PMPRB ceiling price proposed guidelines – November 2019 Oncology Case Studies (2020-02-13 ver1.1)

Introduction

The PMPRB proposed guidelines of November 2019 are used in this analysis to estimate plausible MRPs (maximum rebated prices) of six oncology drugs that have recently been reviewed by CADTH and are now being covered in Canada. These estimates of the MRP these drugs may have gained under the proposed guidelines are compared with plausible estimates of the prices at which these drugs have been covered in Canada (the actual prices at which these drugs are covered are confidential and, thus, estimates of these prices are best guesses). This comparison results in an estimate of the price reduction from our best guess of current prices that would be required for each drug to be considered compliant with the PMPRBs proposed pricing regulations. Depending on the size of these price reductions, we estimate whether or not the drug is very likely, likely, unlikely or very unlikely to have been supplied in Canada had these guidelines been in place when these drugs were considering entering the Canadian market. This judgement has as an underlying assumption that the PEP, and subsequently the MRP, will be, in effect, transparent to the world under the proposed guidelines.

The value of this analysis is to look at drugs that are now currently available and providing real known benefits to Canadians but are very likely to be assessed as providing poor value for money (under a cost effectiveness framework). Their potential loss to the Canadian health system would have tangible and known effects. By comparison, analysis of drugs that are not yet in our market would have unknown effects, effects in principle, and thus, an unknown sense of loss. We believe this assists us in understanding the value to patients (and society) of drugs that appear to be of low value when assessed solely through the Cost Effectiveness Analysis lens.

The six drugs reviewed to date are:

- Vencexta (venetoclax) – a drug for treating chronic lymphocytic leukaemia (CLL) among patients who have failed at least one prior therapy (and, therefore, have no further treatment options);
- Opdivo (nivolumab) – for (among many other indications) adjuvant treatment of fully resected melanoma;
- Darzalex (daratumumab) – for treatment (in combination with other medicines) of multiple myeloma in patients who have failed at least one other prior therapy (and, therefore, have few further options);
- Blincyto (blinatumomab) – for treatment of pediatric patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia (a small group of patients - 40 a year - who face no alternatives and a very high likelihood of death);
- Unituxiini (dinutuximab) – for use in combination with other drugs for the treatment of pediatric patients with high-risk neutoblastoma who achieve at least a partial response to prior therapy (a group of around 25 to 35 children a year); and
- Tagrisso (Osimertinib) - for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations (a relatively large group of around 2,000 patients annually).

Venclexta (venetoclax)

Estimation of MRP

Indication (coverage requested): As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-Cell Receptor Inhibitor (BCRi)

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		2.59	0.05
Incremental costs (c)		359,506	69,300
Treatment costs (d)		355,409	62,181
PharmacoEconomic Price - PEP (e*(a*b+d-c)/d) - $/mg		0.289	-0.047
Likely current market price - $/mg		0.476	0.476
Submitted public price (e) - $/mg		0.680	0.680
Percent reduction of likely current price			
At PEP		39%	>100%
Where revenue at $37.5M a year		41%	>100%
Where revenue at $62.5M a year		45%	>100%

NOT AVAILABLE

Assumptions:
- Estimation of MRP would be determined from the stated indication.
- Treatment cost is not reported in the CADTH reports so treatment cost is estimated from reported median treatment duration and dosing regimen for the submitted base case and then used as a proportion of the incremental treatment costs reported for the best and worst cases.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].

Interpretation of results

The proposed guidelines intend to use the CADTH Base Case estimates to determine the PEP. Never-the-less, CADTH do not report base case estimates for venetoclax indicating that a base case was not deliberated on or, in essence, adjudicated by an expert committee independent of the PMPRB.

The negative estimate of the PEP under the CADTH Worst Case deliberations indicates that venetoclax would have to be supplied along with a payment from the supplier for it to be considered compliant with the proposed pricing regulations. Clearly, this is not a possible price for a drug in a market and indicates there are some situations where the proposed formula does not work.

The best and worst case deliberations reported by CADTH indicate that the price reduction from best estimates of the current price would need to be somewhere between 39% and near 100% to be compliant with the proposed regulations.

At the mid-point between these estimates – a 70% price reduction from our best guess of the current price or an equivalent internationally visible price at around 80% below the publicly submitted price, we judge that it would be **very unlikely** that venetoclax would have been submitted for consideration of supply into the Canadian market.

Opdivo (nivolumab)

Estimation of MRP

Indication (coverage requested): as monotherapy, for the adjuvant treatment of adult patients after complete resection of melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases.

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		1.31	0.92
Incremental costs (c)		87,974	87,191
Treatment costs (d)		96,062	102,856
PharmacoEconomic Price - PEP (e*(a*b+d-c)/d) - $/mg		17.732	13.538
Likely current market price - $/mg		13.755	13.755
Submitted public price (e) - $/mg		19.650	19.650
Percent reduction of likely current price			
At PEP		0%	2%
Where revenue at $37.5M a year		0%	5%
Where revenue at $62.5M a year		0%	10%

NOT AVAILABLE

Assumptions:
- Estimation of MRP would be determined from the stated indication.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].

Interpretation of results

The proposed guidelines intend to use the CADTH Base Case estimates to determine the PEP. Never-the-less, CADTH do not report base case estimates for venetoclax indicating that a base case was not deliberated on or, in essence, adjudicated by an expert committee independent of the PMPRB.

The best and worst case deliberations reported by CADTH indicate that the price reduction from best estimates of the current price would need to be somewhere between 0 and 10% to be compliant with the proposed regulations.

At the mid-point between these estimates – a 5% price reduction from our best guess of the current price or an equivalent internationally visible price at around 25% below the publicly submitted price, we judge that it would be **likely** that nivolumab would have been submitted for consideration of supply into the Canadian market.

Darzalex (daratumumab)

Indication (coverage requested): In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

In combination with lenalidomide and dexamethasone

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		3.76	0.71
Incremental costs (c)		622,746	422,874
Treatment costs (d)		498,197	338,299
PharmacoEconomic Price - PEP (e*(a*b+d-c)/d) - $/mg		1.213	-0.742
Likely current market price - $/mg		4.186	4.186
Submitted public price (e) - $/mg		5.980	5.980
Percent reduction of likely current price			
At PEP		71%	>100%
Where revenue at $37.5M a year		72%	>100%
Where revenue at $62.5M a year		74%	>100%

NOT AVAILABLE

In combination with bortezomib and dexamethasone

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		1.72	0.91
Incremental costs (c)		189,690	178,583
Treatment costs (d)		151,752	142,866
PharmacoEconomic Price - PEP (e*(a*b+d-c)/d) - $/mg		2.572	0.790
Likely current market price - $/mg		4.186	4.186
Submitted public price (e) - $/mg		5.980	5.980
Percent reduction of likely current price			
At PEP		39%	81%
Where revenue at $37.5M a year		41%	82%
Where revenue at $62.5M a year		44%	83%

NOT AVAILABLE

Assumptions:
- Estimation of MRP would be determined from the stated indication.
- Treatment cost is not reported in the CADTH reports so treatment cost is assumed to be a constant proportion (80%) of the incremental cost.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].

Interpretation of results

The proposed guidelines intend to use the CADTH Base Case estimates to determine the PEP. Never-the-less, CADTH do not report base case estimates for daratumumab indicating that a base case was not deliberated on or, in essence, adjudicated by an expert committee independent of the PMPRB.

The proposed guidelines intend to calculate a weighted average of the PEP for an indication where there are clear sub-populations for which a PEP for each can be determined. However, the CADTH reports do not provide any information to enable a weighted average to be calculated in this instance.

The negative estimate of the PEP under the CADTH Worst Case deliberations for the lenalidomide with dexamethasone combination indicates that daratumumab would have to be supplied along with a payment from the supplier for it to be considered compliant with the proposed pricing regulations. Clearly, this is not a possible price for a drug in a market and indicates there could be some situations where the proposed formula does not work.

The best and worst case deliberations reported by CADTH indicate that the price reduction from best estimates of the current price would need to be somewhere between 39% and near 100% to be compliant with the proposed regulations.

At the mid-point between these estimates – a 70% price reduction from our best guess of the current price or an equivalent internationally visible price at around 80% below the publicly submitted price, we judge that it would be **very unlikely** that daratumumab would have been submitted for consideration of supply into the Canadian market.

Blincyta (blinatumomab)

Estimation of MRP

Indication (coverage requested): For the treatment of pediatric patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia (ALL).

And for the treatment of all adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL), including those who have had one prior line of therapy (i.e., adult patients who are refractory or patients who are in first or later relapse)

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		1	0
Incremental costs (c)		158,224	158,270
Treatment costs (d)		154,919	154,964
PharmacoEconomic Price - PEP (e*(a*b+d-c/d) - $/vial		757.72	121.33
Likely current market price - $/vial		2,091.08	2,091.08
Submitted public price (e) - $/vial		2,987.26	2,987.26
Percent reduction of likely current price			
Where revenue < $12.5M		46%	91%
Where revenue at $20M		54%	93%
Where revenue at $40M		61%	94%

NOT AVAILABLE

Assumptions:
- Estimation of MRP would be determined from the adult indication given its likely greater prevalence.
- Blinatumomab would qualify as rare and thus its MRP would be adjusted under rules for rare disease drugs.
- Treatment cost is not reported in the CADTH reports but median treatment cycles and cycle cost is reported for the submitted base case. Treatment costs under the best and worst cases are assumed to be the same constant proportion of the incremental cost calculated from the median cycles and cycle costs reported for the submitted base case.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].

Interpretation of results

The proposed guidelines intend to use the CADTH Base Case estimates to determine the PEP. Never-the-less, CADTH do not report base case estimates for blinatumomab indicating that a base case was not deliberated on or, in essence, adjudicated by an expert committee independent of the PMPRB.

The best and worst case deliberations reported by CADTH indicate that the price reduction from best estimates of the current price for blinatumomab would need to be somewhere between 46% and near 94% to be compliant with the proposed regulations.

At the mid-point between these estimates – a 70% price reduction from our best guess of the current price or an equivalent internationally visible price at around 75% below the publicly submitted price, we judge that it would be **very unlikely** that blinatumomab would have been submitted for consideration of supply into the Canadian market.

Unituxiini (dinutuximab)

Estimation of MRP

Indication (coverage requested): for use in combination with GM-CSF, IL-2 and Retinoic acid (RA) for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multi-agent, multimodal therapy (a very small group of patients numbering around 25 to 35 a year in Canada).

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)	60,000		
Incremental QALYs (b)	4.74		
Incremental costs (c)	347,793		
Treatment costs (d)	313,014		
PharmacoEconomic Price - PEP (e*(a*b+d-c/d) - $/vial	10,247.56		
Likely current market price - $/vial	8,995.00		
Submitted public price (e) - $/vial	12,850.00		
Percent reduction of likely current price			
Where revenue < $12.5M	0%		
Where revenue at $20M	0%		
Where revenue at $40M	0%		

Assumptions:
- Dinutuximab would qualify as rare and thus its MRP would be adjusted under the rules for rare disease drugs.
- Treatment cost is not reported in the CADTH reports but the individual costs of the combination treatment are itemised for a full 6 cycles of treatment. Thus the proportion that dinutuximab (90%) makes up of these costs (less isotretinoin) is used to estimate treatment costs as a proportion of incremental costs.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].

Interpretation of results

The base case reanalysis by CADTH indicates that the submitted public price would be below the MRP (assuming market size falls below $12.5M as estimated) and, therefore, compliant with the PMPRB regulations.

Given no price reductions would have been required to be compliant with the PMPRB regulations, we judge that it would be **very likely** that dinutuximab would have been submitted for consideration of supply into the Canadian market.

Tagrisso (osimertinib)

Estimation of MRP

Indication (coverage requested): For the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations.

Compared with gifitinib

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		0	0
Incremental costs (c)		142,401	141,598
Treatment costs (d)		131,147	130,408
PharmacoEconomic Price - PEP (e*(a*b+d-c/d) - $/vial		0.48	0.36
Likely current market price - $/vial		2.58	2.58
Submitted public price (e) - $/vial		3.68	3.68
Percent reduction of likely current price			
At PEP		87%	90%
Where revenue $200M		88%	91%

NOT AVAILABLE

Compared with ofatinib

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		0	0
Incremental costs (c)		138,459	137,686
Treatment costs (d)		130,882	130,152
PharmacoEconomic Price - PEP (e*(a*b+d-c/d) - $/vial		0.53	0.42
Likely current market price - $/vial		2.58	2.58
Submitted public price (e) - $/vial		3.68	3.68
Percent reduction of likely current price			
At PEP		86%	89%
Where revenue $200M		87%	90%

NOT AVAILABLE

Assumptions:
- Treatment cost is not reported in the CADTH reports but median treatment duration is provided for the submitted base case. Together with estimated monthly cost, a cost of treatment with osimertinib is estimated. This cost, as a proportion of incremental costs in the submitted base case, is assumed to be constant in all other cases.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].
- Market size is assumed to be significant for this drug because of the incidence and the duration and price of treatment.

Interpretation of results

The proposed guidelines intend to use the CADTH Base Case estimates to determine the PEP. Never-the-less, CADTH do not report base case estimates for osimertinib indicating that a base case was not deliberated on or, in essence, adjudicated by an expert committee independent of the PMPRB.

The proposed guidelines intend to calculate a weighted average of the PEP for an indication where there are clear sub-populations for which a PEP for each can be determined. However, the CADTH reports do not provide any information to enable a weighted average to be calculated in this instance.

The best and worst case deliberations reported by CADTH indicate that the price reduction from best estimates of the current price for osimertinib would need to be somewhere between 86% and 91% to be compliant with the proposed regulations.

At the mid-point between these estimates – a 88% price reduction from our best guess of the current price or an equivalent internationally visible price at around 91% below the publicly submitted price, we judge that it would be **very unlikely** that osimertinib would have been submitted for consideration of supply into the Canadian market.

Administrative and technical observations

- The guidelines anticipate that the cost effectiveness analysis required to make the PEP and MRP calculations will be available from recognised public authorities (i.e. the public HTA bodies used by Canadian jurisdictions) in the form required to make the calculations. Currently, not all the information required to make the calculations is available in the public records from CADTH (note: information from INESSS was not reviewed in this project). While the information may be available in information shared between these public bodies and the PMPRB, these case studies illustrate that the missing information will not have been deliberated on by CADTH's expert committees unless its assessment processes are changed. Thus, unless the assessment processes change, it won't be able to be claimed that all the information used to calculate the PEP has, in effect, been adjudicated by the recognised public HTA body.

- Similarly, the guidelines anticipate calculating a weighted average PEP within an indication where there are multiple treatment sub-groups. Where this occurs, the information to make these weighted averages is not discussed in the CADTH expert committee reports and, thus, is not currently adjudicated by the public HTA body.

- These case studies indicate that there are some circumstances under which the calculated PEP can be negative. While these situations have been encountered in these case studies as a consequence of having to make assumptions about the treatment cost (as this information is frequently missing), it is not valid to conclude that this is an artefact of the assumptions used here. There are realistic scenarios under which the current formula can result in negative numbers being those where the treatment cost makes up a relatively low proportion of the incremental cost. These situations are likely to arise when a new drug is used in combination therapies - which are not uncommon in oncology.