

PRICING FOR MULTI-INDICATION MEDICINES: A DISCUSSION WITH ITALIAN EXPERTS

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SUMMARY

Negotiating the prices of drugs with multiple indications presents important challenges that impact a range of stakeholders and can result in delayed patient access to potential life-saving treatments. A broad range of stakeholders was recently assembled by the UK Office of Health Economics to work toward consensus on the challenges and solutions which promote better patient access and sustainable health care and innovation. The expert panel considered that differentiating payment based on value at the indication-level represents an important part of the solution for multi-indication therapies, for which implementation must recognise divergent country health systems and experience. Considering this conclusion the present paper represents a multi-step project developed by an Italian Board of experts with the primary aim of driving a deeper understanding of the critical issues and solutions relating to access to multi-indication therapies in Italy. By starting from evidence on the positive impact of value-based differential prices on innovation and access to innovative medicines, the experts discussed and defined the specific features of payment models that could be implemented in the Italian context.

Key words

Multi-indication medicines; value, pricing; innovative drugs.

Impact statement

- Negotiating the prices of drugs with multiple indications presents important challenges.
- In the case of extensions of indication throughout a drug lifecycle, it is necessary to perform a specific evaluation applying the principle of value-based pricing.

- Value-based pricing implies that a value framework is agreed, using a multi-inclusive approach, that value is measured, and that a decision-making path that converts a value into a price is defined.
- Value-based pricing managed per indication through specific entry agreements should be integrated and corrected with a price/volume approach every time the new indication extends the patient population from orphan/rare diseases to more prevalent ones.

INTRODUCTION

A cardinal feature of many innovative drugs approved in recent years is that they are effective in a plurality of therapeutic indications. This multi-indications pricing poses two critical challenges.

Firstly, while the regulatory processes proceed, it is usually questioned whether it would be preferable to have a single price for all indications or adopt differential prices for the same medicinal product in its different indications (1). In this respect, various strategies have been suggested for indication-based pricing:

- other brands or different list prices for each indication;
- a “blended” price, obtained as a weighted average (by volumes) of the prices appropriate for the other indications;
- a single list price with differential “adjustments” of the net prices, aligning them to a value-based payment model per individual indication.

Furthermore, value-based pricing for medicines, aimed at determining the price of a drug on the grounds of its added value, is generally well accepted (2, 3), but raises at least two issues: whether the added value should consider dimensions other than the primary endpoints employed in the drug registration trial (e.g., convenience to patients or organizational impact on health care organizations) and which perspective should be used to calculate the net added cost generated by a new medicine. Secondly, a new indication expands the target population, thus challenging budget constraints: a price-cut is expected and often required by payers. This price cut depends on the new target population’s dimension, but the health care system’s budget impacts considerations.

A recent expert consensus report, published by the OHE (4), has investigated policies implication of indication-based pricing. Evidence on the positive impact of value-based differential prices on innovation and access is provided. More specifically, the international experts identified some examples of how to price flexibilities (or lack thereof) have:

- influenced the availability of therapies in individual countries, suggesting that better recognition of value at the indication-level may be associated with improved breadth and speed of access;
- incentivized innovation.

Three main elements characterize Indication-based pricing in Italy. First, when a new indication is approved, companies are asked to submit a full price and reimbursement dossier. Hence, a further indication is considered as a new medicine. Second, among the models mentioned above for indication-based pricing, a single list price with adjustment of net price aligning value-based payments per individual indication has prevailed so far. This choice has been supported by (i) the existence of web-based regulatory certified drug registries that allow tracking medicines use per indication and (ii) a diffused application of hidden discounts and managed entry agreements that permit different prices per indication to be charged to the National Health Service, keeping the public price the same across all indications (5, 6). Third, a price-cut is often requested due to price/volume considerations.

OBJECTIVE AND METHODS

A multi-step project was developed by an Italian Board of eight experts, from different pro-

fessional backgrounds, with the primary aim of discussing the critical issues posed by multi-indication medicines and payment models currently available for their reimbursement.

The experts were requested to express their opinions on what could best address critical issues and, ultimately, offer recommendations and solutions on recognizing differences in value across the different approved uses of a drug. To drive a deeper understanding of the critical issues and solutions relating to access to multi-indication therapies, each one of the eight experts participated in a personal interview followed by a written report approved individually. Finally, in an online Board meeting, the experts discussed the specific features of payment models that could be implemented in the Italian context.

FRAMING THE CRITICAL ISSUES

The first step was identifying the critical issues of the Italian P&R model for new indications.

A general concern was expressed on the presence of spending caps on drugs, which makes the price negotiation anchored only to the budget effects on the pharmaceutical market, disregarding the impact of a drug on other health services and expenditures, such as those linked to the reduction of adverse events, a better efficacy profile and the relevant avoided costs.

A second element is the actual role played by real-world data. It has been highlighted that, despite the emphasis put on their importance, there is no evidence on if and how they are used in the first negotiation (accurate world data on adverse events, available since the product has been already approved for other indications) and re-negotiations (data on effectiveness, cost-effectiveness, and budget impact).

In the past, Italy has successfully adopted a model that published a single public price, with different final net prices, through the use of hidden discounts, financial (e.g., expenditure ceilings by product, price-volume agree-

ments, coverage by companies of the costs of the first cycles of therapy, named cost-sharing in Italy) and outcome-based managed entry agreements (mainly performance-linked reimbursement, called payment by result in Italy) per different indications. However, outcome-based contracts have been increasingly challenged in recent years, and cross-indication discounts or price-cut have prevailed in the negotiation process. The proportion of pure payment-by-result agreements over total Managed Entry Agreements dropped from 55% in 2016 to 52% in 2018 and 44% in 2020 (7). In 2021 and 2002, only payment at results contracts for advance therapies has been signed. Furthermore, in a document signed by the Italian Ministry of Health and by nine other Countries (Draft Resolution aimed at “Improving the transparency of markets for medicines and other health technologies”), the issue of price transparency was raised (i.e., confidential discounts and MEA agreements).

Applying a discount (or price-cut) on all indications when a new one is approved flattens everything, using a purely financial-impact approach, without recognizing the different possible value to each indication. Furthermore, the discount/price-cut is questionably presumptive (i.e., based on estimates of future volumes).

Off-label use can also be seen as symptoms of the problem and evidence that change is needed.

DEFINING CONCEPTUAL ELEMENTS BEHIND THE SOLUTION

There was a consensus that health value must be the driver for defining the price of a drug. This requires to structure of the logic that converts such value into price models. Value-based pricing from an operational viewpoint implies that a value framework is agreed, that value is measured, and that a decision-making path that converts a value into a price is defined (2, 8).

Regardless of the final model to be adopted, indication-specific value-based price-set-

ting and reimbursement decisions should be agreed upon.

Current value frameworks need to be adapted to specific situations

It would be important starting for a broader definition of the value of a drug (9) considering the unmet medical and social need, the added value (and the quality of the evidence supporting its), including different dimensions such as the clinical impact and patient-reported outcome, implications for caregivers and the general impact on clinical pathway and health care organizations.

Value frameworks and economic impact

On the one hand, the actual value of a pharmaceutical innovation depends on its long-term incremental benefits and net incremental costs (*i.e.*, on value for money). On the other budgetary constraints cannot be denied, and the impact on a budget should be the second pillar of evaluating the economic impact. Impact on health care costs, and, if possible, costs in the perspective of the society, should be considered in such an economic assessment. It would also be necessary to assess the value over the entire life cycle of the drug, systematically collecting real-world evidence data to re-assess the value as these data are generated, confirming the original assumptions or modifying them in any positive or negative direction (10). Actual world data must be collected using electronic health records following the regulatory authorities' specific requirements and standards. Optimally, and to minimize additional administrative effort, these would be facilitated by data extraction from routinely collected datasets (11). Mainly, it must be done compliant with data protection regulations.

Value-based pricing requires identifying an applicative model

Value-based pricing has been applied according to two models: (i) direct models driven by cost-effectiveness (mainly applied to the incre-

mental cost-effectiveness ratio - ICER); and (ii) indirect, multi-attribute models characterized by greater discretion on the integration among the different value domains and the consistency evaluation between costs and value. In Italy, the second has prevailed so far, but the role of cost-effectiveness in the negotiation of prices should be better clarified.

Pricing and reimbursement decisions should recognize the uncertainty on evidence at market launch and the impact of medicines in real life

It is necessary to reconsider the benefit of pricing and reimbursement models that are outcome-based and adaptive. Conditional reimbursement mechanisms (*i.e.*, performance-linked reimbursement) of outcomes-based payment can improve the final allocation result, especially in the case of high uncertainty on the impact of medicines at market launch. Indeed, in the case of an outcomes-based mechanism, the reimbursement can be made conditional on actual therapeutic results as certified from real-world-evidence data registries (12).

IMPLEMENTING A PRICING AND PAYMENT MODEL FOR MULTI-INDICATION DRUGS

General recommendations (*i.e.*, applicable to any price negotiation)

Value-based pricing implies that a drug's value for money mainly drives prices and that the impact on budget (sustainability) is a second-order variable of price regulation. In general, and in the case of extensions of indication throughout a drug lifecycle, it is necessary to perform a specific evaluation applying the principle of value-based pricing. This assessment must respect a logical chain of drivers. First, there is the demonstration of value. For each patient under treatment, there should be an assessment of the consistency between value and cost (value for money) and, finally, consistency between the impact on bud-

get and the available funding for the National Health Service.

The added therapeutic value must be appropriately considered in the price negotiation process. It is necessary to define an actual evidence-based ranking for the additional therapeutic value that instructs the application of a premium price. This same approach should also be used when there is an extension of indication. A price negotiation process is much easier when a point scale of additional therapeutic value is established to obtain a premium price compared to existing comparators (or standard of care) and, therefore, avoiding an excessive price reduction due to problems of affordability by the health system.

Another relevant aspect is represented by the existing comparators and the reasonable cost. In addition to the value, it is also important to consider the characteristics of the comparators. This issue is also essential when there is an extension of indication as these comparators and having a differential value concerning the new indication of a drug already existing may have a different cost. This aspect must be governed by defining *ex-ante* the standard comparators and trying to understand how to balance the presence of many low-cost comparators and any added therapeutic advantage of the new indication.

Value-based pricing also implies that informative uncertainty on value be considered when prices are set. Outcome-based managed entry agreements should be re-implemented for this purpose, through either a population-based (*i.e.*, post-marketing study to verify the medicine's impact in real life) or a payment-by (or at-)result contract in which the industry give back money for non-responders (or payers pay only for responders to therapy).

Specific recommendations (*i.e.*, applicable to pricing negotiation for new indications)

Price negotiation should be indication-specific. Generally, it is not always possible to envision a single contextual negotiation for

the different indications of a drug that will be launched in the future, as very often the timing between one indication and another is different, spanning even several years, and there are a series of variables that are only partially predictable. Therefore, it is usually, although not always, more efficient to use individual negotiations for each indication unless the other new indications are expected to be discussed/approved very soon. Notwithstanding, separate negotiations for each indication should rely on the transparent sharing, between the HTA/payers' authorities and the pharmaceutical industry, of the horizon-scanning regarding the possible arrival of future indications.

When a new indication is approved, a choice must be made between two main approaches to convert the value into a pricing model. As mentioned before, pricing a further indication on value grounds can be mainly performed through two main courses (the third solution, *i.e.*, having different brands for different indications and prices per brand, is very rare). The first involves establishing a different price for each indication and, consequently, negotiating possible various managed entry agreements only when certain conditions are met or when there is significant uncertainty about the value of the drug (*i.e.*, single list price with adjustment of net worth to align with value-based payment per individual indication). The second approach involves redefining the price based on the weighted average value: when there is a new indication, the price for all indications of the drug about the weighted average value must be renegotiated (*i.e.*, "blended" price, obtained as a weighted average of the costs appropriate to the different indications and the volumes associated with each indication).

The first approach would be preferable as:

- reflects more the value per indication, while the blended price requires a complex assessment of the weighted average value (where the 'weights' could be based on the size of the target population, which is estimated for the new indication, whereas

for the indications already approved in the past there should be evidence on the number of patients treated);

- makes negotiation more flexible: if, for example, for the new indication the added therapeutic value compared to comparators is low, there are no significant uncertainties about this value, and the impact on other costs is limited, a discount can be negotiated on the price valid for that indication, not affecting the other indications.

However, this approach is undoubtedly more complex to manage as it requires usage tracking by indication. Thanks to the drug registers, this is possible in Italy, but these registers have an administrative burden.

Price/volume should be a second-order driver of price negotiations. The price/volume logic (increased discounts due to increased volumes) should also be considered. This should occur when the extension of the indication provides for the transition from a minimal target to a more prevalent disease, considering, however, that if the effect of the launch on the new indication is the replacement of another therapy, the problem is more minor.

Finally, cross-coverage of multiple indications in the same patient should be considered. Sustainability assessment also requires considerations of specific situations. In the same patient, comorbid conditions are treated with a multi-indication drug; there is a cross-coverage of indications on the same individual. Such cross-coverage represents an economic advantage for the Payer System that must be considered when calculating the budget impact.

CONCLUSIONS

In recent years, due to advancements in biotechnology, agnostic targets definition, and the development of trans-nosography pharmacology, many pharmaceutical products are efficacious in multiple indications. However, the degree of such effects could differ substantially. The price and reimbursement conditions should be re-negotiated every time a new indi-

cation is approved. These re-negotiations are challenging to prospectively manage, *i.e.*, capturing in one *ex-ante* model through a horizon scanning activity all new indications, expected to be approved in two/three years. The current tendency to enforce automatic mechanisms (*i.e.*, pre-defined price-cut based on expected volume increase) has proven to have serious flaws preventing the development of new indications. New models based on selective value considerations per further indication approved have now been discussed worldwide.

In general, value-based pricing implies that value frameworks are adopted, using as much as possible, a multi-inclusive approach, which computes pre-specified value expected metrics and, by looking at the total economic implications, weighs in value-for-money and budget impact as a first- and second-order criteria respectively. There are two models for pricing new indications according to value: (i) establishing a different price for each indication on the grounds of outcome value, through discounts and managed entry agreements (mainly of the payment by result type) or (ii) redefining the price based on the weighted average value of the product for all indications. The first approach, despite it, requires maintaining regulatory and payer-certified drug registries. It is preferable to reflect the value per single indication, making subsequent negotiations more flexible. On the other hand, a single price reimbursement system per product would be rigid and unable to adapt to the evidence reflecting the effectiveness of various indications. In addition, patients could be delayed or denied access to drugs in a product-based single pricing and reimbursement model. At the same time, sponsors are discouraged from investing in developing other promising indications.

At the same time, value-based pricing managed per indication through specific entry agreements should be integrated and corrected with a price/volume approach (budget impact consideration) every time the new indication extends the patient population from orphan/rare diseases to more prevalent ones.

Regardless of the existence of outcome-based agreements, it's essential assessing the value over the entire life cycle of the drug per every single indication, systematically collecting real-world evidence data to re-negotiate the value as these data are generated, confirming that the original assumptions were correct or modifying them by increasing or decreasing the reimbursement in agreement with the data collected at least every other year or until the market access penetration and equilibrium have been completed.

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ETHICS

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Conflict of interests

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All the activities for the realization of the article (choice of topics, selection of contents, drafting of texts, choice of sources, selection and involvement of Authors) were carried out in full autonomy by Authors without any interference.

Authors' contribution

All authors wrote and contributed to manuscript revision, read, and approved the submitted version.

Availability of data and materials

The data underlying this manuscript are available in the article.

Ethical approval

N/A

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