Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

March 3, 2008

Sylvie Dupont, Secretary of the Board
Patented Medicine Prices Review Board
Box L40, Standard Life Centre
333 Laurier Avenue West
Suite 1400
Ottawa, Ontario
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Dear Sylvie:

We are writing on behalf of the Common Drug Review (CDR) and the Canadian Expert Drug Advisory Committee (CEDAC) in response to the call for written feedback to the Discussion Paper "Options for Possible Changes to the Patented Medicines regulations and the Excessive Price Guidelines" released on January 31, 2008. Our comments are confined to two aspects of the Discussion Paper.

Section III, A, ii, 2: When the scientific information/evidence available at the time the medicine was first introduced was not sufficient to determine with confidence its category of therapeutic improvement, or when new post-market evidence suggests the initial categorization was inappropriate.

We are generally supportive of the need for PMPRB to develop a life-cycle approach in keeping with the proposed Progressive Licensing Framework of Health Canada, and would add the following comments on this section:

- The three scenarios outlined in the Discussion Paper (IND/SAP drugs, NOC/c drugs, drugs for a rare, life-threatening disease) will only address a small number of agents. It is our observation that there appears to be an increasing number of drugs granted NOC/c status in recent years. These medications are frequently approved based on evidence of effectiveness that is focused solely on surrogate endpoints. Defining whether such a medication represents an important therapeutic advance is impossible. This could also be seen as a circumstance where an interim (lower) price may be appropriate, awaiting further evidence of effectiveness based on clinical endpoints. Furthermore, it will be important to ensure that this is in alignment with the direction of the Progressive Licensing initiative.
- It is not clear from the Discussion paper if this approach could be applied to not only increase price if new evidence supports a greater therapeutic advantage than originally thought, but also to decrease price if there is new evidence that the drug is less effective than originally thought. We suggest that both options apply.
- While not directly related to this point of consultation, we also believe that if there is a new indication for an existing medicine and subsequent significant market expansion, the

PMPRB should be able to review the price in the context of that expansion of market. For example, we are now seeing biologic such as anti-TNF agents introduced for a relatively small market such as Crohn's disease but with subsequent market expansion to conditions such as rheumatoid arthritis, psoriasis and ulcerative colitis.

Section III, B, ii: Categories of Medicines

We are supportive of the need to differentiate and carefully define "breakthrough/substantial improvement", "moderate improvement" and "little or no improvement" and suggest that this needs to consider not only the level of evidence from clinical trials but also the outcomes studied in the clinical trials. This could be done on the basis of an effect on important clinical outcomes versus validated surrogate outcomes versus unvalidated surrogate outcomes and we have provided some general input on these definitions below:

Breakthrough/Substantial improvement: We recommend opportunities be explored to align this definition with the CDR definition for a priority review drug, which is currently defined as being effective for the treatment of an immediately life-threatening disease or other serious disease for which no comparable drug is marketed in Canada. The evidence for this should be based on statistically significant and clinically meaningful improvement in mortality, morbidity and/or quality of life outcomes.

Moderate Improvement: Refers to a therapeutic improvement over existing therapies as evidenced on the basis of statistically significant and clinically meaningful scales or validated surrogate outcomes.

Little or No Improvement: No clear evidence of a therapeutic advantage over existing therapies.

To address the need for a life-cycle approach and the uncertainty in the evidence of a therapeutic advantage at the time of regulatory approval (as described in Section III, A, ii, 2 mentioned above), consideration should also be given to an additional category, "possible improvement", as described below:

Possible Improvement: This category refers to medicines for which there is promising evidence for improvement of clinically meaningful outcomes on the basis of preliminary studies, interim analyses of studies or completed clinical trials using unvalidated surrogate outcomes. Conceivably, this could be applied to medicines in both the "breakthrough/substantial improvement" and "moderate improvement" categories. This approach could be used in situations when it is not possible to determine whether a medicine in fact provides substantial or moderate improvements in meaningful outcomes. In such cases, it would be appropriate that there be an "interim price", which could be reassessed when further information from randomized controlled studies measuring clinical endpoints is available.

We appreciate the opportunity to comment on the Discussion Paper and would be happy to further discuss these issues with you.

Sincerely,

Mike Tierney
Vice-President
Common Drug Review

Braden Manns
Chair, CEDAC