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Initiative to develop a multi-indication pricing framework for Belgium

Multi-stakeholder initiative

Report

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Colophon

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Executive Summary

In recent years, more and more products targeting multiple indications (uses) have been brought to market. The number of indications under development for one and the same molecule is also increasing over time. Which means that more and more different indications for one medicine can be submitted for reimbursement in a short time or even around the same time. Our current pricing & reimbursement model is focused on the reimbursement of one specific indication (one indication at a time) and is not adapted to this situation. This affects patients, payers, and companies.

Belgian pricing and reimbursement authorities are aware of the issues and attempted to create a pricing mechanism specifically for multi-indication products, such as linear price cuts, based on the increase of volume justifying a price reduction. Since authorities are exploring ameliorated forms of Managed Entry Agreements (MEA's), we focused on **multi-indication pricing (MIP) mechanisms** - also referred to as an indication-specific pricing (ISP) mechanism –to combine value and volume elements.

In some countries, such MIP-models are applied, and Inovigate has conducted extensive research on these MIP models and studied pilot-cases in other countries. This has resulted in four possible models that can be considered for Belgium:

> Model 1: The same product is marketed under different medication pack presentations or brand names for different indications (or based on different dosages), each with different prices. Each might have different prices for the use of the same product but for different indications.
>
> Model 2: A "weighted-average" price, based on an average of the value across all indications. This weighted average is used for the reimbursement of all indications. The weighted average is the average of all indications but whose value is most influenced by the indications with the highest weight.
>
> Model 3: Proactive discounts based on volume or value. This mechanism starts from a single price reflecting the indication with the lowest volume or the highest value (for the already known indications). The differential discounts for the consecutive indications are applied based on their relative volume or value with respect to the lowest volume or highest value indication. A common form of application is through risk-sharing agreements.
>
> Model 4: Retroactive claw backs based on volume or value. This model starts from a single price reflecting the indication with the lowest volume or highest value. Differential discounts are applied based on their relative volume or value with respect to the lowest volume or highest value indication. Claw backs are claimed based on the actual volume or value of the product. This claw back has no effect on the agreed list price.

Model 2 is also called uniform pricing, which is the opposite of differential pricing, and which is the basis of models 3 and 4.

We examined the feasibility of the 4 models in the Belgian context. During in-depth interviews with representatives of the key Belgian stakeholders (RIZIV, cabinet of minister of health, sick funds, clinicians, academia, patient organizations), feedback on these four model types was collected. Notwithstanding some reluctance, it is fair to say that there is an emerging alignment among stakeholders that we can improve access to multi-indication medicines by evolving the access approach.

The stakeholders were asked to evaluate the models based on predefined criteria such as financial sustainability, traceability, feasibility, flexibility, etc. Multi-stakeholder preferences on each of the models were collected, resulting in two models, model 2 and model 4, with attractive elements for most of the interviewed stakeholders. The stakeholders felt that the preferred model should take both volume and value into account, but that an average weighted and blended price is also attractive from a simplification point of view. These attractive elements have been combined into one overall preferred MIP model for Belgium, with a specific dynamic-in-time, and uniform-across-indications, pricing mechanism. This combination model had the broadest support from stakeholders and was subject to a multi-stakeholder debate.

The resulting Belgian MIP model proposal is based on a dynamic-in-time pricing mechanism and also uniform-across-indication pricing mechanism. In this model the base price is calculated based on a weighted average price across indications, and which might vary (based on or real-world evidence on value or volume, being generated over time to address uncertainties). Therefore, a lower price considering uncertainties is more realistic, however, with the condition that the price becomes dynamic and flexible over time and can increase when more evidence becomes available. This requires a performing real-world data infrastructure and a supporting funding and governance model for data access, as well as a good real-world evidence collection methodology.

The transition to a new model will not happen overnight. A “learn and adapt” principle will be more favorable, which means starting with an optimal model but adapting and improving over time based on key learnings. Also, we need to do this in dialogue with all stakeholders to make it work.

We would like to underline the importance of the multi-stakeholder conversation for such complex issues. It is relevant for authorities, “buyers and payers”, as well as for all stakeholders in medicines policy to try to seek alignment, and to build mutual understanding and trust. These are the first steps towards further detailing and optimizing the new model.

1. The need for an MIP framework

1.1 Today's challenge

The number of new and existing drugs with multiple indications, used alone or in combination, have increased in recent years and this trend will continue in the future (e.g., 75% of major cancer medicines are for multiple indications) [1]. Emerging treatments targeting diseases with common underlying mechanisms have highlighted the need to rethink reimbursement mechanisms. (E.g., Sildenafil, Aflibercept, Everolimus, …). Those treatments are targeting underlying pathways for multiple indications, or also called pathway therapies.

Today's pricing and reimbursement (P&R) model and procedures are not equipped to handle this because reimbursement is granted per indication, one by one and linear price cuts are applied when more indications come to market. A more appropriate way of setting the price across a bundle of indications is needed. In Belgium, there have been some attempts to have a pricing mechanism specifically for multi-indications, such as "linear price cuts for new indications", and a decision tree, where price is reduced to limit the incremental budget impact and based on the cost and the value of each indication. Those methods, however, do not consider the value[2] of the treatment per new indication and are not suitable in case of a large number of indications requesting reimbursement in a short notice or at the same time. The value of a drug varies between indications; therefore, our product-based pricing and reimbursement system does not align with the true value of the drug.

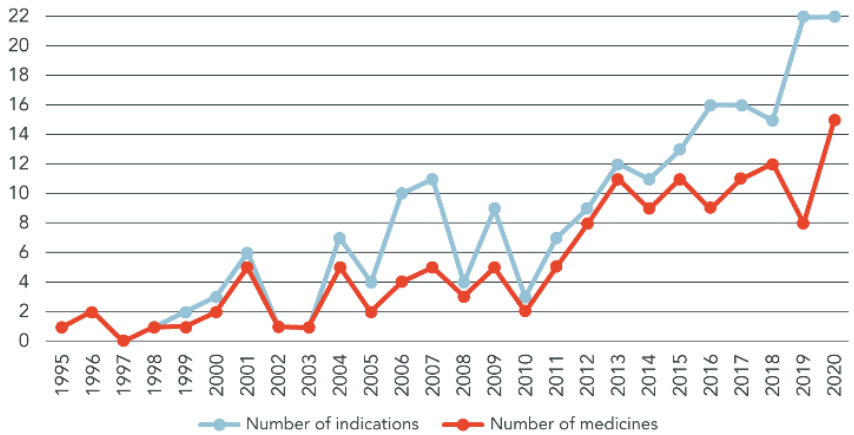

Figure 1: Number of EMA-approved cancer medicines vs. indications

To have a value and volume-based framework we can build on some of the building blocks that already exist today such as Chapter IV, the Tardis data registry, multi-year-multi-indication agreements, etc.

In today's situation, prices can be different across indications despite a single list price. In case of a multitude of indications, the timelines of the different procedures, revisions, negotiations, re-negotiations, … end up in a complex and time-consuming tangle. The reimbursement of additional indications for the same medicine in a management entry agreement (MEA) requires going through a new reimbursement procedure and new financial conditions to be

[1] Mestre-Ferrandiz, Alcala, Ferro, Santos

[2] "For a health economist, "value" captures the impact of introducing a new health technology in terms of its clinical and other benefits over and above the standard of care as well as implications on costs and resource use. Central to our understanding of "value" is making sure that we capture the most important and relevant outcomes that matter to patients. The impact of a treatment on a patient's quality and length of life is an integral part of the treatment benefits captured and evaluated through health technology assessment. But our understanding of patient outcomes, patient preferences, and how these should be captured and measured continues to evolve. Any discussion of value-based care and value-based pricing should encompass and incorporate the patient's perspective in defining that value." Cole, A., Neri, M. and Cookson, G., 2021. Expert Consensus Programme: Payment Models for Multi-Indication Therapies. OHE Consulting Report, London: Office of Health Economics. Available at: https://www.ohe.org/publications/payment-models-multi-indication-therapie

agreed upon. These procedures and negotiations are time consuming for both parties. The current decision tree can support more predictable pricing when there is a request for a new indication for the same medicine, but it does not support a full value-based approach, due to the linear price cuts that are only based on limiting budget impact and increased volume. Also, systems today do not allow for the application of different prices across indications due to data infrastructure limitations, and incentive schemes are not sufficiently designed to generate and use data to support MIPs.

Therefore, instead of a request for a reimbursement dossier and negotiation per indication, a solution for a group of indications in one assessment of variable health benefits across multiple indications in the mix (as a bundle of indications) should be developed**. Such a procedural pathway based on a bundled assessment is called a multi-indication pricing (MIP) framework.** Multi-indication pricing is an instrument which allows the price to vary according to its indication, based on value-based pricing and taking volume into account as well. 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.

1.2 Identification of a preferred MIP model for Belgium

We have performed an extensive literature search on possible models and solutions for multi-indication products, investigated cases and pilots in other countries, and reflected on the obtained experiences. We have spoken to experts and academia involved in studying MIP models.

In-depth one-on-one stakeholder interviews were performed in 2021 with each of the stakeholder representatives, to collect their viewpoints on possible models and on the feasibility within the Belgian context.

The following topics were asked during the interviews:

- Their perspective on the problem and burning platform
- Their suggestions for a multi-indication pricing solution
- Their perspective and preferences on possible multi-indication pricing models
- Initiatives and actions to be undertaken for its implementation

Finally, a multi-stakeholder debate took place to further finetune the proposed model.

The different stakeholder representatives involved in this project are:

- RIZIV
- sick funds
- clinicians
- patients
- cabinet of the minister of health
- industry
- academia

See the list of representatives that took part in the evaluation the list of contributors in the colophon.

The aim of this multi-indication framework project is to co-create, with the stakeholders from the Belgian health authorities, the most optimal solution based on the common ground across stakeholders.

1.3 Risks and benefits on multi-indication pricing

Based on the literature review, the benefits and risks for each of the stakeholders have been listed. The scheme below summarizes the benefits and the risks for payers, patients, companies and prescribers.

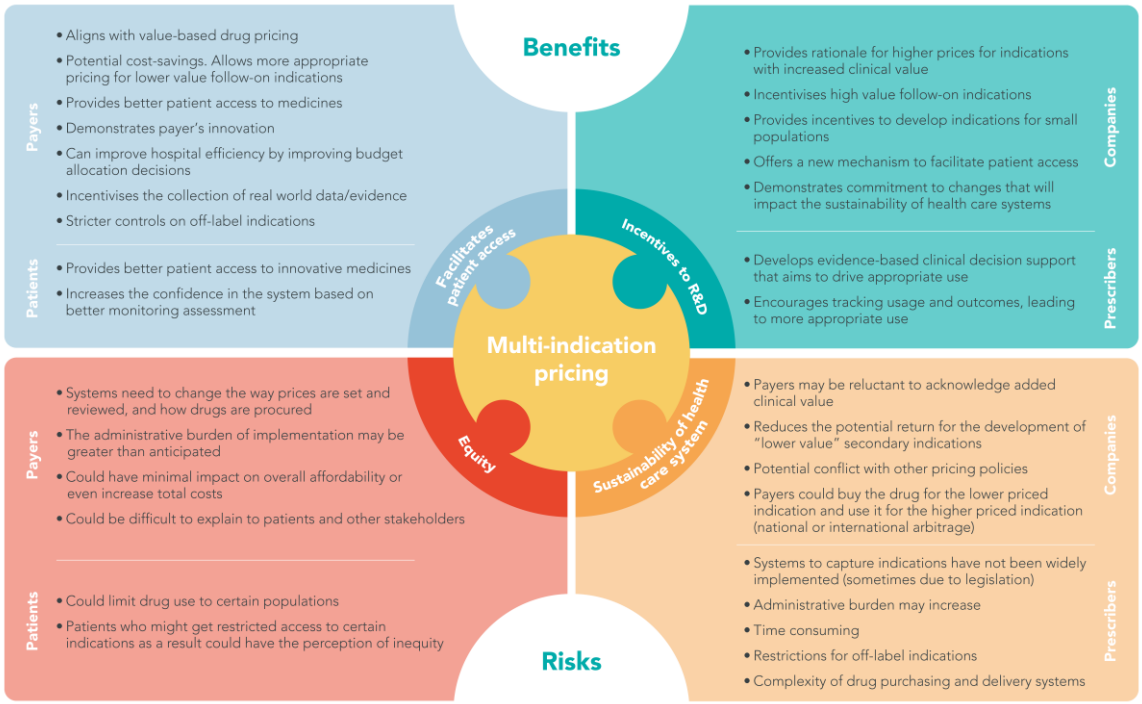

Figure 2: Benefits and risks of an MIP [3]

A MIP framework has a lot of benefits but also some risks for all stakeholders. Benefits are mainly to facilitate patient access, incentivize R&D (expansion to other new indications), reduce workload and associated costs to submit and evaluate new indications, and increase predictability of price and budget impact.
Risks are most associated to equity and the sustainability of the healthcare system.

The Belgian stakeholders each indicated different reasons for adapting the current model. From the patient perspective, getting access to medicines for certain indications will not be possible, or access may be delayed because companies may be discouraged to invest in new uses. From the payer's perspective, there is a need to control the budget better if more patients gain access to the treatment and to offer access to valuable innovative medicines in a sustainable way. From the industry perspective, there is fast price erosion when more indications are added, which discourages investment in future indications or bringing them to market. Industry is currently incentivized to focus only on those indications resulting in sufficiently high returns because of the fast price erosion, that are a result of linear price cuts.

Most stakeholders tend to agree that the actual P&R model can be optimized, to allow better access to more indications. A new MIP model would need to address the issues that most of the stakeholders are facing, in order to become successful.

Based on the stakeholder interviews it became clear that all stakeholders indicated similar reasons to consider a MIP framework for pathway therapies. To:

- Ensure patient access, as fast as possible. This is considered a very important criterion because the common cause of all stakeholders is to create correct access for valuable medicines and, thus, indications.

[3] Mestre-Ferrandiz J, Zozaya N, Alcalá B, Hidalgo-Vega Á. Multi-Indication Pricing: Nice in Theory but Can it Work in Practice? Pharmacoeconomics. 2018

- Prioritize valuable medicines and de-prioritize medicines not offering sufficient clinical and societal value.
- Reduce administrative burden and workload. However, this is according to most of the stakeholders, not a realistic objective to achieve. A single submission will not reduce the burden because evaluation per indication and even follow-up after additional evidence has been gathered will still be required.
- Deal with therapeutic uncertainty and spending on uncertain outcomes.
- Decrease budget unpredictability. This is difficult to achieve in case price needs to remain flexible to allow for adjustments each time new evidence is gathered. It should rather be redefined as “more budget control”.

The objective is that the MIP model would better support effective care (“doelmatige zorg”), based on a more holistic evaluation of the medicine. It would hopefully prevent constant renegotiation.

1.4 Key design criteria for an optimal MIP framework for Belgium

Stakeholders suggested similar design criteria for an optimal MIP framework. It should be flexibly adaptable per indication, based on true risk sharing and address the missing evidence challenge.

An optimal MIP framework for Belgium, that meets the common ground across stakeholders, will need to be based on the building blocks that are summarized in Figure 3.
It consists of four basic principles, four implementation aspects and four modalities.

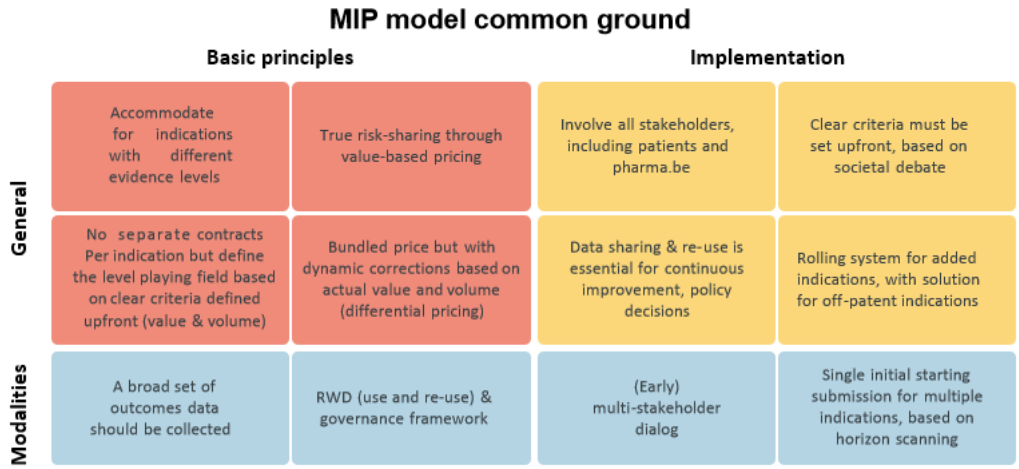

Figure 3: Principles, implementation aspects and modalities of an optimal Belgian MIP

The implementation of such a MIP framework, requires optimal real-world data access and a rolling system to adjust price per indication in a bundle.

2. A MIP solution and framework for Belgium

2.1 Four models were identified for further consideration

There are two important groups of pricing models for multi-indication products, mentioned in literature. One is differential pricing, which means a different price per indication, and the other is uniform pricing, or the same price for all indications. But it is not as easy as this dichotomy might suggest. For example, we can have a combination of a uniform list price with differential discounts, distinguishing between "list" and "net" prices. Moreover, how to determine the "uniform" price is also critical. The single (blended) price might be weighted according to either volume, value or both. Also, retrospective or prospective (Multi-Annual Multi-Indication agreements) corrections might be applied.

This can be brought back to four possible models as the archetypes for a possible MIP framework:

- Model 1: Different prices for the use of the same product based on patient diagnosis, or different medication pack presentation per indication
- Model 2: One single average price for all indications based on weighted average value for the whole indication portfolio
- Model 3: Proactive dynamic pricing, based on average “blended” pricing (at list price level), proactively set, based on volume or value
- Model 4: Retroactive dynamic pricing, based on average “blended” pricing (at list price level), retroactively corrected, based on volume or value

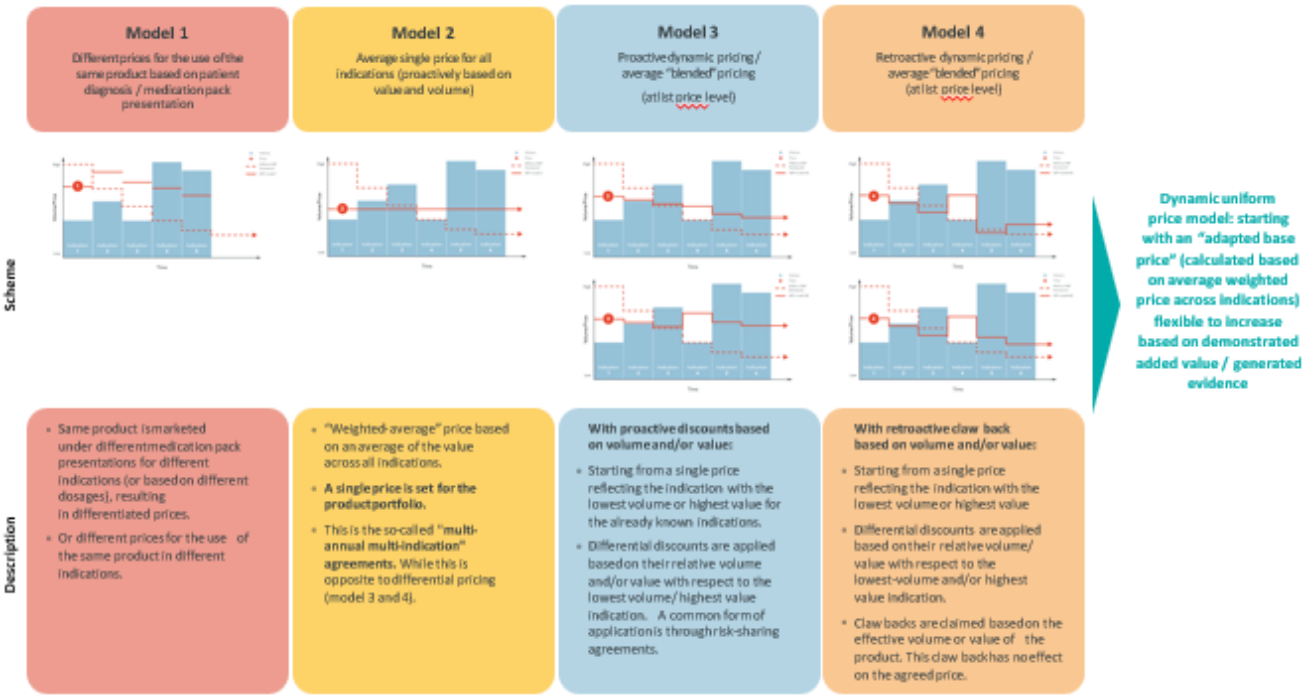

Figure 4: The four multi-indication pricing models that were evaluated in stakeholder engagement

Each of the four models is further detailed below together with the collected feed-back and evaluation by the stakeholder representatives in in-depth interviews.

Model 1: Different prices for the use of the same product based on different medication pack presentations

A first model is based on the principle that a same product is marketed under different medication pack presentations for different indications, different dosages, or even different brand names, resulting in different prices per pack or brand name, or different prices for the use of the same product in different indications.

Examples of this model are:

- Sildenafil: marketed as Viagra for erectile dysfunction but Revatio for pulmonary arterial hypertension
- Aflibercept: different brands in oncology and ophthalmology
- Everolimus: different brands for indications in solid organ transplants, oncology, rare diseases

In the figure below a visual representation of model 1 is displayed, where price is shown by the red lines, volume is represented by the blue bars, and each bar represents a different indication. The x-axis represents moving forward in time. The dotted line represents the price evolution of today without a multi-indication framework, where the price descends when more indications come to the market over time. The full line represents the price evolution in model 1 where every indication will be evaluated separately to identify and agree on the price.

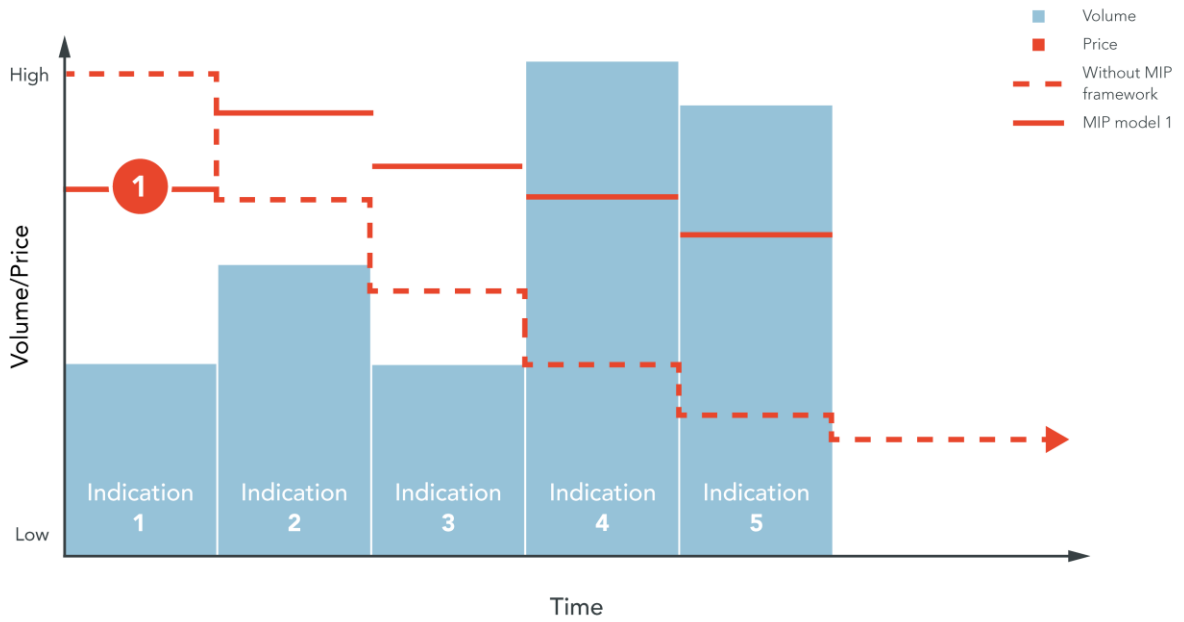

Figure 5: Model 1 - Different prices for the use of the same product based on different medication pack presentations

The evaluation of this model by the different stakeholders can be summarized in the following points:

- The challenge will be to track patients and negotiate a different price per diagnosis/brand, because the required data infrastructure and capability is missing.
- The launch sequence of each brand may have a large impact on the price.
- High administrative burden, as per brand a separate dossier has to be prepared and evaluated.
- It is perceived as an artificial solution, not supported either by the payer nor by the industry.

Model 2: Average single price for all indications (proactively based on value and volume)

The second model is based on a single average price set for the whole indication portfolio. This single price is calculated based on a "weighted-average" price consisting of an average of the price per volume across all indications. In this model the average price is most influenced by value that is expressed in the highest weight. This is the so-called "multi-annual, multi-indication" agreement.

This model was applied for Erlotinib in Germany and Australia, and Vertex's cystic fibrosis treatments in Denmark, Ireland and Sweden.

In the figure below, a visual representation of model 2 is outlined. Here the dotted line represents the price evolution today, without a multi-indication framework, where the price descends when more indications come to the market over time. The full line represents the price evolution in case of model 2, which is the result of a weighted-average price based on the average value and volume across all indications for the whole bundle of indications. This results in the same price for every indication.

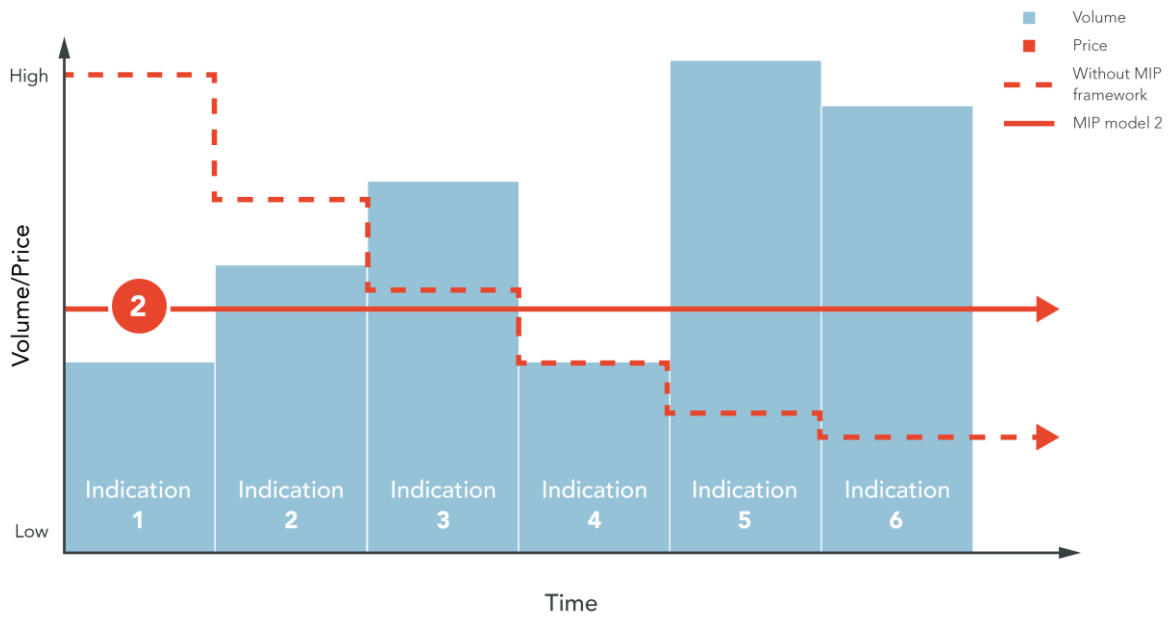

Figure 6: Model 2 - Average single price for all indications (proactively based on value and volume)

The stakeholders evaluated this model as more attractive compared to model 1, because:

- It requires less administrative burden, as one file will be required for the whole bundle of indications
- The price is calculated on the value of each indication and is weighted based on its expected volume in the whole mix of indications
- The sequence of launches does not impact the price
- Underestimation/overestimation of the price is a possibility, but can be remediated after revision of the contract (after 3 years)

Model 3: Proactive dynamic pricing with proactive discounts based on volume or value

The third model is a proactive pricing model with two options (A and B), one of which is based on volume adaptations and the other on value adaptations per indication, based on the assessment at the start (at launch, without adaptations later on).

Model 3A In this model proactive discounts based on volume are applied. It starts from a single price reflecting the indication with the lowest volume in the indication bundle. The differential discounts per indication are applied based on their relative volume with respect to the lowest volume indication. A common form of application is through a risk-sharing agreement.

Examples of this model are tisagenlecleucel (Kymriah) which uses indication specific prices and nivolumab, used for metastatic gastric cancer in Spain.

In the scheme below you can see a visual representation of model 3A. The dotted line represents the price evolution today without a multi-indication framework, where the price descends when more indications come to the market over time, due to volume increase, without considering value for the consecutive indications. The full line represents model 3A where the price is adjusted up or down starting from the average blended price level based on the volume for the added indication.

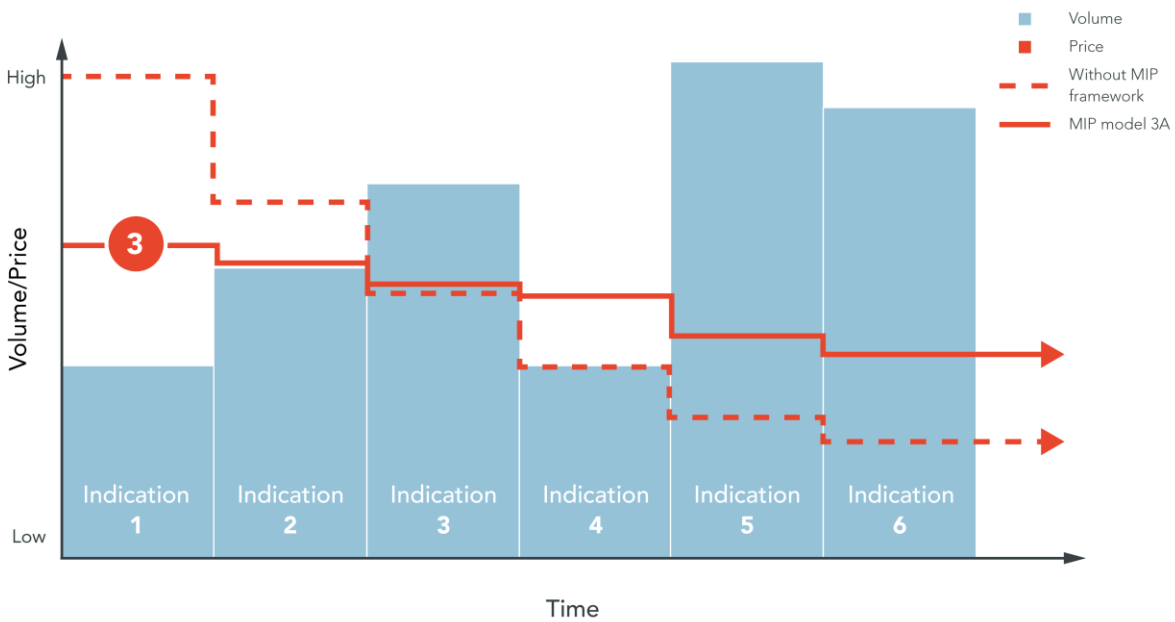

Figure 7: Model 3a - Proactive dynamic pricing with proactive discounts based on volume

This model is evaluated by stakeholders as:

- Proactive, that gives most certainty about the revenues for companies and the cost/budget impact for the payer
- One in which patients will need to be tracked, making implementation more complex

Model 3B implements proactive discounts based on value. It starts from a single average price reflecting the indication in the bundle with the greatest value. The differential discounts are applied based on their relative value with respect to the highest value indication. As with model 3A, a common form of application is through risk-sharing agreements.

Examples of this model are:

- dupilumab in Australia, US and Germany applied by individual insurers - ICER value-based price
- anti-TNF α
- IL-3i
- Other anti-inflammatory drugs

In the scheme below you can see a visual representation of model 3B. The striped line represents the price today without a multi-indication framework, with price decreases per new indication. The full line represents model 3B where price is adjusted up or down starting from a single price reflecting the indication with the greatest value and adapted on the basis of value per added indication.

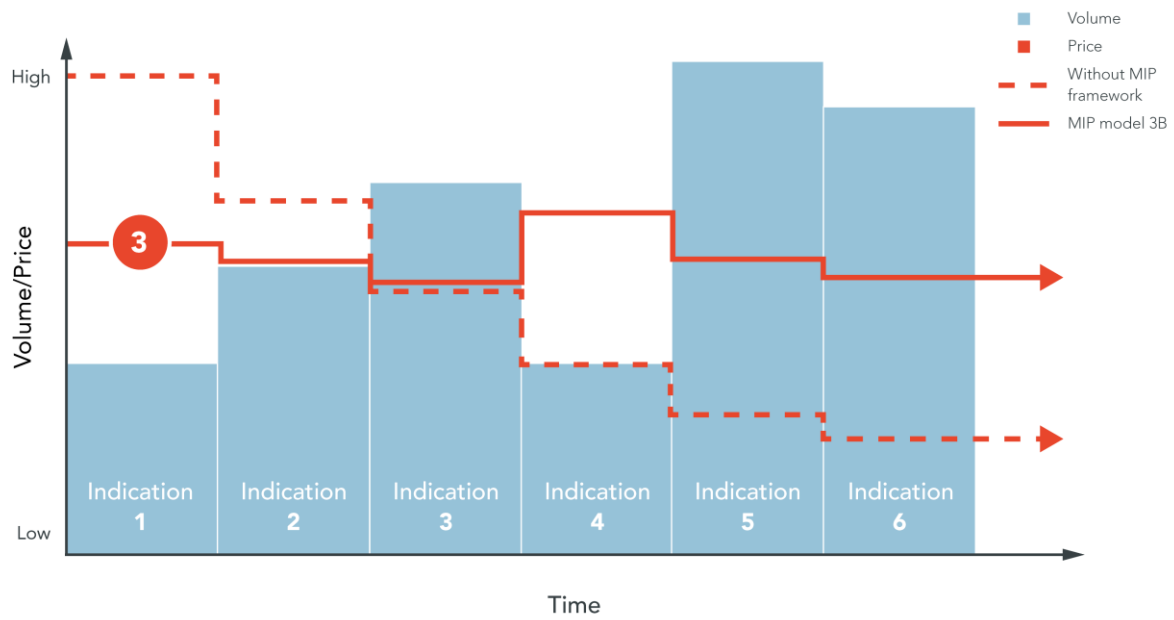

Figure 8: Model 3b - Proactive dynamic pricing with pro-active discounts based on value

This model is evaluated by the different stakeholders as follows:

- Proactive, providing certainty on the revenues for companies
- and on the cost/budget impact for the payer
- Patients will need to be tracked, which makes implementation more complex

Model 4: Retroactive dynamic pricing with retroactive claw backs based on volume or value

The fourth model is a retroactive pricing model also with two variations, one of which is based on retroactive volume and the other on value adjustments, via claw backs. The value assessment is based on actual or demonstrated outcome in real world and real-world evidence. And also, for volume the actual volume in the market is considered.

Model 4A uses retroactive claw back based on volume
This model starts from a single price reflecting the indication with the lowest volume. Differential discounts are applied based on their relative volume with respect to the lowest volume indication. Claw backs are claimed based on the effective volume of the product in real life.

The scheme below is a visual representation of model 4A. The striped line represents the price today, without a multi-indication framework, where the price descends when more indications come to the market over time. The dotted line represents the average blended price based on the estimated volume of all indications. The full line represents model 4A where the retroactive price adjustment up or down started from the single price reflecting the indication with the lowest volume and claw backs adjusting the difference between the estimated and real-life volume.

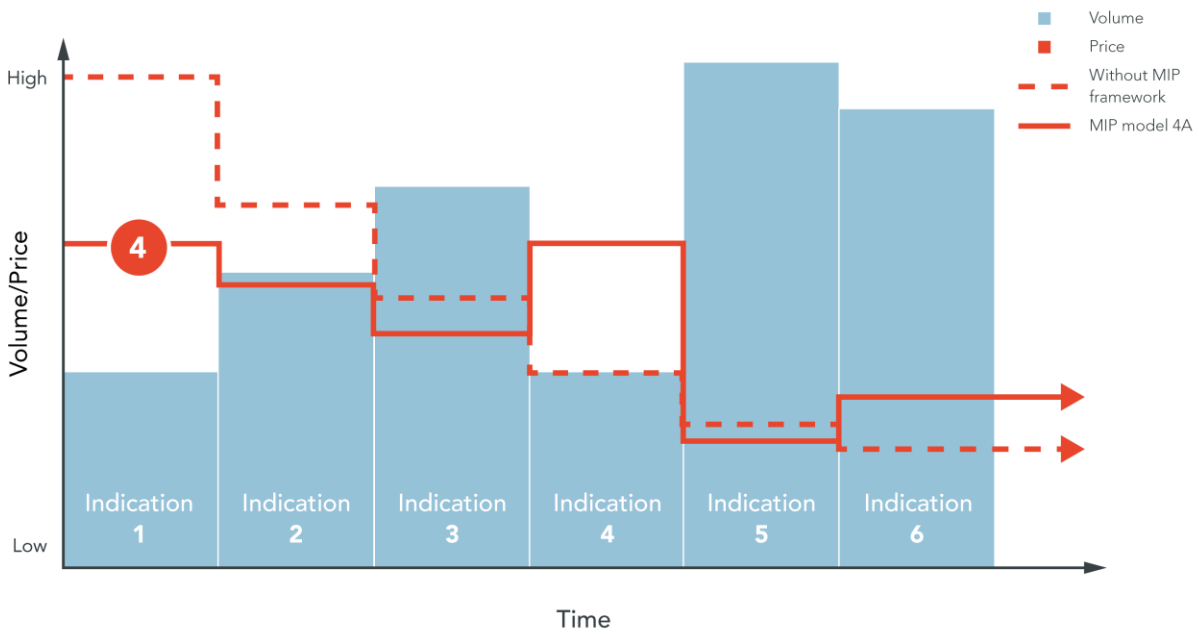

Figure 9: Model 4a - Retroactive dynamic pricing with retroactive claw backs based on volume

This model is evaluated by the different stakeholders as follows:

- Patients will need to be tracked, which makes implementation more complex
- This retroactive model will need an infrastructure and capabilities for real-world data access
- Uncertainty on revenues for companies as well as cost and budget impact for the payer remains

Model 4B uses retroactive claw back based on value, starting from a single price reflecting the indication with the highest value. Differential discounts are applied based on their relative value with respect to the highest value indication. Claw backs are claimed based on the effective value of the product in real life.

The scheme below is a visual representation of model 4B. The striped line represents the price today, without a multi-indication framework, where the price descends when more indications come to the market over time. The full line represents model 4B where the price is retroactively adjusted up or down started from the single price reflecting the indication with the highest value and claw backs to adjust for the difference between the estimated and real-life value.

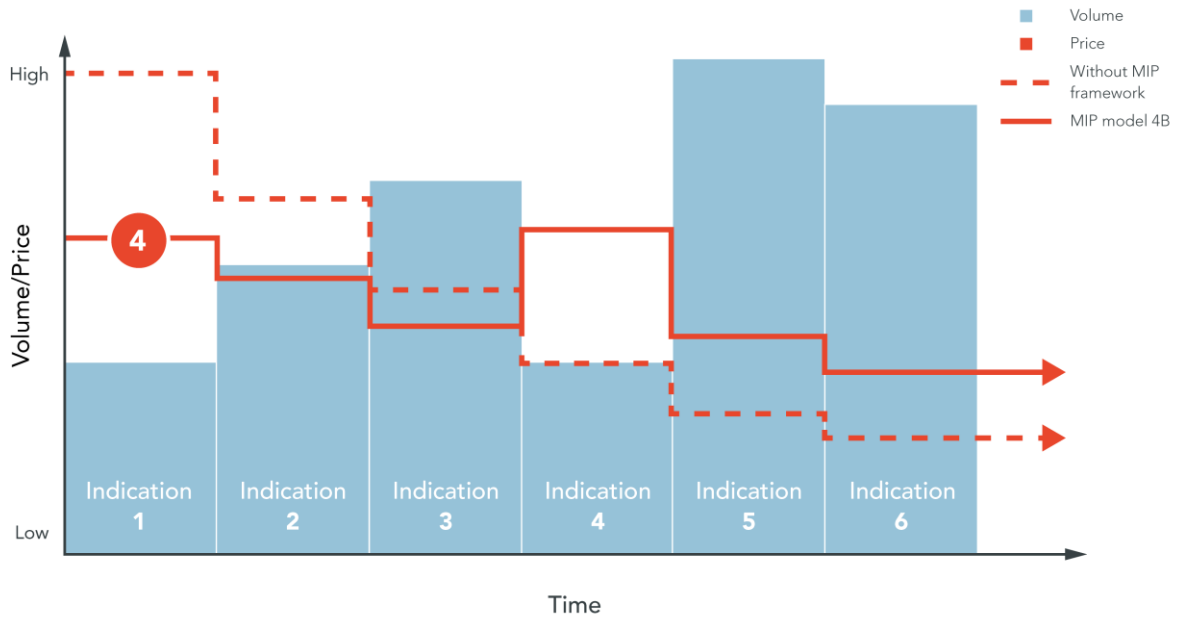

Figure 10: Model 4b - Retroactive dynamic pricing with retroactive claw backs based on value

This model is evaluated based on interviews with the different stakeholders as follows:

- Patients will need to be tracked, which makes implementation more complex
- This retroactive model will also need real-world data
- Uncertainty remains about the revenues for companies and costs and budget impact for the payer

2.2 The common ground MIP solution, preferred by stakeholders

The four proposed models were evaluated by the stakeholders, and multi-stakeholder preferences on each of the models were collected in interviews. The evaluation of the four models were based on seven key objectives and design criteria for an ideal model. The evaluation pointed to a new hybrid fifth model (model 5), based on a combination of elements from models 2 and 4.
It is a combination of a mechanism based on a "dynamic-over-time pricing model and a mechanism where we start from an average blended price-across-indications.

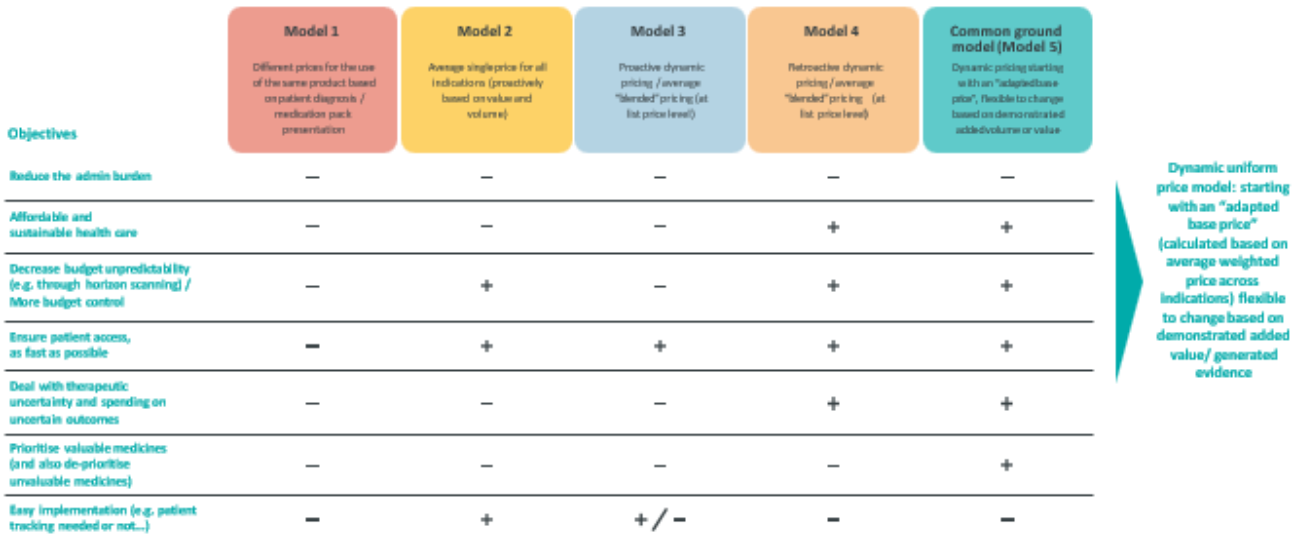

Figure 11: Stakeholders' preferences pointed to an MIP framework based on a combination of elements of model 2 and 4.

The preferred model is dynamic over time, and starts from a "base price", calculated on an average weighted price across indications. The base price is based on a weighted average across the bundle of indications, based on value and volume per indication, that are available at the time of negotiation. This base price can then be adapted over time per indication, on the basis of demonstrated real world evidence (reflecting value) and realized volumes.

This uniform list or net price is based on a weighted average across the bundle of indications based on value and volume per indication and can become a moving average uniform price over time resulting from the adjustments for the individual indications. The criteria for the adjustments based on value and volume must be defined in the initial negotiation.

The resulting net price per indication remains flexible in time, based on these pre-defined criteria (volume as well as further evidence on value), with post hoc "correction"; this implies that the net price may be adapted based on demonstrated added value and generated evidence or decreased in case of lack of evidence/value. The price for the indications initially evaluated having insufficient evidence is also increased once evidence has been built and value proven. If there is no evidence available for the evaluation, the indication will be de-prioritized.

There are 3 categories of evidence for the indications:

- "unknown": no evidence is available for this indication at the start and therefore it is difficult to evaluate the value and set a price.
- "uncertain": insufficient evidence available for the evaluation at the start and evidence needs to be build.
- "known": sufficient evidence is available.

For the indications with "unknown" and "uncertain" value, evidence has to be generated and will result in a dynamic pricing starting from an average blended base price, that can be adapted on the basis of generated evidence in real-world (to be provided by the company).

Indications with an "unknown" value, can move in time to "uncertain" or "known" indications based on additional evidence generated. The indication-specific price is decreased when, for example, actual expenditure was higher than

originally expected, and companies would need to offer rebates to compensate for the extra spending. The rebates are ex-post, after financial reconciliation.

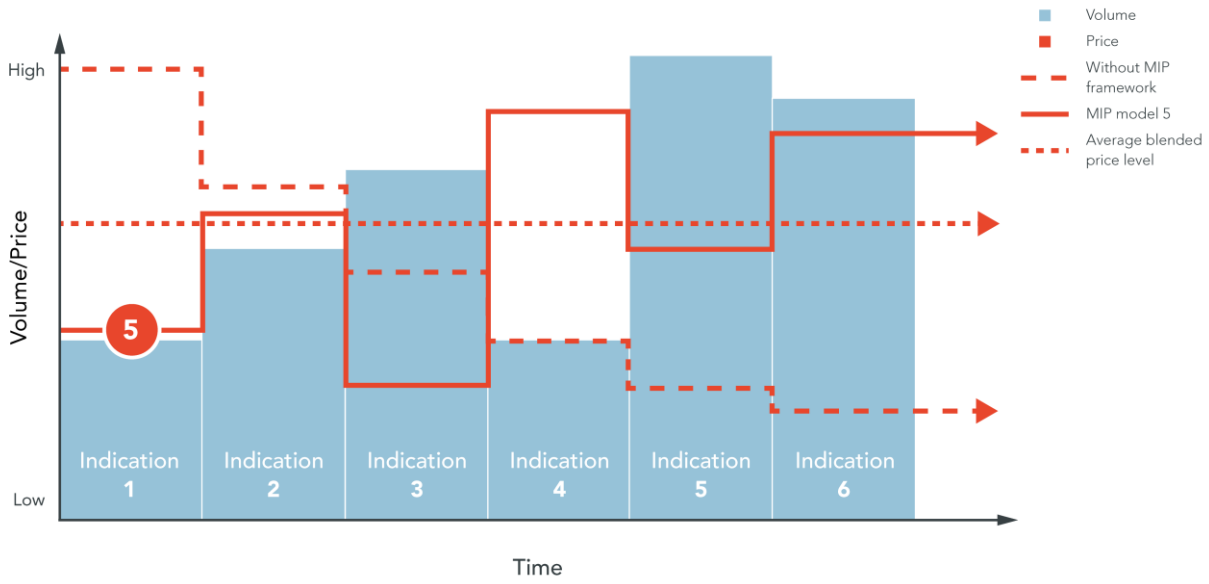

Figure 12: Model 5 - Common ground model

This proposed hybrid MIP model was discussed in a multi-stakeholder round table. During the round table, alignment was reached on the following key principles for a suitable MIP framework for Belgium:

1. Flexible and dynamic pricing over time, in-line with generated evidence on value and volume.

In this MIP model, it is proposed to bundle all indications and determine a weighted average blended price based on estimated volume and value of each indication at launch. The net price per indication will remain dynamic and flexible over time, based on forthcoming real-world evidence and actual volume in the market.

The starting price should be lower than the average list price until the value and volume are proven in real life. The price will therefore remain flexible and accurate to the effective performance. Regular price adjustments based on pre-defined criteria reflecting the value of the product will be required. Experts and appropriate tools are required for the implementation in practice.
Academia and clinicians are responsible for the accuracy of data – on a national and/or international level. Decision-making can be automated in case of pre-defined criteria set at the start.

Round table participants agree that the determination of the starting price for a bundle of indications will be the most important challenge. Volume data can already be determined reasonably accurate based on the number of patients, but this remains uncertain as volume can be influenced by prescribing behavior and marketing efforts of companies. The evaluation of value is more difficult since proof of evidence might be missing. Even in clinical trial phase III, evidence is often insufficient for an accurate appraisal of the value of a medicine; real-world evidence generation is in any case required.
It is clear that we need policies, manpower and sufficient data for the accurate appraisal of the value of a medicine.
Today, we see often that the first indication receives an overly high price because of the overestimation of the value, but the price decreases as more indications come to market, based on linear price cuts on accumulated volume.
Stakeholders agree that the starting net price should be lower than the average list price until the value and volume have been proven in real life and realized volumes are known. The starting price can be reviewed over time, based on more evidence on real-world volume and value data collected: higher volume in real life results in a price decrease and higher proven value in real life results in a price increase.
This can influence the price positively, if the treatment performs better than expected, or negatively, if the treatment performs worse than expected. The price will therefore remain flexible and accurate to the real-world performance.

The legal framework to support such a pricing mechanism must be clear. For example, there should be no discussion about the pre-defined criteria and mechanism on the effect of generated real-world evidence on the price.

The price should not remain dynamic forever but should be flexible over a limited period. After a long enough time, e.g., 5 years, a product is more stable in volume and value and the price can be fixed or adjusted over a slower interval, thereby reducing the administrative efforts.

2. Horizon scanning, in combination with a yearly updated unmet medical need (UMN) list based on the input from clinicians, academia, and patients.

The model rests on an insight in forthcoming indications. This is guaranteed by horizon scanning, based on input from the pipeline of the pharma companies. Horizon scanning and a yearly updated UMN list will enable authorities to define priorities and to identify the priorities of the payer/buyer.

Stakeholders agreed that horizon scanning should be held at the international level. It allows to obtain a clear view on the future treatment landscape for a particular indication, including competing drugs. Moreover, it should estimate the urgency of the medical need and to which extent clinicians and patients prioritize the indication. The UMN list should be updated regularly based on all available information from all stakeholders.

Each stakeholder has a specific responsibility in order to make the model work. Industry will have to inform authorities on their pipeline to enable horizon scanning. Authorities will inform industry on prioritized medical needs. The role of the payer will evolve to a real buyer-approach, with an interested but critical regard to innovations.

The model opens the possibility for an early conversation between buyer and industry in a more transparent manner than ever before. It encourages industry to take into account the priorities of the authorities on the basis of their priorities, and it adds a more demand-driven element to the actual P&R-process, that is too offer-driven.

3. Implementation of a real-world data infrastructure and governance model which involves the collection of evidence as a prerequisite for price adjustments over time.

Early dialogue will be necessary to prepare the real-world data infrastructure and agree on the evidence generation plan. The dialogue should start as early as possible to define the evidence generation strategy and prepare the data infrastructure in time.

Recognized reference centers will play an important role in the collection and evaluation of real-world data and create the evidence that is required. This requirement is aligned with the political intention to develop specialized centers for expensive therapies that require high expertise.
Such reference centers are critical success factors for the collection of high-level data for the generation of evidence. Patients should also be encouraged by their treating physicians to participate in data collection.

P&R regulations distinguish forfait 1/forfait B (FA/FB) reimbursement categories, and this framework can be a possible solution to apply “differential pricing” without a contract for additional indications. This mechanism allows delinking price (economic affairs) from the basis of reimbursement (social affairs) via RD article 35/5, allowing net cost to be retrospectively calculated. It could be applied as follows: I do

- For a first indication a contract with a certain price is agreed. This is the basis for reimbursement and is the ex-factory price.

- Additional indications without contract with reimbursement category FA/FB enter the market. In the hypothesis of insufficient evidence, the price does not change, but the basis for reimbursement will be proportional to the evidence generated over time. After revision, the new basis for reimbursement increases but the ex-factory price remains the same. The company sells at the ex-factory price, but the hospital pharmacy only receives the basis for reimbursement. The financial responsibility for the difference is taken by the company.

- Tracking reimbursed revenues can be done via Farmanet or chapter IV in the IMA database, or - preferably - via a register to eliminate the time gap

Today FA/FB is not used in this context, but it could be applied. However, FA/FB could only be applied for indications with available evidence - the so called “known” indications: the FA/FB-forfaits imply final reimbursement of the medicine. Eventually, a revision could solve this issue.

2.3 Procedural pathway for the newly proposed MIP framework

Horizon scanning is essential in the context of MIP framework, to identify which products and associated indications are forthcoming. The horizon scanning based on the pipeline input of companies should be cross-checked with a yearly updated UMN list to identify those medical needs that requires prioritization and will be eligible for reimbursement. The UMN list should be defined by clinicians, academics, and patients. The UMN list and the criteria used to develop the list can function as a guidance to companies on the development of future products and indications. Early dialogue between authorities and industry will be required to discuss how to bring the required indications to the patient.

The order in which indications receive market authorization (or, better, a positive CHMP-opinion) is also the order in which reimbursement will follow, and which the payer considers the new indications in a MIP.

An early dialogue platform – comparable to scientific advice at EMA on clinical trials - is required to support the MIP framework and should help prepare the evaluations. Preferably this should be done at European level.
The platform should determine the data specifications and the infrastructure. A discussion on real-world data and evidence generation will be required in this early dialogue to prepare the local infrastructure and data access in time.
An agreement on the evidence to be generated must be outlined in "the evidence plan for the medicine", which should indicate commitments on evidence to be provided by the applicant, as well as timeline and source of data for the medicine throughout the whole lifecycle of the product (from early discussions to post hoc reimbursement).
In the early dialogue, decisions on evidence requirements and method of evaluating the results of the clinical program will be agreed. It will help to prepare the data needs in time and make it more feasible for the authorities to keep following the current MEA timeframe.
Sharing of real-world data and evidence within BeneluxA (and other countries) would be preferable.

At CHMP opinion, the initial price in Belgium must be decided, based on the estimated value and volume.
The positive CHMP launches the process of considering the available indications (the bundle of indications) in the MIP framework for reimbursement.
For the available indications in the bundle, at that time an assessment of value or HTA, the predicted volume per indication and a calculation of the average weighted uniform list/net price must be conducted. The price will remain dynamic in time based on pre-defined criteria (volume, value/evidence) with post hoc adjustments based on the real-world situation.
The challenge will be to track patients and diagnosis over time for the post hoc adjustment. The availability of a robust data infrastructure and approach able to capture and share patient-level information is a prerequisite to the implementation of the proposed MIP framework.

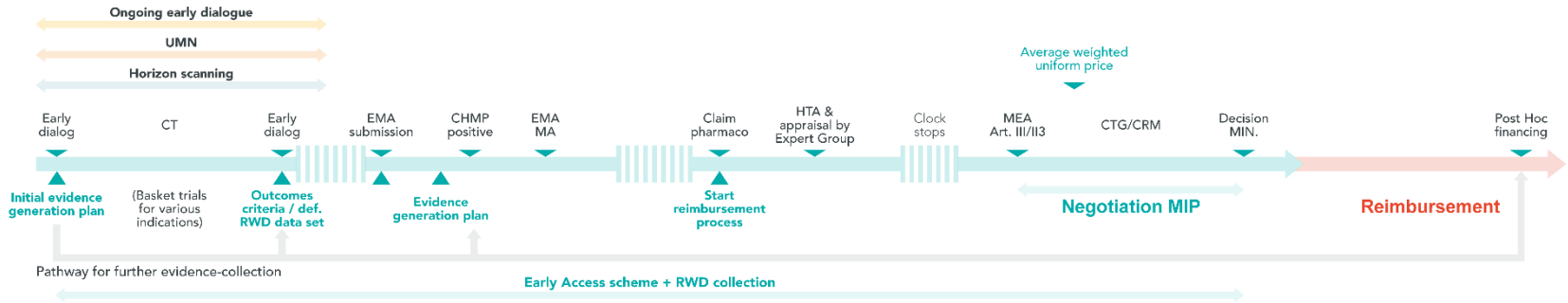

Figure 13: Proposed MIP pathway and timeline

3. An illustrative example to demonstrate the possible application of the MIP framework in practice

Disclaimer:
The fictive example below has the intention to illustrate the MIP model mechanism but does not correspond to reality. The numbers used are fictive. The methodology used is based on Mestre-Fernandez et al. (2018). The calculation and methodology in this example were evaluated end executed by Prof. Steven Simoens from KULeuven.
This theoretical example case assumes that all indications for the same product have been launched closely one after the other in an accelerated mode. Therefore, we want to emphasise that given all these limitations, this example must be taken as a theoretical exercise only.

The list price in Belgium for a hypothetical multi-indication product is €539.46. For all reimbursed indications, the out-of-pocket payment by patients in Belgium is €12.10 or €8 (for the increased compensation or WIGW statute). The price of the hypothetical product decreased significantly in 2018, at patent expiry, and the immediate arrival of a biosimilar.

The hypothetical products are reimbursed for nine approved indications. Based on the ICER and price, a value-based price can be calculated per indication.

Indication	**ICER (per QALY)**	**Price (year of reimbursement)**
Indication A	34,417	1,087
Indication B	50,000	1,180
Indication C	150,000	1,046
Indication D	30,319	1,161
Indication E	38,127	1,161
Indication F	30,538	1,161
Indication G	29,827	1,185
Indication H	20,000	1,185
Indication I	15,500	1,046

All numbers in this table are in euro (€).

Table 1: ICER and price calculation per indication for a hypothetical case

This results in the following value-based prices (assuming all indications come to market in a short time period, assuming a value threshold of €29,600 per QALY:

Indication	Value based price
Indication A	€790
Indication B	€590
Indication C	€174
Indication D	€957
Indication E	€761
Indication F	€950
Indication G	€993
Indication H	€1,481
Indication I	€1,687

We calculated a volume-weighted average value-based price, on the basis of the estimated number of patients treated with the hypothetical product in the EU, per indication. This resulted in a uniform weighted list price of €1,052.
The adapted base price is estimated at a 5% deduction on the uniform weighted list price which resulted in approximately €999.
This would become the starting price for the first indication, that would allow to calculate the price per indication, on the basis of demonstrated real-world evidence on value and actual volume.

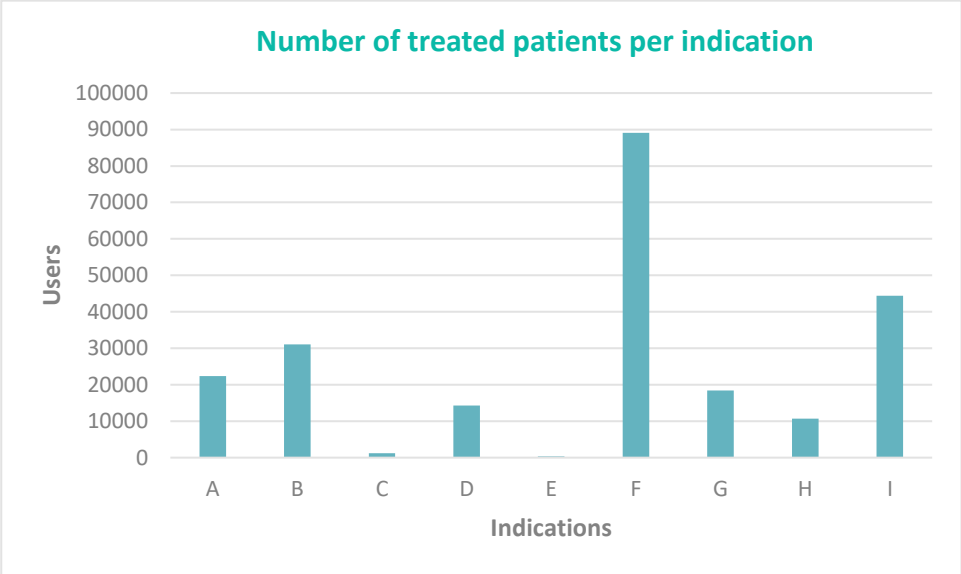

Figure 14: Group size estimation of patients per indication for the hypothetical case

$$\frac{(31102\text{x}590) + (18414\text{x}993) + (10692\text{x}1481) + (14256\text{x}957) + (89101\text{x}950) + (351\text{x}761) + (22394\text{x}790) + (44431\text{x}1687) + (1188\text{x}174)}{31102 + 18414 + 10692 + 14256 + 89101 + 351 + 22394 + 44431 + 1188}$$

$$= 1052$$

Figure 15: Calculation of the volume-weighted average value-based price

That would be the basis for the calculation of the net price per indication.

We add that the illustrative example is a fictive case and it allows us to show how the model could eventually work.

Some additional features of this model are that the price could still be adjusted if volume and/or value estimates change. If new indications are approved, the model can be implemented in the context of a managed entry agreement. And, last but not least, it would guarantee predictability of expenses.

4. Conclusion and next steps

Stakeholder interviews and the multi-stakeholder round table illustrated a wish, if not a need for an appropriate P&R-model for the growing number of multi-indication medicines, the so-called “pathway medicines”. Those medicines have the characteristic that they bring a large number of indications to the patient in a short period of time.
The multi-stakeholder conversations inspire mutual understanding and trust, that underpin transparency as a first step towards a new MIP model and framework.

Because it is difficult to determine value in the absence of real-world evidence, it is realistic to start at a lower (list/net) price, based on the first assessment of value and estimated volume, under the condition that the price becomes dynamic and flexible over time and can decrease or increase on the basis of the generated evidence and actual volumes in real-life.

As a conclusion of the multi-stakeholder consultation on an adapted Belgian MIP framework, we summarize the following recommendations:

Recommendation 1:
A MIP framework, based on the principles outlined in this report, would facilitate access to patients to more valuable indications that the buyer also wants, based on clinical value, and allowing better budget follow-up.

Recommendation 2:
There is consensus on the need for a performant health data infrastructure that supports value-appraisal and volume-assessments in real time.

Recommendation 3:
There is a need to define tools and mechanisms, based on pre-defined criteria and accepted by academia, in order to support automated value- and volume-assessments.

Recommendation 4:
The transition to a new model requires good preparation, regular evaluations, and adjustments on the basis of a shared ‘learn and adapt’-principle.

Abbreviation list

CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
EU	European Union
Fa/Fb	Forfait A/ forfait B
HTA	Health Technology Assessment
IMA	Inter Mutualistic Agency
KB	“Koninklijk Besluit” (Royal Decree)
MEA	Managed entry agreement
MIP	Multi-Indication Pricing
P&R	Pricing and reimbursement
QALY	Quality adjusted life-year
R&D	Research and development
NIHDI	National Institute for Health and Disability Insurance (RIZIV)
RWD/E	Real-world data / real-world evidence
TNF	Tumor necrosis factor
UMN	Unmet medical needs
WIGW	Weduwen, Invaliden, Gepensioneerden en Wezen
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
EU	European Union

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