Multi-indication and Combination Pricing and Reimbursement of Pharmaceuticals: Opportunities for Improved Health Care through Faster Uptake of New Innovations

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Abstract Many pharmaceuticals are effective in multiple indications and the degree of effectiveness may differ. A product-based pricing and reimbursement system with a single price per product is insufficient to reflect the variable values between different indications. The objective of this article is to present examples of actual pricing and reimbursement decisions using current value-based pricing in Sweden and to discuss their implications and possible solutions. The value of several cancer drugs was estimated for various indications based on a willingness-to-pay threshold of 1 million SEK (EUR 104,000) per QALY gained. For some drugs, the estimated value was higher than the drug acquisition cost in several indications, whilst in others, the estimated value was lower than the drug acquisition cost. Drugs used in combination present a special case. If a drug prolongs survival and consequently also a continued use of the anchor drug, the combination use may not be cost effective even at a zero price. In a product-based pricing and reimbursement system, patients may not get access to drugs or access may be delayed and manufacturers may be discouraged to invest in future indications. To overcome these issues, there are several approaches to link price and value. One approach is a “weighted-average” price based on an average of the value across all indications. Another is “multi-indication pricing,” which enables price differentiation between indications. However, there are several barriers for applying multi-indication pricing and reimbursement schemes. One barrier is the lack of existing administrative infrastructure to track patients’ indications.

Key Points for Decision Makers

- The value of several cancer drugs differs between indications, and therefore a product-based price and reimbursement system does not accurately capture the value of a drug.
- A pricing and reimbursement system that would allow for different prices in different indications may secure early access and improve patient access in lower-value indications.

1 Introduction

Many pharmaceuticals are effective in multiple indications. More than 50% of major cancer drugs marketed in 2014 were for multiple indications, and this share is estimated to grow to 75% in 2020 [1]. The degree of effectiveness of a drug may differ between indications, treatment line and patient characteristics. For example, cancer drugs are usually introduced for patients at very severe conditions, and then for adjuvant treatment in patients with less severe illness. Typically, these drugs are then proven effective in
other types of cancers. Consequently, the effectiveness, and thus the value of a drug, may differ between usage and patients.

Pricing and reimbursement systems with one single price (product-based pricing) are insufficient to meet the conflicting policy objectives of access, efficiency and cost control. If the price of a drug with varying value in multiple indications is set based on the high-value indication, the price may be too high to be cost-effective in lower-value indications. As a result, the treatment will not be reimbursed for these indications and patients will not get access to the treatment. Manufacturers may be discouraged from applying for regulatory approval in markets where price is based on the lower-value indication and they may be discouraged from new drug development in the long run.

The value of a drug may also vary when used in combination with other drugs compared to when used as monotherapy. A typical example of combination drug therapy is when new cancer drugs stimulate the immune system, allowing the body’s defense to recognize and destroy the cancer cells. These drugs can be used as monotherapy and often receive a high value as such. Used in combination with other drugs the total benefit to the patient increases, but it is challenging to determine what value each drug contributed to the improvement. If the drugs are marketed by the same manufacturer, it is possible for the manufacturer and payer to make a price-volume agreement for the combination use. When the individual products are marketed by different manufacturers, combination pricing is challenging.

Use of combination therapy is not new. Oncology’s chemotherapy regimens, HIV/AIDS, hepatitis C and diabetes treatment all use a combination of drugs. However, recently there has been an increasing prevalence of highly effective and patented branded combination therapies. This trend is expected to become even more common in the future due to the development of targeted therapies.

Currently, the price and reimbursement decisions and treatment recommendations in many countries do not consider how the value of a treatment change when the drug is expanded to cover more indications or when used in combination with other drugs.

The objective of this article is to describe Value Based Pricing (VBP) reimbursement decision-making in Sweden, using HTA appraisals by the Dental and Pharmaceuticals Benefits Agency (TLV) and the New Therapies council (NT-council) as examples. Furthermore, we analyze weaknesses in the current VBP approach and suggest various solutions to improve the decision-making process related to multi-indication and combination pricing and reimbursement.

2 Estimating the Value of Drugs in Multiple Indications

Sweden has based reimbursement on VBP since 2002 [2, 3]. The national reimbursement authority TLV, makes decisions for prescription drugs based on equity, disease severity and cost-effectiveness. A socio-economic perspective is used and includes cost offsets in sectors other than healthcare. However, it is the county councils at a regional level that are responsible for the drug budget. Since 2009, the NT-council makes recommendations to the county councils on the use of new drug therapies administered in hospital care. Recommendations on some (reimbursed or not) prescribed drugs are also made upon requests by individual county councils. The TLV supports the NT-council with health economic assessments in these cases. Whereas the price of prescribed drugs reimbursed by the TLV is an official list price, the agreements negotiated by the NT-council often involve discounts.

Although there is no explicit threshold value for the cost of a QALY in Sweden, a willingness-to-pay of 1 million SEK/QALY is generally accepted in severe diseases such as cancer [4]. In accordance with this, recent research shows that the willingness-to-pay for cancer treatment in the general public is at least 1 million SEK/QALY [5].

We present examples of drugs used for multiple different indications and their monthly drug acquisition cost for a typical patient in Sweden. By estimating the justifiable price given a willingness-to-pay threshold value of 1 million SEK (about EUR 104,000, 1 EUR = 9.6 SEK) per QALY gained, we estimated the value of several drugs in multiple indications. The formula below was used to estimate the value

$$\text{Value}_{\text{NEW}} = (\text{WTP} \times \Delta \text{QALY}) + \text{Treatment cost}_{\text{SOC}} - \text{Treatment cost}_{\text{NEW}}$$

NEW is the new drug, SOC is the standard of care used as a comparator, and WTP is the Willingness-to-Pay threshold. The treatment cost of the standard of care includes the drug acquisition cost and other health-related treatment costs. The treatment cost of the new drug includes other health-related treatment costs, whereas the drug acquisition cost is set to zero. The treatments cost is mainly public expenditure, but it also includes patients’ co-payments, which is a maximum of SEK 2200 for drugs and SEK 1100 for healthcare visits and hospitalizations per 12 months. The drug acquisition costs are estimated from official list prices. Other health-related treatment costs include administration, healthcare visits, hospitalizations, and the cost of side effects. Indirect costs or other unrelated costs were not included in these examples.
Calculations are based on official data from the health economic assessments provided by TLV to the NT-council [6] and assessments included in the national treatment guidelines for breast and colon cancer [7].

Figure 1 illustrates how the estimated value of drugs varies per indication. For example, for a typical patient with breast cancer the monthly drug acquisition cost of trastuzumab, estimated from the official list price, is around SEK 24,500. However, our estimates (Fig. 1a) show that the estimated value in metastatic breast cancer is slightly higher (SEK 33,100), whilst the estimated value in adjuvant treatment of breast cancer exceeds that with a value of SEK 81,000 per month (Table 1). The difference in the estimated value between the metastatic compared to the adjuvant treatment is due to the higher value associated with a lifesaving treatment. However, as new cancer therapies are usually tested and approved in severe patients with metastatic cancer, the price is based on the lower-value metastatic indication.

Another example of a drug approved in multiple indications is bevacizumab (Fig. 1b). The estimated value of this drug is lower than the monthly drug acquisition cost for patients with metastatic carcinoma of the colon or rectum and particularly in metastatic breast cancer. The difference in the estimated value is highlighted when comparing two new indications for bevacizumab. In platinum-resistant epithelial ovarian cancer, the estimated value of the drug is SEK 76,600 per month, whilst the estimated value in platinum-sensitive epithelial ovarian cancer is just SEK 28,000 per month. Consequently, the NT-council recommends use of bevacizumab in platinum resistant, but not in platinum sensitive, ovarian cancer.

Nivolumab is another drug approved for several indications. The dosing is similar in all indications selected for this example, and therefore the monthly drug acquisition cost of a typical patient is the same (Fig. 1c). However, in our estimates, the value of the drug is higher than the monthly drug acquisition cost in all indications albeit to varying degrees. The health economic assessments were based on a fixed treatment duration of 22.5 months for renal cell carcinoma, adenocarcinoma and squamous cell carcinoma non-small-cell lung cancer. Without the fixed treatment duration, the drug acquisition cost is higher than the estimated value (Table 1). The NT-council recommends the use of nivolumab in all indications, with fixed treatment durations, in accordance with the negotiated agreement (with confidential discounts) between the manufacturer and the county councils.

**Fig. 1** Drug acquisition cost vs. estimated value per month for a typical patient in several indications. RCC renal cell carcinoma, NSCLC non-small cell lung cancer. *Using a fixed treatment duration of 22.5 months
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3 Examples of Drugs Used in Combinations

As with many forms of cancer, there are challenges with high treatment costs in multiple myeloma [8]. Carfilzomib is an example of a new drug used in combinations with existing therapies. The cost per QALY for carfilzomib in combination with lenalidomide and dexamethasone was estimated to SEK 2.5 million per QALY [9]. Median progression-free survival in patients treated with the combination is 8.7 months longer than in patients treated with lenalidomide and dexamethasone only. A large part of the cost per QALY is due to the prolonged treatment with lenalidomide. In fact, TLV acknowledges that even if the price of carfilzomib was set at SEK 0, the treatment would not be cost-effective. The NT-council states that given the product-based health economic evaluation, it has not been possible to negotiate an agreement for carfilzomib used in combination with lenalidomide and dexamethasone [10].

Similarly, the NT-council does not recommend the use of elotuzumab for multiple myeloma in combination with lenalidomide and dexamethasone due to an estimated cost per QALY of SEK 3.9 million [11]. Again, the cost is largely driven by the prolonged treatment with lenalidomide.

The cost per QALY for carfilzomib in combination with dexamethasone only was estimated at SEK 2.7 million by the TLV [12]. As a result of negotiated confidential discounts, the combination treatment was considered cost-effective and the NT-council recommends that the county councils use carfilzomib in combination with dexamethasone [10].

Bortezomib is another drug for multiple myeloma that is used in combination with other drugs; however, the treatment has a fixed treatment duration. Bortezomib is used for up to 24 weeks in combination with thalidomide and dexamethasone, and for up to 54 weeks in combination with melphalan and prednisone. Thus, new drugs that are used in combination with bortezomib will not have the same challenges as those combined with lenalidomide, as there are no additional costs of bortezomib in prolonged survival.

4 Challenges and Possible Solutions

This study illustrates that the value of a drug may differ between indications by providing examples of the current product-based pricing and reimbursement system in a Swedish setting. If the price does not correspond to the value of a drug, there are several implications. Firstly, if the price is too high in relation to the value there is a risk
that patients will be denied access or have delayed access to treatment for certain indications. Secondly, if the price is too low in relation to the value, it could discourage development of new drugs in the long run as manufacturers are not rewarded for their innovation.

Even though price discrimination between indications is unusual in practice, manufacturers can use price discrimination by differentiating the product, for example by different dosing regimens and/or modes of administration. One example is everolimus, which is marketed under several brand names, each with a different dosing regimen for a specific indication: Certican, for prevention of transplant rejection; Afinitor, for several oncological indications and Votubia, for tumors associated with tuberous sclerosis. The price for Votubia and Afinitor is similar, around SEK 180 per mg, whereas the price for Certican is around SEK 80 per mg.

Another consequence when value differs between indications is that manufacturers may withdraw the product from an existing low-value indication in order to relaunch it in a new high-value indication market in order to obtain a higher price. This is a detriment to both the patient and from a societal perspective as patients of the initial indication will not get access to the product.

We suggest two principles to modify the current VBP system in order to account for the varying value of a drug. One approach is to use a single “weighted-average” or “blended” price based on an average value across all indications, weighted by expected patient volumes. France, Germany, and Australia use systems in line with this “weighted-average” price for multi-indication drugs [13].

Another approach is multi-indication pricing that would enable price differentiation between indications. A prerequisite for this system is stringent data collection so that the volume can be traced per indication and allow for separate discounts. Italy has developed risk-sharing agreements based on indication-specific patient registries to track volumes, and to some extent outcomes, for each indication, and in some cases by line of treatment. Manufacturers pay €30,000 per year for each registry relevant to its products [13, 14]. In the USA, a large manager of prescription-drug benefits has adopted multi-indication pricing for some cancer drugs [15]. In the UK there is a pilot project testing the feasibility of multi-indication pricing based on the NHS’s Systemic Anti-cancer Therapy (SACT) data set [13].

Combinations of drugs can be considered a special case for multi-indication pricing and reimbursement. If the various drugs can be combined in a single pill or dose, the valuation and the pricing and reimbursement process by HTA organizations is straightforward. Product-based pricing can be used and there is no need to attribute a proportion of the price explicitly to a specific component. The prices of these drugs when used as monotherapy would not be affected. In type 2 diabetes, for instance, long-acting and short-acting insulins are combined into new drugs. One example is the new drug Xultopy, which is a combination of liraglutide (Victoza), a GLP-1, and insulin (degludec). A one-pill combination may be challenging if one of the components is a biologic and the dose must be based on patient specific factors such as weight. Other complications may arise if the dosing regimens of the components needs to be varied, or if the components are provided by different manufacturers.

These specific examples of combination of drugs used to treat multiple myeloma show that combination pricing is particularly challenging when a new drug is used in combination to prolong the survival and when the treatment duration is not fixed. The challenge is similar to the case of life-extending drugs given to dialysis patients, as the prolonged survival induces the high background costs of dialysis [16, 17].

Assume a case where a new drug prolongs survival and, consequently, a prolonged use of the anchor drug. In a product-based pricing and reimbursement system, the anchor drug is priced in accordance with its value as a monotherapy (Fig. 2a). The new drug fails to show cost-effectiveness as it prolongs survival and continued drug use (Fig. 2b).

In an alternative payment system, the anchor drug and the new drug could be priced in accordance with the value they bring as monotherapies, but both drugs could be distributed free of charge for the additional months of survival (Fig 2c). The high-value price can then be maintained when the drugs are used as monotherapies.

Similarly, a pricing and reimbursement system that could price differentiate between indications would allow for different prices for a specific drug used in monotherapy versus combination, in order to achieve overall cost effectiveness (Fig 2d).

Another possibility could be to price the anchor drug equal to the marginal cost of producing the good when it is used in combination therapies (not illustrated). One could argue that such approach would be more “fair” as the manufacturer of the anchor drug already receives its revenue from the value it brings as monotherapy, whereas the manufacturer of new drug must bear all the investment cost in the development of the combination therapy.

In a payment scheme that differentiates pricing between indications, countries using international reference pricing [18] might reference the price for the lower-value indication. Therefore, we predict that manufactures would be unlikely to agree to such a payment model. However, this practice could be avoided by keeping an official list price and using confidential rebates linked to the use per indication. In addition, there is a risk that healthcare providers
within a country may try to obtain the drug for treatment of higher-value indications for the price of lower value indications.

In the case of combination pricing, there is a risk that the manufacturer of the anchor drug will not agree to lower the price when used in combination with the newer drugs. The manufacturer may fear that such a price drop may spread from the lower-value combination therapy to other indications where the drug is used as monotherapy. Furthermore, if manufacturers do agree to combination pricing of products, there is a potential legal challenge as manufacturers may be accused of having pricing cartels. Therefore, in order for this payment model to be successful three-party agreements with payers are needed.

5 Previous Literature

Multi-indication and combination pricing and reimbursement has previously been discussed and explored in the literature [13, 19–21]. Garrison and Veenstra highlight the challenges associated with the changing value of a drug over its product life cycle. Trastuzumab is used as an example to illustrate that the future value of the drug changes as the adjuvant treatment reduces the future incidence of metastatic disease [19]. In the early development of the Swedish valuation process, two TLV employees suggested a dynamic pricing and reimbursement approval process considering subsequent expected indications [22].

Similar to our study, Bach estimated the value of drugs used in different indications based on life years gained in the US setting [20]. For example, trastuzumab had a current monthly price of US$ 5412, whereas the estimated value (based on achieving a value of US$ 150,000 per year of life gained) was US$ 24,867 for adjuvant treatment and only US$ 6000 for metastatic treatment of breast cancer. Bach and colleagues have developed a drug pricing tool, relating the price of cancer drugs to the value in terms of survival, side effects etc., in the US setting [23].

A recent study investigated the probability of cost-effectiveness for combination therapies used in breast cancer patients based on the published literature. The study indicated that regardless of the clinical value and drug price, almost all of the selected new combination therapies had

![Fig. 2 Product-based pricing and multi-indication pricing for combination therapies](image)
little or no chance to meet the thresholds of cost-effectiveness [24].

In a report commissioned by NICE, the challenges when assessing combination therapies that are not cost-effective even at a zero price were discussed [25]. One proposed solution was to classify costs that are incurred solely due to increased survival as unrelated, and consequently exclude such costs from the incremental cost-effectiveness ratio. Another solution was to properly account for the benefits, such as the application of end of life QALY weights.

6 The Way Forward

Alternative payment schemes, including multi-indication pricing schemes and performance-based payment schemes, have proven challenging to implement. This is partly due to high costs of data collection [26, 27] and subsequently there has been a trend towards minimizing the administrative burden of alternative payment schemes [28]. Therefore, where possible, multi-indication pricing should rely on existing administrative infrastructure to track the number of patients per indication. The Nordic countries have a long history of health registers and National Quality registers, but the existing structures do not support the tracking of patient indication unless linkages are made between different registers [29]. Furthermore, they often have long data lags not conducive to these payment models. In the Nordic countries, the addition of a field for the diagnosis code in the prescribed drugs registers would enable an implementation of multi-indication pricing schemes.

In conclusion, these examples from Sweden illustrate that the value of a drug can differ substantially between indications, patients’ degree of severity and when used in combination. A multi-indication pricing and reimbursement scheme may better reflect the full value of a drug compared to a product-based pricing and reimbursement system whilst having the potential to enable a faster uptake, and improve patients access to new innovative drugs.

Author Contributions UP developed the main conceptual ideas, contributed to the design, analyzed results and contributed to the writing of the manuscript. JMN reviewed documents, made calculations, analyzed results and contributed to the writing of the manuscript.

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References


△ Adis
25. Davis S. Assessing technologies that are not cost-effective at a zero price. Report By The Decision Support Unit. University of Sheffield; 2014.