**ORIGINAL RESEARCH ARTICLE**

# From Indication-Based Pricing to Blended Approach: Evidence on the Price and Reimbursement Negotiation in Italy

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## Abstract

**Background** New indications for existing medicines are increasing over time. In most countries, drug pricing and reimbursement conditions are renegotiated every time a new indication is approved. There is a growing interest in the price negotiation model for new indications, specifically comparing an indication-based versus blended approach. However, little evidence currently exists regarding the complexity of these negotiations and their impact on actual prices. Italy has recently transitioned from an indication-based approach to a blended price model. This study aims to measure the impact of price and reimbursement negotiation of new indications on discounts (i.e. actual prices) and on the negotiation duration, used as a proxy of its complexity.

**Methods** We considered new indications approved through a European centralized procedure from January 2013 to March 2022 for which the price and reimbursement status was approved in Italy between January 2015 and March 2022, amounting to 52 new indications. Data on the timeframe of the Italian price and reimbursement process and its phases were obtained from publicly available sources. Discounts for the first indication and their subsequent increases for new indications were estimated by comparing ex-factory prices and tendered prices. To calculate $p$-values, we employed the Mann–Whitney test, and multiple regression models were utilized to examine correlations between negotiation time and the characteristics of the medicines.

**Results** The mean time to reimbursement was 603 days, in contrast to 583 days for the first launch. Price negotiation took longer for rare diseases, cancer drugs, and in case of therapies with minor added therapeutic value. On average, the additional discount (on top of discounts for prior indications) was 13%, significantly lower than the mean discount for the first indications approved (24.9%). The discounts increment was lower, but negotiation took longer if a Managed Entry Agreement accompanied the final agreement. Additionally, discounts have increased over the years.

**Conclusion** The negotiation for new indications takes longer than the first one, and provides, on average, an additional discount of 13%. While our findings bear the potential for significant policy implications, they necessitate prudent interpretation due to a limited number of observations. The increasing trend in additional discounts over time applied to all indications in recent negotiations, may suggest a descending trend of value for new indications and a shift from an indication-based pricing approach to a blended model. Otherwise, budget impact considerations might have outweighed a value-based approach in the recent negotiations. If so, two potential options for restoring a value-based approach are returning to an indication-based pricing or giving explicit and higher weight to value within a blended model.

## 1 Introduction

Medicines to treat multiple indications have increased over time and are expected to increase in the future [1]. Pricing models for new indications have been classified into three categories [1]: (1) Brand Model, i.e. different brand (and therefore different price) for each indication; (2) Indication-Based Pricing (IBP), i.e. a single price and discounts and/or Managed Entry Agreements (MEAs) differentiated by indication; and (3) Blended Price Model (BPM), i.e. a single price for all indications set as a virtual weighted average of the prices per indication.

A recent systematic review of pricing models for new indications [2] indicates that the IBP model presents the advantages: (1) to align the price with the drug's value for each specific indication; (2) to help pharmaceutical companies in focusing their investments in Research and Development (R&D) towards indications that are expected to bring value to the healthcare systems, thus linking price

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**Key Points for Decision Makers**

In Italy, time to reimbursement of new indications takes longer than the time required for the first launch, and is affected by price negotiation more than by the scientific assessment.

In Italy, discount increment for new indications is half of that observed at the first launch and is lower in the presence of Managed Entry Agreements.

Discount increment for new indications has raised over the years, reflecting a shift from an indication-based pricing approach (different actual price per indication and discount increment applied only to new indications) to a blended model (single price as a weighted average of price per indication and discount increase applied to all indications). This could suggest that budget impact considerations have come to outweigh value considerations when the price for new indications is negotiated.

to value; and (3) to facilitate patient access to medicines. The same review evidences that only Italy has adopted an IBP model thanks to the presence of drug registries, since the IBP model requires tracking drug use by indication [3]. Furthermore, the IBP model may impose an administrative burden, depending on the complexity of the agreements by indication. This is why the BPM model is more widely adopted. Furthermore, where the BPM model is adopted, it predominantly relies on confidential discounts differentiated by indication, rather than MEA. This observation aligns with the context of critical revaluation surrounding MEA and outcome-based agreements [4]. Two recent contributions have designed models that could partially overcome the problems of outcome-based agreements [5, 6].

An Expert Consensus Report published by the Office of Health Economics [7] advocates a more flexible approach when negotiating prices for new indications. By acknowledging the value of a drug with its newly approved indication, this approach has the potential to recognize the value of the drug in the new approved indication. This would produce faster and more widespread patient access to medicines and encourage the development of innovative therapeutic solutions. The IBP model is identified as the model that best fits these characteristics. The BPM model faces criticism, primarily because it is potentially more driven by budget impact considerations than value aspects since the actual price per indication (that could better reflect the value) is not revealed. Furthermore, the size of the target population is known for the already approved indications and is often used to weigh the prices by indication, while it is estimated for new ones, thus incorporating into prices the risk of incorrect estimates.

Finally, the BPM model causes an indirect renegotiation of prices and/or discounts for all indications. If net prices are publicly available, pharmaceutical companies would prefer not to launch new indications in countries where they expect a higher price cut and/or discount, since these countries can become a benchmark for cross-reference pricing [8].

Similar conclusions have been drawn from a Discussion Paper issued by an Italian working group [9]. The IBP model produces a greater consistency of prices with the value per indication, avoids the risk of missed launch for the new indication (generated by an overall reduction in effective prices for all indications) and does not require identifying a weighting system (that often refers to the size of the target population), which is estimated for the new indication.

All contributions remark on the paucity of empirical evidence on the impact of new indications. A recent study examined the impact of 100 new indications, approved between 2009 and 2019, for 25 cancer drugs across seven countries (Australia, Canada, France, Germany, England, Scotland, and USA) [10]. The analysis highlighted that new indications, compared with the first approved, (1) produce a lower health increment in terms of survival and quality-adjusted life-years (QALYs) saved; (2) target a wider patient population; and (3) are often not reimbursed or affected by restrictive reimbursement recommendations. The same paper highlights that when the price and reimbursement (P&R) for new indications is negotiated, public prices are cut in France and Germany, while relevant companies increased prices in the US. Another paper scrutinized Health Technology Assessment (HTA) recommendations for sequences of multi-indication cancer medicines (31 drugs and 118 indications evaluated) across Germany, France, England, Scotland, Canada, Australia, and USA. Among its findings, it noted a lower magnitude of the European Society of Medical Oncology (ESMO) clinical benefit scale (MCBS) for the first indication launched but a higher proportion of HTA coverage recommendations; the study concluded that discordance in the value of first versus subsequent indications can pose major challenges in systems that define the price based on the initial indication [11].

Despite that there is growing empirical evidence on the impact on new indications, neither the effects on net prices nor the impact on P&R negotiations have been investigated thus far. Furthermore, all the above-mentioned analyses did not include Italy, which is an interesting case study since it has adopted an IBP model in the past but has recently moved from an IBP model to a BPM model.

In Italy, P&R negotiations for new medicines and indications are managed by the Italian Medicines Agency (AIFA) [12]. The Italian P&R process starts when the applicant submits an application consisting of a dossier structured

according to a standardized format (Common Technical Document [CTD]), which is published on AIFA's website [13]. P&R negotiation considers the unmet need, the added therapeutic value, the cost of comparators, the size of the target population, the cost-effectiveness profile, and the drug and healthcare budget impact [14]. To date, AIFA's decision making is supported by two distinct committees—the Technical-Scientific Committee (CTS) and the Price and Reimbursement Committee (CPR). The CTS provides scientific support to P&R negotiations, e.g. if the CTS determines that the risk-benefit profile of a new product is comparable with other drugs for the same indication, the CPR cannot allow a premium price over the comparator(s) for the new products. The CPR, on the other hand, negotiates the P&R with the marketing authorization holder, complementing the scientific evaluation provided by the CTS with economic considerations [14]. After ratification by the AIFA's Board of Directors (BoD), the outcomes of the P&R agreements are published in the Italian Official Journal (OJ) [Determina AIFA].

The P&R negotiation process for new indications is equivalent to the first launch: companies must submit a full P&R dossier. In addition, the P&R process for new indications poses some challenges related to the value by indication since the value a drug delivers across indications may vary substantially. As previously mentioned, Italy was the first country to adopt an IBP approach through discounts and/or MEA by indication [2, 10, 15], supported by drug registries that allow to track the use of drugs by indication [3]. However, in recent years a BPM-based approach has prevailed: public prices and/or discounts, applied to all indications, are renegotiated when a new indication is approved [9].

Pharmaceutical companies may also consider applying for innovative status for each indication approved, and the CTS then appraises the applications and decides on full, conditional, or non-innovativeness status. The former lasts 3 years and provides for a dedicated fund and immediate access to regional markets; conditional innovativeness lasts 18 months and can subsequently be converted into full innovativeness on the grounds of real-world data, but provides the relevant products only for speedier access to the regional markets [14]. The innovativeness status is decided on the grounds of the unmet need, therapeutic added value, and quality of the evidence provided [16]. Unmet need and added therapeutic value are evaluated using a five-level scale (maximum, important, moderate, poor and absent) [17], whereas the quality of the evidence through a four-level scale (high, moderate, low, very low), known as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method [17]. The added therapeutic value and the quality of the evidence are the most important drivers of the innovativeness appraisals [14, 17, 18].

Our analysis aimed at covering the information gap on the impact of new indications on P&R negotiation complexity and on net prices, using Italy as a case study due to its transition and IBP approach to a BPM approach. The duration (time to reimbursement) of new indications compared with first indications procedures was used as a proxy of P&R complexity. Discount increment following the negotiation of P&R for new indications was used to capture the impact on net prices. In addition to determining the overall impact of new indications on the P&R negotiation process, we stratified the results based on different characteristics, including orphan indications and the presence of MEA. Furthermore, to understand the broader implications of the shift from an IBP model to a BPM model, we also analyzed the P&R process duration and discount increment over time.

## 2 Methods

Drugs that received the first marketing authorization in the European Union between January 2013 and March 2022 and for which a Determina of P&R was published in the Italian OJ between January 2015 and March 2022 have been included. Therefore, all drugs authorized before 2013 were excluded from the analysis due to challenges associated with sourcing data, such as tendered prices and innovativeness reports, before the set cut-off date, in particular for pharmaceuticals with multiple indications and without market exclusivity. Furthermore, only drugs whose new indication was requested through a European centralized procedure were considered (i.e. mutual recognition and decentralized procedures were excluded). All medicines for which an agreement on P&R was not reached have also been excluded.

We created a database in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), with each row corresponding to a new therapeutic indication (i.e. unit of analysis) and containing all the relevant information; all the sources for the parameters described are available in Online Resource 1. Initially, European Medicines Agency (EMA) dates were collected using the European Public Assessment Report (EPAR) [19] and the European OJ (EUR-Lex) [20]. P&R dates and drug prices in Italy were sourced from the Italian OJ [21]. Ex-factory prices (PEX) were found in the respective Determina published in the Italian OJ for the new indications. Notably, while the Determina informs whether a confidential discount has been negotiated, it does not specify the magnitude of the discount. Therefore, the size of discounts was calculated by comparing the awarded price, found in the regional and local purchasing tenders, with the PEX, net of the mandatory discounts (AIFA Determination of 3 July 2006 and 27 September 2006) when applicable. We assumed that the tendered prices equated to the prices negotiated with the AIFA. In fact, additional discounts through

tenders are rare for patented medicines since there is only one supplier [22].

Furthermore, the analysis aimed to observe differences in the P&R timelines and discounts for new indications compared with first indication procedures (same medicines considered), and it was run through a comparison with a specific internal database created and provided by Pharmalex Italy S.p.a. that tracked P&R timings for first indication procedures only. The total number of observations for first indications was fewer than 52 since the database had been populated starting from 2016, therefore lacking records of first indications approved between 2013 and 2016; Online Resource 2 outlines the characteristics of the first indications dataset.

The timeframes were divided into six STEPS as shown in Fig. 1:

- Step 1: From the Committee for Medicinal Products for Human Use (CHMP) opinion to the publication of the marketing authorization in the European OJ (EMA's administrative timeline for approving the new therapeutic indication).
  - Step 1.1: From the CHMP opinion to the START date (the date when the pharmaceutical company submits the P&R dossier to the AIFA; the START date is not always disclosed in the Italian OJ).
- Step 2: From the START date (when available) to the opening of the procedure by the CTS.
- Step 3: From the date of the CTS opening to the date of the last opinion issued by the CTS (time for the CTS to provide scientific advice on reimbursement of the new indication).

- Step 4: From the last CTS opinion until the date of the last P&R Commission (CPR) opinion (time to conclude the P&R negotiation).
- Step 5: From the date of the last CPR opinion to ratification of the P&R by the AIFA's BoD, which is required for formal approval of the P&R agreement.
- Step 6: From the BoD ratification to the publication of the AIFA determination in the Italian OJ (that formally corresponds to the starting date of reimbursement).

We grouped medicines according to the orphan designation, the target disease (rare vs. non-rare; oncology-immunomodulatory drugs—Anatomical Therapeutic Chemical [ATC]: L01 vs. others), the innovativeness status (noting that the innovativeness report is publicly available only if the request is submitted by the pharmaceutical company), the presence of an MEA, the requirement of a Monitoring Drug Registry, and the reimbursement status (Class H—medicines reimbursed exclusively in the hospital setting; Class A—medicines reimbursed in all settings; and Class A/PHT—medicines reimbursed in all settings but directly distributed by health authorities if used outside hospitals). For each line extension procedure, the net prices have been tracked and the hidden discounts calculated.

For each STEP, we calculated the mean, median, minimum, maximum duration (in days), and the standard deviation (SD). In order to test if the differences in timings and discounts for all the above-mentioned categories were significant, we appraised median values through the Mann–Whitney test (MedCalc Software; Mariakerke, Belgium, version 20.014), with a significance level $p < 0.05$. This test was adopted since it does not require any assumptions on the symmetry of the two samples.
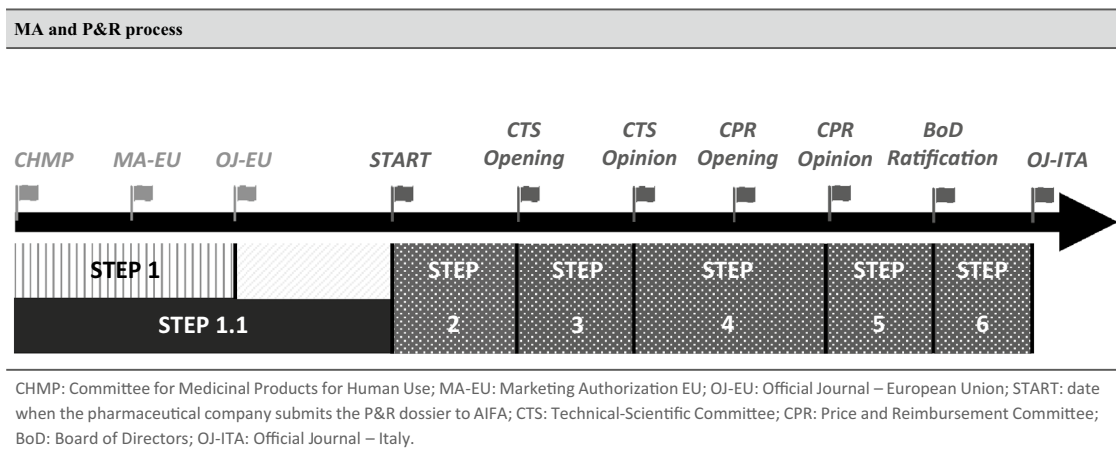
**MA and P&R process**



CHMP: Committee for Medicinal Products for Human Use; MA-EU: Marketing Authorization EU; OJ-EU: Official Journal – European Union; START: date when the pharmaceutical company submits the P&R dossier to AIFA; CTS: Technical-Scientific Committee; CPR: Price and Reimbursement Committee; BoD: Board of Directors; OJ-ITA: Official Journal – Italy.

**Fig. 1** Timeline of market access in Italy: from CHMP positive opinion to the publication of P&R status (seven steps). *P&R* price and reimbursement, *AIFA* Italian Medicines Agency

To test whether specific drug characteristics could have potentially influenced the P&R negotiation duration we utilized STATA 17 software (StataCorp LLC, College Station, TX, USA) to conduct multiple regression models. In these models, the duration of the P&R negotiation process—defined as the duration of the CPR (STEP 4)—served as the dependent variable, while added therapeutic value and the presence of an MEA served as the independent variables. Multivariate linear regression models were applied to assess the magnitude of the impact of different explanatory variables on the dependent variable (duration of the CPR assessment in days). The relative $p$-values are to be considered nominal.

## 3 Results

Overall, we identified 94 new indications, of which 42 were excluded for various reasons (i.e., those whose process had yet to be completed as of 30 March 2022, new indications not reimbursed, and new indications whose process is not centralized), as reported in Table 1 and Online Resource 3. The sample of 52 new indications is mainly composed of 'first' new indication procedures ($n = 44$). Consequently, we observed only eight 'subsequent' new indications since the included medicines are mostly recently approved. Notably, the majority of the analyzed procedures refer to oncological and immunomodulatory medicines (61.5%, data not shown). The new indications negotiated with MEA were 9/52, with only one being outcome-based and the remaining eight being financially-based. In only two cases, a new MEA was applied to a new indication, while in all the other seven cases the existing MEA from the previous indications was extended to the new indication. As many as 20 new indications were negotiated by removing the previously applied MEA. The last indication was negotiated with an MEA date of January 2021, and no new MEAs were applied to a new indication subsequent to the first indication. Additionally, for 24 indications, the pharmaceutical companies have applied for innovativeness status, with 13, 6 and 5 being assessed as innovative, conditionally innovative and not innovative, respectively.

The entire P&R process for new indications (Steps 1–6) takes 603 days on average, compared with 583 days for the first launch (Table 2).

The mean duration of the domestic P&R process (Steps 2–6) appears shorter (447 days compared with 515 days) for new indications, but the result is not significant. Within the domestic appraisal process, duration of the P&R negotiation process (Step 4) is, on average, longer for new indications compared with first indication procedures. In contrast, the scientific assessment and appraisal (Step 3) are shorter for new indications procedures.

**Table 1** Characteristics of the Italian new indication procedures according to the Italian Medicines Agency

| Characteristics | N | % |
|---|---|---|
| New indications tracked/included | | |
| Total new indications tracked | 94 | 100.0 |
| New indications excluded from the analysis | 42 | 44.7 |
| New indications included in the analysis | 52 | 55.3 |
| First/successive new indications ($n = 52$) | | |
| First new indications | 44 | 84.6 |
| Successive new indications | 8 | 15.4 |
| Italian Official Journal publication date ($n = 52$) | | |
| 2015 | 1 | 1.9 |
| 2016 | 2 | 3.8 |
| 2017 | 7 | 13.5 |
| 2018 | 5 | 9.6 |
| 2019 | 11 | 21.2 |
| 2020 | 15 | 28.8 |
| 2021 | 9 | 17.3 |
| 2022 | 2 | 3.8 |
| Request for innovativeness ($n = 52$) | | |
| No request for innovativeness | 28 | 53.8 |
| Full innovativeness | 13 | 25.0 |
| Conditional innovativeness | 6 | 11.5 |
| Not innovative | 5 | 9.6 |
| MEAs ($n = 52$) | | |
| New MEA | 2 | 3.8 |
| Extending MEA from the previous indication | 7 | 13.5 |
| Indications negotiated without an MEA, of which | 43 | 82.7 |
| Previous indications without an MEA | *23* | *44.2* |
| Indications that have lost an MEA | *20* | *38.5* |
| Reimbursement status ($n = 52$) | | |
| Class A[a] | 4 | 7.7 |
| Class H[b] | 40 | 76.9 |
| Class A/PHT[c] | 8 | 15.4 |
| Orphan designation status ($n = 52$) | | |
| Orphans | 13 | 25.0 |
| Non-orphans | 39 | 75.0 |
| Rare disease status ($n = 52$) | | |
| Treatment of rare diseases | 24 | 46.2 |
| Treatment of non-rare diseases | 28 | 53.8 |
| AIFA web-based monitoring register to control prescriptive appropriateness ($n = 52$) | | |
| With web-based monitoring register | 34 | 65.4 |
| Without web-based monitoring register | 18 | 34.6 |

*AIFA* Italian Medicines Agency, *MEA* Managed Entry Agreement

[a]Class A: Medicines reimbursed in all settings

[b]Class H: Medicines reimbursed only in the hospital setting

[c]Class A/PHT: Medicines reimbursed in all settings but directly distributed by health authorities if used outside hospitals

Overall, the procedural times (Steps 1–6) are progressively increasing year by year within a 5-year timeframe (2017 = 450 days; 2018 = 590 days; 2019 = 584 days; 2020 = 580 days; 2021 = 790 days). This upward trend can be attributed to several factors, including an increase in the time spent by the AIFA commissions to complete the assessment, the approval and submission times of the dossiers, and the administrative time following the negotiation phase. It is worth noting that the context of 2020–2021 was marked by the impact of the coronavirus disease 2019 (COVID-19) pandemic on drug evaluation processes, which likely contributed to the prolonged timelines. Online Resources 4, 5 and 6 illustrate a comprehensive view of P&R durations across different drug categories, revealing significant variability. For instance, Step 4 (P&R negotiation) takes longer for rare disease indications, possibly due to the higher level of uncertainty faced by payers regarding the evidence from pivotal trials, compared with non-rare diseases.

The multivariable linear regression model was focused on Step 4 (P&R negotiation) since it is significantly longer for the new indications compared with the first approved indication (Table 3).

The added therapeutic value ranked in five levels (dichotomized in >3/≤3) and the presence of an MEA (yes/no) were chosen as independent variables. The added therapeutic value is only available for indications subject to innovativeness appraisal (e.g. pharmaceutical companies can decide whether to apply for innovativeness appraisal), thus limiting the number of observations ($n = 24$).

**Table 2** Italian market access and price and reimbursement duration, overall and into subsequent procedural steps (from Step 1 to Step 6[a]), in strata of new indications and first indications of the same medicines.

| Timeframe of the MA and P&R processes[a] | Overall new indications (days) | | | | | | Overall first indication (days)[b] | | | | | | *p* value for comparison |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $N$[c] | Mean | SD | Median | Min | Max | $N$ | Mean | SD | Median | Min | Max | |
| Step 1 | 52 | 74 | 18 | 71 | 36 | 120 | 28 | 100 | 14 | 99 | 62 | 148 | **<0.001** |
| Step 1.1 | *39* | *174* | *194* | *95* | *11* | *938* | *13* | *179* | *342* | *81* | *7* | *1292* | *0.249* |
| Step 2 | 39 | 114 | 56 | 105 | 12 | 342 | 14 | 109 | 85 | 87 | 45 | 371 | 0.196 |
| Step 3 | 52 | 61 | 76 | 30 | 0 | 289 | 28 | 124 | 175 | 82 | 0 | 751 | 0.211 |
| Step 4 | 51 | 186 | 114 | 182 | 11 | 574 | 28 | 119 | 69 | 106 | 12 | 288 | **0.010** |
| Step 5 | 48 | 42 | 36 | 39 | 1 | 232 | 28 | 41 | 23 | 31 | 3 | 91 | 0.971 |
| Step 6 | 49 | 47 | 18 | 43 | 19 | 114 | 28 | 16 | 7 | 16 | 2 | 35 | **<0.001** |
| Steps 2–6 | 39 | 447 | 125 | 437 | 214 | 811 | 14 | 515 | 205 | 483 | 294 | 920 | 0.499 |
| Steps 1–6 | 52 | 603 | 224 | 552 | 286 | 1702 | 28 | 583 | 425 | 458 | 97 | 2157 | **0.025** |
| Steps 3–4 | 51 | 252 | 116 | 253 | 64 | 686 | 28 | 237 | 157 | 201 | 12 | 792 | 0.248 |

Step 1: From the CHMP opinion to publication of the marketing authorization in the European OJ; Step 1.1: from the CHMP opinion to the start date (the date when the pharmaceutical company submits the P&R dossier to the AIFA)

Step 2: From the start date (if available) to the opening of the procedure by the scientific commission (CTS)

Step 3: From the date of the CTS opening to the date of the last opinion issued by the CTS (time for the CTS to provide scientific advice on reimbursement of the new indication)

Step 4: From the last CTS opinion until the date of the last CPR opinion (time to conclude the P&R negotiation)

Step 5: From the date of the last CPR opinion to ratification of the P&R by AIFA's BoD that is required for formal approval of the P&R agreement

Step 6: From the BoD ratification to publication of the AIFA determination in the Italian OJ (i.e., the starting date of reimbursement)

*MA* market access, *P&R* price and reimbursement, *SD* standard deviation, *Min* minimum, *Max* maximum, *CHMP* Committee for Medicinal Products for Human Use, *AIFA* Italian Medicines Agency, *CPR* Price and Reimbursement Committee, *BoD* Board of Directors, *OJ* Official Journal, *CTS* Technical-Scientific Committee

[a]Timeframes of the Italian MA and P&R processes starting from CHMP opinion

[b]The total number of observations for the first indication negotiated (same medicines considered) is < 52 since the analysis was run through a comparison with a specific internal database created and provided by Pharmalex Italy S.p.a. that tracked P&R timings just for the first indication procedures and had been populated starting from 2016. Therefore records of first indications approved between 2013 and 2016 are missing. The yearly distribution of the Italian OJ publication date for the first indication sample is as follows: 2016: $n = 8$ (29%); 2017: $n = 6$ (21%); 2018: $n = 8$ (29%); 2019: $n = 5$ (18%); 2020: $n = 1$ (4%)

[c]The number of observations varies depending on the availability of the data: Steps 1.1/2: $n = 13$ start dates are missing because AIFA stopped disclosing them for a period of time; Step 4: $n = 1$ CPR opinion is missing because the price assessment seems to have been skipped, likely because it was not considered necessary to renegotiate the price; Steps 5/6: $n = 3$ BoD dates are not available probably due to the fact that in all three cases, the new indications had been approved under the same price conditions

The expected mean duration of Step 4 at baseline was 138.9 days when considering a new indication with lower added therapeutic value ($\leq 3$) and not negotiated through an MEA. A higher added therapeutic value ($> 3$) results in a reduction in the time required for P&R negotiation (Step 4), whereas MEA are strongly and directly correlated with an extended time for the P&R negotiation assessment (model $R^2 = 0.61$).

Table 4 illustrates our findings for the absolute increase in discounts after a P&R negotiation of new indications ($\Delta$ discount). The average $\Delta$ discount is 13% for new indications, starting from an average of 24.9% for the first indications (Online Resource 7). There is a statistically significant difference between the negotiated discount for the first indication approved and the $\Delta$ discount negotiated in the new indications (Online Resource 8). These results were expected given that applying a $\Delta$ discount to all indications through a blended model makes the negotiation process more complex for pharmaceutical companies.

The mean and median $\Delta$ discounts for antineoplastic agents are significantly higher than those for non-antineoplastic drugs. As expected, negotiating the P&R of new indications with MEA provides for a significantly lower $\Delta$ discount, since MEA and the discounts represent two partially complementary negotiation strategies (Table 4). These patterns apply also to the first indication procedures, although the results are not statistically significant (Online Resource 7).

## 4 Discussion

The goal of our study was to analyse the P&R duration (as a proxy for negotiation complexity) and its impact on the actual prices of new indications for medicines in Italy.

As for the P&R duration, the analysis highlighted that (1) the overall time to access (from CHMP Opinion to publication of the P&R status on the Italian OJ) is longer for new indications (603 days on average) compared with the first indication (583) despite the difference being small; (2) the time between submission to the AIFA of the P&R dossier and formal publication of the P&R status does not show any significant difference; and (3) both of these durations exceed

**Table 4** The increase in discounts due to a new indication price renegotiation

| Category | New indications discount increase ($\Delta$ discount)[a] | | | | *p* value |
|---|---|---|---|---|---|
| | *N* | Mean (%) | SD | Median (%) | |
| Orphan | 13 | 12.8 | 0.089 | 15.7 | 0.475 |
| Not orphan | 39 | 13.1 | 0.127 | 10.5 | |
| Rare disease | 24 | 13.4 | 0.09 | 14.9 | 0.302 |
| Not rare disease | 28 | 12.7 | 0.139 | 8.0 | |
| Antineoplastic drugs (ATC: L01) | 32 | 14.5 | 0.103 | 14.9 | **0.030** |
| Other drugs | 20 | 10.6 | 0.135 | 5.1 | |
| MEA applied | 9 | 7.2 | 0.126 | 3.4 | **0.012** |
| MEA not applied | 43 | 14.2 | 0.113 | 14.4 | |
| Innovative | 19 | 14.6 | 0.092 | 14.0 | 0.179 |
| Not innovative | 33 | 12.1 | 0.129 | 8.0 | |
| With registry | 34 | 13.1 | 0.094 | 12.6 | 0.276 |
| Without registry | 18 | 12.7 | 0.154 | 3.3 | |
| Class A and A/PHT[b] | 12 | 10.3 | 0.095 | 8.7 | 0.416 |
| Class H[c] | 40 | 13.8 | 0.123 | 12.8 | |
| *Overall* | *52* | *13.0* | *0.117* | *12.5* | *–* |

Bold *p*-values are significant

Italic values indicate the average value for all the sample (*n* = 52) (i.e. not clustered)

*ATC* Anatomical Therapeutic Chemical classification system, *MEA* Managed Entry Agreements, *P&R* price and reimbursement

[a]$\Delta$ discount: difference between the discount in force before the new indication P&R and the discount in force after

[b]Class A: Medicines reimbursed in all settings; Class A/PHT: Medicines reimbursed in all settings but directly distributed by health authorities if used outside hospitals

[c]Class H: Medicines reimbursed only in the hospital setting

the maximum 180 days foreseen for completing pricing and reimbursement decisions, set by the European Union Council Directive 89/105/EEC of 21 December 1988.

The scientific assessment takes less time for new indications; this result was expected since this assessment is likely to be easier due to pre-existing knowledge of the drug, including a well-established mechanism of action and safety profile, when a new indication is approved. On the other hand, more time is needed for P&R negotiation since

**Table 3** Multivariable regression impact of different variables on the duration of P&R negotiation (days)

| P&R negotiation (days) | Coefficient | Standard error | *p* value | 95% CI |
|---|---|---|---|---|
| Added therapeutic value > 3[a] | −79.6 | 36.3 | **0.023** | −3.6 to −155.6 |
| Managed entry agreement (yes) | 140.8 | 68.9 | **0.048** | 5.8–275.8 |
| Baseline | 138.9 | 48.3 | 0.010 | 37.9–239.9 |

*P&R* price and reimbursement, *CI* confidence interval

[a]The added therapeutic value is published only for indications subject to innovativeness appraisal, thus limiting the number of observations (*n* = 24)

finding an agreement on a discount increase is not easy and additional discounts could affect all previous indications. Furthermore, this duration has increased over the years. The gradual shift from an IBP model to a BPM model makes it more challenging to find an agreement on a discount increase that is applied to all indications.

Our analysis reveals that the mean Δ discount is 13% for new indications (specifically, 12% for the first new indications and 17% for subsequent new indications), compared with a 24.9% discount for the first approved indication (Online Resource 8). The observed increase in discounts with new indications was expected due to the application of a price/volume trade-off (larger volumes, lower price); a public price cut with new indications was also found in other countries [10]. The Δ discount is significantly higher for antineoplastic agents (class ATC: L), which is expected considering their higher unit cost.

Discount increment for new indications has raised over the years (Online Resource 8), reflecting a shift from an IBP approach (different actual price per indication and discount increment applied only to new indications) to a blended model (single price as a weighted average of price per indication and discount increase applied to all indications). This could suggest that budget impact considerations have come to outweigh value considerations when the price for new indications is negotiated.

The Δ discount is lower when accompanied by an MEA in the final agreement. This is consistent with the purpose of MEAs, which are implemented to manage uncertainty of the outcome and the financial impact of medicines. This often has the effect of replacing or reducing the straight discounts with a more complex scheme that reduces prices based on the level of drug use or effectiveness. Additionally, lower discounts are observed for innovative medicines that offer a higher added therapeutic value, which is consistent with a value-based pricing approach (higher prices for higher value) [23].

The overall time to access for first and new indications is longer than that reported in the existing cross-country comparisons: 436 days from European marketing authorization for all medicines approved from 2017 to 2021, and 477 for orphan medicines [24]. No further evidence has been found regarding the time to access for new indications; however, there is some evidence that positive HTA outcomes are less common and clinical restrictions are more frequent for the new indications of cancer medicines, compared with the first indication [10].

Likewise, no further evidence emerges of the impact on discounts for other countries. There is only one empirical evidence of public price erosion [10]. Price cuts in Germany are higher than in Italy (− 16.6% for the second indication, − 2.1% for the third indication, and − 42.7% for the fourth

indication, compared with the first indication), but are lower in France compared with Italy (− 7.7% for the second indication, − 14.1% for the third indication, and − 17.0% for the fourth, compared with the first indication). Higher price cuts in Germany are expected because prices are freely set at the first market launch and are generally higher than in other countries. Lower price cuts in France, as compared with Δ discounts in Italy, could be attributed to the fact that in France, P&R agreements are always complemented by price-volume agreements.

## 4.1 Limitations

The primary limitation of our analysis is represented by the limited number of observations (we could rely on 52 new indications, represented mainly by 'first' new indications) and by the uncertainty on the start date (i.e. when the pharmaceutical company submits the P&R dossier to the AIFA) since this is not available for 13 new indications. The former limitation suggests caution when drawing conclusions on statistical significance, while the latter makes it difficult, in some cases, to differentiate the 'domestic management' of P&R from what happens before the company submits the P&R dossier to the AIFA.

Other minor limitations include the following:

- The difference in the total P&R and MA duration between first and new indications might be slightly correlated with the different annual distributions of the two samples. In fact, the assessment of first indications occurs before new indications if the same medicines are considered. A descriptive statistic of the first indications sample is available in Table 2.
- Step 4 is calculated as the period between the conclusion of the scientific and P&R evaluations: administrative time to switch the dossier from scientific to P&R is not available and has been entirely allocated to Step 4.
- Discounts have been estimated assuming that awarded prices (from regional procurement documents) equal to the confidential price negotiated between the AIFA and the pharmaceutical company. The awarded prices may include some additional discounts at the regional level, but this is very unlikely for public procurement of new medicines/indications; cross-checks have been made by checking regional documents that usually exhibited the same awarded price (i.e., it is very likely that the awarded discount equals the discount that has been negotiated with the AIFA, since, for patented medicines, there is usually only one supplier) [25, 26].
- Linear regression analyses may reveal associations but it is important to note that residual confounders in multivariable models cannot be excluded.

- Due to the limited number of records currently available, the regression analyses are primarily intended to describe the magnitude (intensity) and direction (positive or negative) of the coefficients of the explanatory variables, in relation to the outcome variable of interest.
- The comparison between databases for the two analyzed groups (new indications vs. first indication procedures) could lead to potential imbalances when comparing the samples over time.

# 5 Conclusions

This research provides valuable insights into the assessment and pricing of new indications for existing medicines, a topic of critical importance for policy makers, industry, and patients. In particular, discounts and the impact on the negotiation duration, which was considered a proxy of the negotiation complexity, were investigated.

In our analysis, we observed an increase in discounts over time, accompanied by a shift from an IBP model to a BPM model, that allows for the applications of the new (higher) discounts to all indications. However, this is not consistent with a value-based approach unless the added therapeutic value of new indications and the value of the other indications decrease over time. It seems that (drug) budget impact has been the primary driver of price negotiations for new indications.

While budget issues are undeniable, it is crucial to not disregard the importance of value. A possible solution might be found by implementing a more transparent BPM approach, where the dimensions of 'value'/'budget impact' and price-volume trade-off are explicitly outlined. However, restoring the IBP model would be desirable if the value significantly varies across indications and is accompanied by MEA for indications with a highly uncertain benefit or target population [2]. Of course, this would bring some additional administrative burden. Nevertheless, unlike other countries, Italy can rely on drug registries, where the use per each indication is already tracked. If selectively employed, the IBP model could facilitate more value-driven, flexible and potentially faster negotiations, since prices for all previous indications are not necessarily renegotiated when a new indication is approved. This in turn could mitigate the risk of pharmaceutical companies deciding not to launch the medicine for a new indication.

## Declarations

**Conflict of interest** Claudio Jommi reports serving as an advisory board member and a paid speaker for Amgen, AstraZeneca, BMS, CSL Behring, Gilead, Incyte, MSD, Roche, Sanofi, and Takeda, outside the submitted work. Elvio Rossini, Carlotta Galeone and Chiara Lucchetti have no affiliations with, or involvement in, any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

**Availability of data and material** The datasets generated and analyzed during the current study are not publicly available for confidentiality reasons but are available from the corresponding author on reasonable request.

**Author contributions** Conceptualization: EER, CG, CL, CJ. Data curation: EER. Formal analysis: EER, CG. Investigation: EER, CG, CJ. Methodology: EER, CG, CL, CJ. Project administration: CJ. SupEERvision: CJ. Validation: EER, CG, CL, CJ. Writing – original draft: EER, CG, CL, CJ. Writing – review and editing: EER, CJ.

**Ethics approval** Not applicable.

**Consent to participate** Not applicable.

**Consent for publication (from patients/participants)** Not applicable.

**Code availability** Due to the sensitive nature of the data involved in this study, which includes confidential drug pricing information, we regret that we are unable to share the raw data used in our analysis publicly. Our primary concern is to protect the confidentiality and integrity of this proprietary pricing data while avoiding cross-reference pricing between countries. However, we are committed to providing aggregated and anonymized findings, summary statistics, and the methodology used in this research to ensure transparency to the fullest extent possible, while adhering to data privacy and legal restrictions. Researchers interested in accessing the summarized results or replicating the analysis are encouraged to contact the corresponding author for further collaboration and discussion.

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