according to expected volume of use	A single price is set for the product, but it is usually adjusted downward to reflect new indications and expected increases in use	This is the model used in *most of the European settings* analyzed at the national level (i.e. *Spain*)	Local settings may be able to incorporate into pricing conditions regulated at the national level certain elements that approach an IBP system in a more tangible way (i.e. *Spain*)	*Nivolumab* (gastric metastatic cancer and breast metastatic cancer HER2+)	[4, 22, 24]
Average single price weighted by use and value	A single price is set for the product, but it is usually adjusted to reflect new indications, expected increases in use and the differential value of indications	Used in *Australia*, but the mechanism for adjusting prices based on differences in value and the relative weight of this variable are unknown (i.e. *Germany*)	*Australia*, *Germany*, *UK*	*Erlotinib*	[4, 22, 25, 30]
Single price with differential discounts based on volume or value	The single price reflects the indication with the greatest value of all existing indications; for the rest, differential discounts are applied based on their relative value with respect to the highest-value indication A common form of application is through risk-sharing agreements	No known applications	There are some examples of the use of this approach by some insurers in the *USA, Australia, Germany*	Tisagenlecleucel (Kymriah) (indication specific prices) dupilumab (price according to ICER value-based price) AntiTNF, IL3i and other anti-inflammatory drugs	[12, 14, 16]
Risk-sharing agreements, performance-based reimbursement schemes, patient access schemes, innovative pricing models, etc	Pricing agreements are established for each indication, which are linked to the outcomes obtained by the product in actual practice	This approach has been used in *Italy* since 2006, with selected products The *UK* has a similar scheme, the "patient access scheme (PAS)", although it mostly involves simple discounts on the single price or financial schemes	In most of the countries analyzed, these types of agreements are established at the regional level or even at the level of individual hospitals. Examples found in this review include *Spain, Sweden, France, Australia, Holland, Belgium and the UK, USA*	Gefitinib, azacitidine, bevacizumab, bortezomib, brentuximab, catumaxomab, erlotinib, everolimus, lapatinib, lenalidomida, nilotinib, ofatumumab, panitumumab, pazopanib, ranibizumab, sorafenib, sunitinib, trastuzumab	[4, 21, 22, 24, 25, 28, 30], [36–39]

1. The development of an IBP system requires adequate infrastructure and organization in order to obtain and record the necessary clinical information.
2. The increase in administrative costs associated with the identification of indications, the differentiation of value and the purchasing and payment process may be higher than the benefits derived from the new pricing system.
3. To determine the value of a medicine in each indication, a VBP system is needed, which in turn calls for a suitable institutional framework for the evaluation of medicines, including economic evaluation and the definition, explicitly or implicitly, of a threshold that reflects maximum social willingness to pay for one year of life or for one QALY.
4. The rules of an IBP system can be breached as may happen when the hospital is under budget constraints and has an incentive to purchase the product stating that its use will be limited to the indication for which its price is low.
5. It is possible that there will be a net increase in spending as a result of the application of IBP, since such pricing could increase access to medicines that otherwise would not be paid for at the asking price.
6. Legal and regulatory constraints specific to each regulatory environment could hinder the application of multiple prices.

4 Discussion

The contribution of this review of the literature on IBP systems, which builds on the review by Towse et al [8], lies in the inclusion of 15 additional articles on IBP published subsequently, up to September 2018 [5–7, 11–19, 21, 23, 32]. This contribution can be broken down basically into three areas: (a) the theoretical foundations of IBP systems and their theoretical advantages and disadvantages, (b) the taxonomy of the various pricing approaches that in the literature are considered more-or-less pure applications of IBP and (c) the identification of current uses of these IBP approaches at the international level.

The magnitude of the undesirable outcomes—barriers to access and disincentives to R&D—of uniform pricing for a medicine with several indications for which there is no competition, whether used alone or in combination, will vary depending on whether the uniform price is set closer to the level for the indication with the highest value or the level for the indication with the lowest value. From the perspective of economic theory, the logic of IBP systems should be examined taking into account that, on the supply side, IBP is a form of price discrimination (the same medicine is sold at different prices), while on the demand side, depending on how it is applied, IBP is equivalent to a system of value-based pricing, with prices reflecting the differential value of each indication [7]. The literature reviewed only partially analyzes the overall theoretical implications of these two economic concepts in a rigorous and critical manner [4, 7, 11], which could muddle and weaken some of the economic arguments put forward in relation to IBPs, especially in the case of pure IBP. This article aims to partially bridge that gap.

A pure IBP system would assume, from the point of view of the monopolist producer, perfect (first-degree) price discrimination in which, if the producer is able to set the price at the level of maximum willingness to pay of each group of consumers—patients with different indications in this case—the producer will be able to keep all surplus [27]. In this situation, social welfare is maximized, as all groups of patients have access to the medicine, and the producer's profit is also maximized. This perfect price discrimination enables the monopolist to obtain a higher profit than would be obtained with uniform pricing—maximum profit—by capturing the totality of consumer surplus. Such perfect price discrimination is only possible in the case of medicines with more than one indication if: (1) the monopolist is able to accurately determine the maximum amount that the individual or collective payer is willing to pay for each indication—group of patients; (2) the buyer is not or does not exercise purchasing power as a monopsonist or majority buyer; (3) there is no therapeutic competition between drugs for the same indication; and (4) the producer can effectively avoid arbitrage (for example, transfer of a drug purchased at a lower price to consumer groups with greater willingness to pay).

The possibility of arbitrage, together with potentially high transaction costs, may prevent the application of pure IBP systems—for example, when the same product is sold under different brand names, but prescribers and patients are aware of this and have incentives to use the low-price brand for high-value indications. Financing, price regulation and purchasing policies on the demand side, as discussed below, can limit the effect of the first three conditions mentioned and, under the right circumstances, can maximize social welfare and prevent the producer from keeping all consumer surplus by applying a mixed or blended IBP system. In Neri et al the importance of the distributive effect of IBP (transfer of surplus from consumer to producer) is minimized, and it is argued that therapeutic competition will lead to a lower price than VBP, an argument that requires empirical verification and is not borne out in the majority of cases, as little or no therapeutic competition exists [25].

On the demand side, IBP systems with a pricing approach based on the value of each indication have been identified [7, 9, 12]. Here, the need to align prices with value (leaving aside the question of how value is measured) should not be confused with proposing a price that represents the maximum willingness-to-pay threshold. This could run counter

to economic price theory [28, 33, 34]. If the price is equal to the maximum willingness-to-pay threshold (for example, a maximum cost limit per QALY gained), this does not mean that this price is appropriate but that it represents a maximum price, and with that price all consumer surplus becomes producer surplus (profit), which maximizes the benefit to the monopolist in the situation we are concerned with here.

Blind application of prices based on generous thresholds of cost per QALY gained favors the exercise of monopoly power by the innovating industry and the application of high prices that are not justified by the cost of the innovation, while also reducing the bargaining power of payers. Applying a VBP system that sets the price on the basis of the willingness-to-pay threshold (price endogenization) is tantamount to transferring the full benefit of an innovation to the producer and reducing the net health benefit to the health system to zero [28, 35], even if the price would be efficient for society, irrespective of the surplus distribution between producer and consumer. Distribution of the social surplus between consumers (payers) and producers depends on price negotiation, which serves to divide the surplus, but maximum willingness-to-pay thresholds are not, strictly speaking, useful for setting the optimal price, nor are they of much help in price negotiation, since the costs are unknown. The optimal price will depend on two benchmarks: the lowest price necessary for the producer to recover production and R&D costs and the highest price that society is willing to pay. Hence, it is possible to design a blended IBP system that reflects value, but is not based solely on value, nor are prices necessarily set at the level of maximum willingness to pay, because a blended system can also make it possible to maximize welfare (i.e. maximum access) without allowing the producer to capture all surplus.

In practice, three main pricing approaches have been identified—one of them with a variant—that a number of the papers included in this review deem to be applications of the IBP model. However, in all except the first approach (different brands with different pricing for each indication), a single price is used (mixed or blended IBP). This sets them apart from what is strictly defined as IBP. A single price model—with the price set when each new indication is approved or revised in accordance with clinical outcomes under real conditions and weighted by the differential features of each indication as valued by the purchaser and not only by maximum willingness to pay—turns out to be the most widespread means of applying IBP systems that reflect value [6–8, 12, 14, 16, 17, 20–28, 36–39]. This is not surprising given that perfect price discrimination results in a distributive effect that reduces consumer surplus to zero.

An extreme case of blended IBP is the second approach observed (a single price weighted by volume), since it moves away from a VBP system (and one based simply on value) and since, in essence, it amounts to a simple price-volume agreement in which only budgetary impact is taken into account [6–8, 12, 14, 16, 17, 20, 30, 32]. A situation even further removed from a value-based system would occur if the single price were systematically revised downward by regulators or payers regardless of the number of patients using each new indication, which could have negative effects on access to indications with a small number of patients.

Dynamic weighting based on the value of each new indication approved or on observed outcomes in actual clinical practice, together with differential discounts (second and third approaches), constitutes a blended form of IBP involving price discrimination by value, which can help to maximize access and social welfare and partially mitigate the distributive problem of pure IBP systems. Single price systems that are dynamically weighted or adjusted according to the value of new indications (generally the value at the time of market entry) also take account of at least the budgetary impact or the expected volume of prescriptions for the new indication [6–8, 12, 14, 16, 17, 20, 30, 32].

The main limitation of this review is that we found published experiences in English and only from European Union countries, Australia, and the USA, which are usually the countries that pioneer such experiences. We cannot rule out the possibility that in other countries there may be applications of true IBP models that have been adequately evaluated and published in other languages, and that the characteristics and outcomes of such experiences might alter the findings of this review (Tower of Babel bias), although not substantially.

Apart from the analysis undertaken here on IBP models from the perspective of economic theory, another limitation is the lack of information on the extent of actual implementation of what, in the literature reviewed, are deemed to be approximations of such models, as well as the dearth of rigorous evaluations, which makes it difficult to draw any definitive conclusions about the real outcomes and consequences of the models currently being applied around the world.

Finally, in most instances the types of criteria and pricing models found in the literature are not general but specific for individual drugs, do not result from a given formula but from negotiations between authorities and companies. Additionally, since pricing and agreements are usually confidential, details are not reported, and no further information can be obtained through a systematic review.

5 Conclusions

As no practical applications of pure IBP models at the national or local level were found, but only approximations of such models, there is insufficient empirical evidence reported to make it possible to pinpoint their practical

consequences and whether or not they offer advantages in relation to single pricing. From an economic theory perspective, there are solid arguments that cast doubt on the advantages attributed to IBP systems if they entail perfect price discrimination. The controversies that have arisen make it clear that the theoretical debate has not been settled and underscore the need to undertake a more thorough analysis based on economic theory and to assess its validity against empirical evidence that still does not exist. Given the abovementioned limitations, studies different from reviews are needed to capture their intricacies and specificities.

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Compliance with Ethical Standards

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