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human health care

August 4, 2020

Dr. Mitchell Levine
Chair, Patented Medicine Prices Review Board (PMPRB)
333 Laurier Avenue West, Suite 1400
Ottawa, Ontario K1P 1C1

Dear Dr. Levine:

Re: Patented Medicine Prices Review Board (PMPRB) Guidelines Consultations

On behalf of Eisai Limited (Eisai), we would like to take the opportunity to provide our input on the June 2020 draft guidelines developed by the Patented Medicine Prices Review Board (PMPRB) to operationalize the August 2019 amendments to the *Patented Medicines Regulations*.

Eisai is the Canadian subsidiary of Eisai Co. Ltd., a *human health care (hhc)* company seeking innovative solutions in disease prevention, treatment and care for the health and well-being of people in Canada and around the world. Our company's *hhc philosophy* is based on a clear understanding that patients as well as their caregivers are the key players in healthcare, and at Eisai, we strive to develop new drug therapies that meet the needs of these patients and their caregivers while improving their quality of life. Since opening its doors in Canada in 2010, Eisai has been working hard and responsibly to help facilitate health system adoption of its medicines for cancer, epilepsy and in other areas of high unmet needs.

Eisai has made drug launch decisions and significant investment decisions in Canada based on the current, reasonably predictable pricing environment. The prices of our products that are already commercialized in Canada were deemed to be compliant with the current PMPRB rules, have been thoroughly reviewed by CADTH, negotiated by the pan-Canadian Pharmaceutical Alliance (pCPA) and considered cost effective and affordable by public and private payers. We therefore do not think it is appropriate for the PMPRB to reassess price ceilings for these medicines.

The proposed PMPRB pricing controls are difficult to predict and will prevent and delay health system adoption of new therapies with significant duplication of government resource and effort, considering the role of CADTH, PCPA, public and private payers in ensuring new medicines are cost-effective and affordable to Canadians. The new pricing guidelines unduly penalize Eisai, who has been a good partner and corporate citizen. The unintended consequences of excessive downward price pressure significantly beyond the OECD median will hurt the commercial viability of our growing organization in Canada. Eisai recommends that the economic factors (i.e pharmacoeconomic, market size, GDP per capita) not be used for price compliance decision making. However, if it were to be considered, it should only be relied upon in the context of board hearings. Eisai's participation in this consultation is not intended and should not be interpreted as being supportive of the amendments to the *Patented Medicines Regulations*. As a member of BIOTECanada, we have contributed to and supported the association's submission in response to the June 2020 draft PMPRB guidelines. We are providing additional and complementary feedback through this submission.

The PMPRB has made several revisions to the November 2019 draft PMPRB guidelines. However, the changes do not go far enough to address our concerns related to the unreasonable price decreases that

will still be required for innovative medicines, in addition to the lack of certainty and predictability on how we can price our medicines in Canada. In fact, the revised guidelines are more complex than the previous version and introduce several new concepts and formulae, which generate new concerns that would require more significant engagement with industry to minimize operational challenges and unintended consequences.

Unless substantive changes are made to the June 2020 draft PMPRB guidelines, they will make it very difficult for our organization to make innovative therapies available to Canadian patients now and in the future. We have outlined below the key areas of concern with the guidelines that need to be addressed.

Concern #1: The Maximum List Price (MLP) will lead to excessive price decreases, uncertainty and inconsistencies

- **Benefits are required to be reported but are not factored into assessing compliance with the MLP for Grandfathered, Gap and Category II medicines**

Under the revised guidelines, reported benefits will be considered for the purposes of assessing compliance with the Maximum Rebated Price (MRP) for Category I medicines, which include high cost medications and/or those exceeding the market size threshold. However, reported benefits for patented medicines classified as Category II will not be considered for the purposes of assessing compliance with the MLP. This creates an inconsistency in terms of how reported benefits are factored in for the purposes of compliance with the various price ceilings.

Eisai recommends that reported benefits be taken into consideration when assessing compliance with the MLP for all patented medicines, including Grandfathered, Gap and Category II medicines.

- **Removing the Lowest International Price (LIP) floor will make it more challenging to commercialize Gap medicines**

The November 2019 draft guidelines established the LIP as the price floor for calculating the MLP. We recommend that this be reintroduced for Gap medicines. Consistent with what has been proposed previously by the PMPRB, Gap medicines are still required to comply with the lower of the median international ex-factory list price (MIP) or the current guidelines' Non-Excessive Average Price (NEAP). The certainty afforded by having the LIP as a floor has been removed without providing a clear rationale. Under the current guidelines, reported benefits are considered for the purposes of complying with the NEAP. However, this no longer appears to be the case for Gap medicines, and yet Gap medicines are still required to comply with the NEAP if it is lower than the MIP.

To account for this discrepancy and given that the PMPRB has previously proposed the LIP as a price floor, the PMPRB should reintroduce the LIP as the floor for calculating the MLP for Gap medicines.

- **Inconsistencies exist with how price increases/decreases are factored into the calculation of the MLP**

The rules related to increases and decreases of MLP are inconsistent. While an immediate price drop is required if the MIP is 10% lower than the MLP, immediate price increases are not permitted if the MIP is 10% greater than the MLP. The PMPRB has proposed that MLP increases be adjusted based on the

actual lagged change in the consumer price index (CPI), in keeping with consumer protection.

Therefore, Eisai recommends that MLP decreases be transitioned year over year to a value percentage equivalent to the adjusted allowable increases based on CPI, in keeping with patentees' need for business sustainability.

Concern #2: The application of the pharmacoeconomic factor poses fundamental problems and creates significant uncertainty that will limit access to new patented medicines in Canada

- **Canadian Agency for Drugs and Technologies in Health (CADTH) / Institut national d'excellence en santé et en services sociaux (INESSS)'s re-analysis of the manufacturer's submitted cost utility models are non-transparent, subjective and flawed and result in significantly higher ICERs which decreases our ability to make launch decisions based on lack of predictability in pricing decisions**

Eisai Canada works with its global affiliates to make launch decisions based on the predictability of pricing decisions. However, given the high level of unpredictability created using the pharmacoeconomic factors, these decisions will be challenging to make for Canada.

Specifically, the proposed use of the pharmacoeconomic factors is not appropriate for the following reasons:

- Cost utility analysis are subjective in nature and can vary significantly based on the assumptions used. Manufacturers have little line of sight into the revised assumptions made by the CADTH and the INESSS, making it very difficult to interpret and debate the assumptions changed by these health technology assessment (HTA) authorities.
- CADTH and INESSS can also have different conclusions on the same pharmacoeconomic analysis, which further increases the level of uncertainty.
- Given that CADTH adopts a public healthcare perspective and fails to value indirect benefits applicable to the entire Canadian population, it is inappropriate for CADTH's analysis to be used in determining price ceilings that will apply to medicines reimbursed by private payers that value indirect benefits.

In sum, this high level of unpredictability, variability and subjectivity will make it very difficult to make viable business decisions for Eisai's products in Canada, which are often made years in advance to regulatory filing.

- **The most innovative, first in class drugs will be particularly disadvantaged by the proposed use of the pharmacoeconomic factor**

Highly innovative patented medicines intended for diseases that do not have effective treatments, often have comparators that are relatively inexpensive and/or highly genericized. These innovative patented medicines will therefore be particularly disadvantaged with the proposed use of the pharmacoeconomic factor. In fact, Eisai makes significant investments in research and development in underserved disease states where the standard of care may be outdated, ineffective, absent and/or genericized.

Eisai recommends that the pharmacoeconomic factor not be used for price compliance decision making. However, if it were to be considered, it should only be relied upon in the context of board hearings.

Concern #3: The proposed use of the market size factor fails to reward innovation, unfairly targets patented innovations in areas of high unmet need and poses implementation challenges

- **Market size adjustments unfairly disadvantage innovations that address significant unmet need for diseases that are highly prevalent in Canada**

The application of market size adjustments unfairly targets innovations intended to treat larger populations of Canadians. Manufacturers that choose to innovate in disease areas of high prevalence and that achieve their intended objective of providing a benefit to a larger market will be penalized by the PMPRB through mandated price reductions. Eisai recommends that the market size factor not be used to further reduce price ceilings.

Eisai recommends that the market size factor not be used for price compliance decision making. However, if it were to be considered, it should only be relied upon in the context of board hearings.

- **The market size factor should not be used to determine the excessiveness of prices as it is dependent on market dynamics that vary over time and are often outside of patentees 'control**

Patentees should not be unduly penalized for exceeding a specific market size threshold, which can often occur due to market dynamics that are outside of their control. For instance, post market cancellations, post-market authorization warnings, new clinical evidence of competitors, competitor supply shortages and changes in clinical guidelines are often difficult to predict and can significantly impact revenues generated by a patented medicine.

Notwithstanding Eisai' aforementioned recommendations about economic factors (i.e. pharmacoeconomic, GDP per capita & market size), PMPRB should have established predictable mechanisms in place that protect patentees from price decreases when economic factor thresholds are exceeded due to factors outside of the patentees' control.

- **No mechanism for patented medicines to move out of Category I if they no longer exceed the $50 million market size threshold**

Based on the revised guidelines, patented medicines that were classified as Category I based on their market size but that stop generating annual sales above $50 million continue to be subject to market size adjustments. This unfairly disadvantages these medicines compared with other innovative medications that never exceeded the market size threshold and were never be classified as Category I.

Eisai recommends including in the guidelines a mechanism that would allow patented medicines to move out of Category I if they no longer meet the market size threshold.

- **Combining all DINs' top line revenues to calculate whether a market size threshold is met creates inconsistencies and inequality in the evaluation of innovation for a product with multiple indications**

DINs can have different indications and provide differing levels of therapeutic innovation for their respective indication. Value of an innovation often extends beyond medicinal ingredients

and includes extensive research and development costs associated with varying doses and differing disease conditions in order to uncover therapeutic value. While we do not support the application of market size adjustments to set ceiling prices for patented medicines, if included in the final guidelines, we recommend that they only apply if actual revenue is exceeding the market size threshold for a specific indication. By pooling the revenue of all DINs to calculate the market size of a product, the PMPRB is disregarding and unduly penalizing innovation value provided by DINs available for additional indications.

Notwithstanding Eisai' aforementioned recommendation on economic factors, PMPRB should differentiate actual revenue realized by indication when determining whether a market size threshold is exceeded. This would avoid penalizing manufacturers that choose to make substantial research and development investments to evaluate whether a product can be beneficial for other disease states. PMPRB should consider establishing a predictable mechanism that account for determining if actual revenue exceeds market size thresholds by indication. For instance, it could derive the contribution of net sales per indication based on factoring in proportion of an indication's prevalence to the total sum of all indications' prevalence for a patented medicine.

- **The calculation of revenues for determining a product's market size is not based on actual transaction prices in Canada, and is therefore not reflective of the marketplace reality**

Revenues are usually calculated using average transaction prices, which factors in reported benefits. However, the way in which the PMPRB is proposing to calculate revenues to determine the market size of a product does not reflect the reality of the Canadian marketplace. As well, additional benefits provided by manufacturers, including investments in the workforce to achieve this market size are not factored in. Ancillary benefits provided by Eisai in the Canadian marketplace that are directly linked to achieving revenues may be compromised in order to avoid significant price reductions by exceeding market size thresholds.

Notwithstanding Eisai' aforementioned recommendation on economic factors, PMPRB should use actual transaction prices, which include all benefits provided in the marketplace, in determining the market size of a product.

- **The anticipated adjustments to the market size threshold are concerning**

Footnote 12 of the revised guidelines state that the market size threshold may be adjusted from time to time and at least every five years to reflect changes in CPI and GDP. We believe that the PMPRB's price determinations for new medicines should not be altered due to market events impacting GDP, which are outside the control of patentees. CPI and GDP will impact the affordability across industries leading to decisions on price adjustments at the marketplace based on market dynamics.

Moreover, the market size threshold was arbitrarily set to meet the PMPRB's goal of capturing 20% of patented medicines. Therefore, there is no logical explanation to justify changing an arbitrarily set threshold based on CPI and GDP.

Concern #4: The use of the pharmacoeconomic and market size factors continue to pose a problem for maintaining price confidentiality

Significant concerns around price confidentiality remain with the proposed use of the pharmacoeconomic and market size factors. Third parties across the world will be able to back calculate the MRP based on the following information: (1) the cost-utility reports published by CADTH and INESSS; (2) the MRP price tests and market size thresholds and adjustments outlined in the revised PMPRB guidelines; and (3) publicly available sources enable accurate estimation of price and revenue data. This type of risk is not acceptable, as it could jeopardize the global business model for a new innovation. Therefore, we recommend against using the new economic factors to set price ceilings. We suggest only using these factors in the context of board hearings.

In addition, payers can continue to benefit from negotiating confidential discounts regardless of whether a market size or cost utility threshold is met or not. Unlike the United Kingdom, where the authoritative body assesses the cost-effective of a medicine and makes recommendations on its reimbursement for public payers, PMPRB is not a part of private and public drug funding programs and decisions on funding.

We therefore recommend that price reductions based on HTA recommendations be achieved through negotiations with payers who are responsible for the reimbursement of medicines.

Concern #5: When a patented medicine loses its exclusivity, all medicines within that class should be reclassified category II

Patented medicines that lose their exclusivity as well as any medicines in the same class should be subject to the same regulatory pricing policies that are applied by the PMPRB to generics and biosimilars**.**

Concern #6: The domestic Therapeutic Class Comparison (dTCC) test will still force innovative therapies that represent a new class of treatments to be benchmarked against generic pricing

Even the top of the dTCC could have generic comparators from older classes of medicines based on the wording “multiple sellers” that is used in the guidelines. This poses a significant barrier to entry onto the Canadian market, particularly in therapeutic areas of high unmet need where innovation has not occurred for a long period of time and the market has become genericized.

Eisai recommends replacing the dTCC tests with the current guidelines’ highest Therapeutic Class Comparison test.

Concern #7: The immense discretion afforded to the PMPRB staff in the context of investigations creates an additional layer of uncertainty

Section 94 of the revised guidelines provide the PMPRB staff with the immense discretion to modify any of the tests described in the guidelines depending on what it believes appropriate in the context of an investigation. This is particularly alarming, as tests can be modified on a whim by the staff with limited transparency and explanation. PMPRB staff could unilaterally, without stakeholder consultations, change tests and apply them more restrictively leading to even steeper price reductions than originally anticipated. This broad discretion renders the whole pricing framework highly unpredictable.

Concern #8: More meaningful consultations with the industry needed to clarify several aspects of the guidelines before they can be implemented

It would not be appropriate for the PMPRB to implement the guidelines when patentees are still not clear on how they will be operationalized. There are many outstanding questions on the revised guidelines that remain unanswered. This requires more meaningful exchanges between the PMPRB and industry, including through the establishment of technical working groups, as was initially promised by the PMPRB.

More specifically but not limited to, the following aspects of the guidelines need to be elucidated and addressed as part of a meaningful consultation process:

- how the pharmacoeconomic price (PEP) will be calculated
- how cost utility values will be used
- whether probabilistic or deterministic CADTH cost utility estimates will be used for the PEP calculations
- which recognized international price sources will be used
- how reference strength will be determined
- how combination products will be evaluated by the PMPRB, where CADTH's base case cost utility is linked to the combination, but the combination products have differing "relevant indications" and are from different manufacturers (e.g., what mechanisms exists to defend a patented medicines value when CADTH's base case cost utility is mostly driven by the price of another manufacturer's combination product?)
- how the PMPRB will take into consideration different cost utility outcomes by INESSS, CADTH or other academic/HTA assessments for the same product
- how the PMPRB will reconcile inequitable differences between comparators used in the dTCC price test and comparators used in CADTH's assessment of the cost utility analysis to set the MRP
- whether mechanisms exist to avoid patentees from being penalized if they have products that exceed the market size threshold due to external factors

Finally, we also ask the PMPRB to consult on the Help section of the online filing tool that is expected to be released shortly. We need to ensure that we understand and can provide input on our reporting obligations that will be further detailed in this tool.

To conclude, we hope that our feedback on the guidelines, including our recommendations, will be carefully considered by the PMPRB. Ultimately, we need a clear regulatory framework that provides a predictable pathway in order to commercialize our innovative medicines and to encourage health research investments in Canada. We need to be able to evaluate expected revenues before deciding whether and when to launch a medicine in Canada and the revised guidelines simply do not allow us to do so. Notwithstanding Eisai' aforementioned recommendations about economic factors (i.e pharmacoeconomic, market size, GDP per capita), PMPRB should have established mechanisms in place for patentees to defend rationale for exceeding the economic factor thresholds.

By delaying access to new medicines, the new price controls will jeopardize efforts made by Health Canada and other regulators to ensure patients can access potentially life-changing medications as quickly as possible. An example of this is "Project ORBIS" where Lenvima in combination with Keytruda received an indication to treat endometrial cancer and underwent an accelerated review with three

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regulators simultaneously (i.e., the USFDA, Health Canada and Australian TGA). This accelerated review was undertaken because there have been no new therapies to treat women affected by this cancer for 30 years. We were hoping to provide this combination to patients as quickly as possible. However, the new unpredictable and uncertain PMPRB price controls will make it more challenging for us to quickly commercialize this therapy in Canada.

Further, we believe that the PMPRB should not be reassessing price ceilings for already commercialized therapies. Eisai has made drug launch decisions and significant investment decisions in Canada based on the current, reasonably predictable pricing environment. The prices of our products that are already commercialized in Canada were deemed to be compliant with the current PMPRB rules, have been thoroughly reviewed by CADTH, negotiated by the pan-Canadian Pharmaceutical Alliance (pCPA) and considered cost effective and affordable by public and private payers. We therefore do not think it is appropriate for the PMPRB to reassess price ceilings for these medicines.

Finally, we strongly encourage the PMPRB to take the necessary time to engage the industry and other stakeholders in a real and meaningful discussion to understand the challenges posed by the draft revised guidelines and find ways to address them to ensure that Canadian patients can continue to access new medicines and vaccines in a timely manner, especially at this very critical time for Canadians and our health systems given the ongoing COVID-19 pandemic.

Sincerely,

Pat Forsythe
General Manager
Eisai Limited