CONECTed
Collective Oncology Network for Exchange, Cancer Care Innovation, Treatment Access and Education

RCONECTé
Réseau collectif d'oncologie pour échange, innovation en soin du cancer, accès aux traitements et éducation

Patented Medicine Prices Review Board
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re: Oncology Patient Group (CONECTed) PMPRB 2020 Guidelines Input Submission

Thank you for the opportunity to provide feedback on the draft Guidelines published on June 19, 2020.

We, the signatories to this submission, will describe the background to set the context that underpins our deliberations in which we considered the revised draft Guidelines. We will then provide an updated analysis of the case studies that we had provided in our last submission on February 15th 2020 using the draft Guidelines of June 19th 2020 for your consideration (Appendix A), and will follow with recommendations to remedy the concerns we still find with the approach PMPRB is proposing to addressing the entry level price of patented drugs in Canada.

Basis for our position

As patients and patient groups, we recognize the challenges of a dual federal/provincial jurisdiction that underlines the healthcare system for people across Canada.

We are also aware that there are inequities in coverage for medications across the country due to several factors. Public systems are the responsibility of provinces and territories and of course each has its own economic engine, priorities, demographics and other factors that drive decisions about how much to spend, what to fund and what funding models to implement. In addition, employers, unions, and individuals who can afford them have private plans that provide additional access.

Patients accept that this is the construct we have. We understand that public plans drugs have to make decisions about drugs they fund although we trust that they will use instruments that will help make fair, objective and evidence-based choices. We all want a sustainable system; we want the prices of drugs to permit sustainability. This is no doubt the appeal of a universal single payer pharmacare plan. We are not against it, but it needs to fairly ensure Canadians have access to the care they deserve.

Patient groups, such as the ones we represent, continue to support health technology assessment agencies, CADTH and INESSS, and also pCPA. They each play a key role for the constituents they serve and operate on a value system to provide better health to Canadians.

In the case of PMPRB, we continue to believe its mandate can be modernised at this time by reassessing the current basket of reference countries proposed in the current review. The other agencies listed above have the role of determining clinical and economic value and to negotiate confidential reimbursement prices to reach a mutually agreed drug price with the drug manufacturers and the provinces.

It is important to revisit the history of cancer management in Canada, as it serves as a guiding principle to our position:

- In 2007 the House of Commons Standing Committee on Health heard evidence that cancer treatments required their own health technology assessment process to ensure that value is analyzed based on factors relevant to that complex group of diseases. The Committee agreed with these recommendations. The result of those hearings was the creation of pCODR with a four-part deliberative Framework as its HTA process.
- The federal government also created a cancer strategy stewarded by the Canadian Partnership Against Cancer.
- Provinces have cancer agencies to manage cancer generally, including drug reimbursement, separately from other treatments.

The statistics regarding cancer certainly make the case for this specific focus on cancer:

- It is the number 1 cause of death in Canada.[1]
- It is estimated that 1 of 2 people in Canada will be diagnosed with cancer in their lifetime.[2]
- 1 in 4 will die from it, or 821,000 in Canada this year alone.[2]

This is a huge public health issue that requires a discrete policy approach, as the governments have recognized.

In addition, as we know, there is not just one type of cancer, one stage of cancer or one cause of cancer:

- There are cancers that are uncommon and those that are more common.
- There are cancers for which research has found genetic links that inform prevention and treatment and those that have not.
- There are cancers that can be cured.
- There are cancers that can be effectively treated and have been transformed into chronic illnesses with newer, more effective treatments; yet, there are many that continue to be a certain death sentence within months of diagnosis.

Breast cancer: The most common cancer among women, both young and old people alike, is breast cancer. In 2020, an estimated 27,400 women will be diagnosed with breast cancer and 5,100 will die of this disease. Additionally 240 men will also be diagnosed with breast cancer.[3] Among women, between 5 and 10% of breast cancers are thought to be hereditary. The BRCA1 and BRAC2 have been known to be linked with a higher link of breast cancer.[4] More recently, a study in 2017 found 72 new genetic mutations linked to breast cancer and now under study.[5]

Colorectal cancer: Among cancers, Colorectal Cancer is the second leading cause of death in men, and the third leading cause of death in women.[6] About 50% of cases were found to be diagnosed at stages III and IV,[7] and an estimated 9700 will die of this cancer in 2020.[6]

Lung cancer: It is estimated that this year, 29,800 Canadians will be diagnosed with lung cancer, and 21,200 will die from it.[8] It is the leading cause of cancer deaths for males and females at 25.2% and 26.1% respectively.[9] Contrary to public opinion, it is not just a disease of those who smoke. Unlike breast cancer, most cases of lung cancer are not related to inherited genetic changes.[10] There are certain "signatures" within the lung cancer cell that determine which oral cancer therapies to use.[11] It has a 19% five year survival rate compared to 93% in prostate cancer, 88% in breast and 65% in colorectal.[7]

Paediatric cancers: Every year, around 880 children under the age of 15 are diagnosed with cancer, and 150 die from it. Cancer is the second most common cause of death for children aged 1-14 in the developed world after accidents.[12] Due to access to new treatments, the five-year survival rate for Canadian children has improved from 71% to over 82%.[13] Without treatment these cancers are fatal.[14] While a significant number of children are cured, they face a life time of significant health care impacts including secondary malignancies caused by the treatments that cured them. Cure rates have also plateaued with no improvements in many paediatric cancers over several decades. Reducing the lifelong impacts of treatments and saving the lives of the 20% of children we continue to fail requires new approaches and new treatments.

Blood cancers: Over 21,000 Canadians are expected to be diagnosed with one of 137 different types of blood cancer this year.[15] Dramatic scientific breakthroughs in the past several years have significantly improved our understanding of these diseases and have opened new treatment opportunities that can improve outcomes for patients.[15] Access to the most effective new treatments is therefore especially critical.

Uncommon cancers: There are also uncommon cancers like Gastrointestinal Stromal Tumours (GIST) with unclear prevalence and incidence levels in Canada,[15] but estimated to be about 500 new cases per year.[16] Genetic testing is recommended to guide treatment decisions for high risk resected and advanced GIST.[17]

In our submission, the PMPRB, as a federal government agency, must recognize that government policy has determined that oncology is a discrete group of diseases for public policy purposes. Oncology patient groups and other stakeholders strongly support this policy as a good health policy that is strongly supported in many other countries.

Until the first Guidelines were issued in late November 2019, patient groups had no defined concrete formula or processes by which to determine whether the planned changes will consider public policy regarding oncology, and therefore whether it will be a good public policy instrument or not.

When the 2019 draft Guidelines were released, in order to ensure an objective evidence based and expert analysis of the Guidelines, we asked an external health economist to assist us understand how those formulas in the proposed guidelines would be applied. Specifically, we asked him to look at six oncology drugs for different types of cancer that have been reviewed by pCODR recently, and to compare the outcomes they received through that process with the outcomes we can predict they would have had under the 2019 Guidelines release with the information available to us. The results of these analyses and recommendations based on them were presented to PMPRB during a meeting on February 13, 2020 and submitted formally on February 14, 2020 as a response to the open consultation.

2020 Guidelines – A new opportunity to get it right

We were pleased that the PMPRB delayed the implementation deadline set for July 1 2020 to allow for more time to analyze and comment on the new guidelines released on June 19 2020, with an implementation date now proposed for January 1 2021. In our view, it demonstrated that it had incorporated comments received by the many stakeholders during the February – March 2020 time frame. We welcomed the recognition of the need for a more nuanced approach to assessing "excessive" pricing in the oncology context and that the QALY thresholds that represented major concerns for us had been expanded in a significant way. There are other issues, however, that have emerged with the new guidelines, which we will cover later in this submission.

We provided the 2020 Guidelines to the health economist with whom we had originally worked and asked him to re-evaluate the impact of these changes on our six case study drugs. At the conclusion to this submission is Appendix A, the analysis from the Health Economist.

Revised Case studies analysis

In the appendix we present the new six case studies analysed by the health economist using the 2020 draft Guidelines.

Our conclusions from the cancer case studies analysis using the new formulas

It remains clear that oncology needs its own approach in any Guidelines, as the federal and provincial governments have recognized in other health policies.

It also remains clear that this approach must be flexible enough to recognize the differences between uncommon and more common cancers, different stages of cancer, genetic factors, paediatrics versus adults, comorbidities, Indigenous populations and social determinants of health, to name a few.

We recognize that PMPRB has taken into account our submissions in this area, and has come some way to responding to the concerns of the oncology community. We appreciate the incorporation of a more stratified approach to Category I drugs. It certainly will alleviate some of the concerns we have had about the previous 2019 Guidelines.

In the new iteration of the health economist's analysis, based on expected revenue, and on the Therapeutic Criteria Level(TCL Designation), the MRP calculation requires a percentage reduction of the submitted price by anywhere from 0% (CADTH Best Case) to near 50% (CADTH Worst Case) based on the Therapeutic Criteria Level (TCL) designation.

It is not the role of patient groups to determine what decisions a pharmaceutical company will make about launching new drugs into Canada based on such reductions. It will probably be a case by case decision based on factors which are specific to the business environment and expectations. Decisions not to launch or to delay launch will directly impact access to needed therapies for oncology patients. The uncertainty remains about the availability of a new therapy still exist. In fact, with the introduction of the 4 Therapeutic Criteria Levels, that are assigned to each new therapy,

the PMPRB is introducing a new complexity that will result in an increased uncertainty. It is difficult to feel confident that the new Guideline formulas make it easier, and provide the certainty required, to ensure drug launches in Canada and the availability of clinical trials of medications badly needed by people across the country.

For example, in cancer, depending on the patient's genetic characteristics, a therapy of a lower TCL might work better than one assigned a higher level, therefore possibly impacting the accessibility of this therapy. Definitions of the TCL are open to significant variation in interpretation and it would be wise to have other expert bodies, such as HTA organisations and/or medical experts and including patients to define the value of a new therapy.

CADTH's deliberative framework for oncology drugs, with four considerations, including clinical benefit, cost effectiveness, patient values and feasibility of adoption, has recognized this nuanced, flexible and pragmatic health technology assessment required for oncology drugs. This is a recognition that there are limitations of using a single outcome measure for economic evaluation, since doing so means that important health consequences are excluded. INESSS also takes into account societal and patient values in its health technology assessment considerations.
Based on our review of the entire revised Guidelines provided on June 19, 2020 we submit the following recommendations that will serve to support the modernisation of the PMPRB:

Recommendation #1 – Further consultation is required

We accept that the new 2020 draft Guidelines are an improvement for cancer drugs in general from the 2019 draft Guidelines. The changes that are proposed are significant and will have important consequences.

It must be recognized, however, that decisions about all aspects of drug pricing and launches in Canada, are exclusively within the purview of each company. The decision about whether required price reductions will be acceptable to each company will undoubtedly involve a number of factors proprietary to each company. Therefore, patient groups cannot draw conclusions as to whether these changes will encourage introduction of a drug, and if it will do so in a timely manner. All we care about is that medications be made available to Canadians.

The Guidelines still create a level of uncertainty that may well discourage industry from bringing certain needed drugs to market and this will be detrimental to the health and well-being of patients. The industry has already drawn this conclusion. **Therefore, we ask that further consultations with industry should be undertaken to clarify areas of uncertainty before adoption**. To support this dialogue, we ask that PMPRB provide case studies like we did across the 4 levels of TCL for Category 1 drugs.

Recommendation #2 – Need for Transparent Algorithm

Create and publish an algorithm for how drugs get sorted into the different TCL levels. This algorithm should allow stakeholders to easily identify in which TCL a drug will fall, in order to calculate the associated price reduction.

Current TCL definitions are open to variation in interpretation which could lead to ambiguous cases where it is unclear whether a drug will be considered, for example, TCL1 or TCL2. This ambiguity is problematic since the ICER threshold differences between TCL1 and TCL2 can lead to substantial differences in PEP estimates, and ultimately, the amount of price reduction the drug will be subject to. Likewise, differences in the Reduction Floor values across the TCLs also leads to significant differences in MRP estimates.

This creates uncertainty for key stakeholders such as patentees, pCPA or payer negotiators, who must make pricing decisions in the medium term that match (or better) prices that will be established following PMPRB review.

This uncertainty at the negotiations level can affect decisions by patentees to launch a drug, either leading them to delay the launch until more information becomes available when PMPRB sorts the drug into one of the four TCL levels, or to cancel the launch altogether. This will potentially reduce timely access to much needed drugs, and result in harm to patients.

In conclusion, establishing a clear and transparent algorithm with the input of relevant experts, or more clearly defining the criteria that can be used by key stakeholders to identify the TCL that the drug will fall into, will help prevent potential delays in access for patients that may occur as a result of looming uncertainty.

Recommendation #3 – Implementation in stages

The PMBRB should consider implementing the Guidelines in a staged approach. First, it should implement using the updated 11 baskets of countries as reference for January 1, 2021. The implementation of the pharmaco-economic, GDP and market size factors to follow at a later date closely aligned with our Recommendation #1. A carefully thought out and interrelated roll out with interim evaluations and course correction measures will result in better consequences for all stakeholders.

Recommendation #4 – Multi-stakeholder evaluation and monitoring committee

The Guidelines be amended to provide a multi-stakeholder Committee responsible and accountable to oversee the monitoring and evaluation process of the PMPRB modernisation Guidelines.

This Committee should be tasked with the creation of a multi-stakeholder Panel of experts to review all drugs that are determined to be “excessive” in entry level price by the criteria set out in the Guidelines. This Panel will take into consideration factors other than MRP, including factors taken into account by CADTH in its deliberative framework.

As well a multi-stakeholder subcommittee including patients and patient representatives chosen by oncology patient groups must be implemented to review Category 1 drugs to provide advice to determine the TCL designation for each drug being evaluated.

Recommendation #5 - Patient Engagement

The PMPRB develop a formal patient engagement programme following the ICER model co-created with patient groups chosen by the oncology patient community. https://icer-review.org/announcements/2020_vaf_update/ See particularly pages 50-54.

Recommendation #6- Maintain non-transparency for the benefit of patients

The Guidelines be amended to provide that PMPRB's public decision will provide information that the analysis has either met the PMPRB threshold and is not excessive or that it has not met the PMPRB threshold or other CADTH analysis and is excessive.

No specific economic data or numbers supporting this decision should be made public by PMPRB. This will ensure that the public Canadian price will not put at risk other markets and particularly the U.S. market such that companies will decline to enter, or delay entry to, the Canadian market for that reason.

Thank you for inviting us to provide our comments on the proposed PMPRB guideline revisions. We look forward to hearing back from you at your earliest convenience.

Respectfully submitted,

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APPENDIX A - PMPRB ceiling price proposed Guidelines – June 2020
Oncology Case Studies

Introduction

In June 2020, the PMPRB issued its updated draft Guidelines for determining the ceiling prices of patented pharmaceuticals.

For Category I pharmaceuticals, the draft Guidelines now simply note that the Pharmacoeconomic Price (PEP) will be determined from the re-analysis of the base case provided by Canada's HTABs (being information to be supplied by the patentee). Thus while the equation presented in the 2019 Guidelines has been removed from the document, in essence it remains a reasonable means by which to estimate the PEP (as was made clear during consultation on the 2019 Guidelines, the equation was not meant to be considered definitive but simply a guideline). In addition, the 2020 draft Guidelines amends the ICER thresholds to be used in calculating the PEP which are now dependent on the newly introduced Therapeutic Class Level (TCL) into which the drug falls. Further, to calculate the Maximum Rebated Price (MRP), a second test – the Reduction Floor, its level also dependent on the TCL – is used and the higher of the two prices calculated from the PEP or Reduction Floor becomes the default MRP. Finally, the MRP may be adjusted depending on the market sales with the adjustments also being dependent on the TCL (referred to as the MRP[A]).

The effect of these changes on estimates of the MRP/MRP[A] for six oncology (assumed category I) pharmaceuticals is the subject of this report. Note that the Guidelines provide guidance for estimating ceiling prices for all patented pharmaceuticals. However, in this report we restrict our interest to estimating the effect the proposed Guidelines may have on New Chemical Entities being brought to Canada that, in general, are likely to be classed as category I pharmaceuticals because of the proposed prices and as exemplified by the six drugs considered.

This analysis uses the analysis conducted on the 2019 draft Guidelines for the same six oncology drugs. The information collected from the HTA reports to make the calculations for that analysis is used unaltered to estimate the MRPs likely to result from the new algorithm contained in the 2020 draft Guidelines. In order to see the effect of the new ICER thresholds, the impact of the Reduction Floor and adjustments possible due to market size, estimates are made for all TCLs – thus the potential bias from determining which TCL a drug is likely to fall under is removed in favour of providing a range of results.

The six drugs reviewed in this report are as follows:

- 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).

Background

In February 2020, the 2019 PMPRB draft Guidelines were analysed to estimate the likely ceiling price for the six oncology drugs listed above and, as a consequence of these estimates, their likelihood of being launched in the Canadian market had the 2019 draft Guidelines been in place at the time they were launched. The analysis indicated that the ceiling prices for these six drugs could range from no/small price reductions (two drugs) through to price reductions in excess of 75 percent/100 percent (four drugs). These results enabled a relatively uncontroversial (even though subjective) conclusion to be drawn – it was reasonable to conclude that had the 2019 draft Guidelines been in place, four of the six drugs reviewed would have been very unlikely to have been launched in Canada.

These results are summarised in the table below:

Estimated plausible price reductions required under the 2019 draft Guidelines and impact on Launch

	cf. Submitted price	cf. Current price	Launch?
venetoclax	80%	70%	Very unlikely
nivolumab	25%	5%	Likely
daratumumab	80%	70%	Very unlikely
blinatumomab	75%	70%	Very unlikely
dinutuximab	0%	0%	Very likely
osimertinib	91%	88%	Very unlikely

Results of 2020 draft Guidelines

The results of the updated analysis using the category I (based on price) calculation algorithm for each of the six oncology drugs is presented on the following pages. Below is a summary of the results exploring the sensitivity of the estimates to TCL classification and revenue.

Estimated plausible price reductions – (at $25M revenue)

	TCL 1	TCL 4	Launch?
venetoclax	0%	26%	Likely
nivolumab	0%	0%	Likely
daratumumab	0%	26%	Likely
blinatumomab	5%	26%	Likely
dinutuximab	0%	0%	Likely
osimertinib	10%	26%	Likely

Estimated plausible price reductions – (at TCL 2)

	< $12M	$125M	Launch?
venetoclax	0%	33%	Likely
nivolumab	0%	16%	Likely
daratumumab	0%	33%	Likely
blinatumomab	0%	33%	Likely
dinutuximab	0%	16%	Likely
osimertinib	0%	33%	Likely

Venclexta (venetoclax)

Estimation of MRP/MRP[A]

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 - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		3	0
Incremental costs (c)		359,506	69,300
Treatment costs (d)		355,409	62,181
Submitted public price (e) - $/mg		0.68	0.68
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial		0.98	0.02
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial		0.73	- 0.00
MRP as percent reduction of submitted price with floor test			
If TCL 1		0%	20%
If TCL 2		0%	30%
If TCL 3		0%	40%
If TCL 4		0%	50%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		0%	10%
Where revenue $25M and TCL 2		0%	16%
Where revenue $25M and TCL 3		0%	21%
Where revenue $25M and TCL 4		0%	26%
Where revenue $125M and TCL 1		16%	27%
Where revenue $125M and TCL 2		16%	33%
Where revenue $125M and TCL 3		16%	39%
Where revenue $125M and TCL 4		16%	45%

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.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP. (Note that the submitted price may be lower with the implementation of the draft Guidelines but the PEP cannot be calculated from the CADTH reports using an assumed lower price as the published CEA results depend on the submitted price. However, a lower submitted price will mean a lower price reduction is required to produce the same PEP.)

Interpretation of results

- The range in PEP price estimates (from 98c per mg through to 0c per mg) given the lack of a base case re-analysis from CADTH shows how uncertain a price based on the PEP alone may be.

- The Reduction Floor reduces this possible variation substantially resulting in prices ranging from no reduction relative to the submitted price (assumed to be the MLP) to a 50% reduction.
- Given the first $12M of revenue may be earned at the MLP, the market size adjustment also significantly attenuates the possible range of required price reductions from none through to 26% (at revenue of $25M) and 45% (at revenue of $125M).
- The results also indicate that the potential price reduction required is significantly affected the TCL classification of the drug.

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

The degree of variation in price reductions likely as a result of the TCL determination and the level of unknowns surrounding this determination in the short term would, however, likely introduce a significant level of uncertainty that could lead to decisions not to, or delay, launch.

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 - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		1	1
Incremental costs (c)		87,974	87,191
Treatment costs (d)		96,062	102,856
Submitted public price (e) - $/mg		19.65	19.65
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial		55.25	38.14
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial		41.85	29.36
MRP as percent reduction of submitted price with floor test			
If TCL 1		0%	0%
If TCL 2		0%	0%
If TCL 3		0%	0%
If TCL 4		0%	0%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		0%	0%
Where revenue $25M and TCL 2		0%	0%
Where revenue $25M and TCL 3		0%	0%
Where revenue $25M and TCL 4		0%	0%
Where revenue $125M and TCL 1		16%	16%
Where revenue $125M and TCL 2		16%	16%
Where revenue $125M and TCL 3		16%	16%
Where revenue $125M and TCL 4		16%	16%

NOT AVAILABLE

Assumptions:
- Estimation of MRP would be determined from the stated indication.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP. (Note that the submitted price may be lower with the implementation of the draft Guidelines but the PEP cannot be calculated from the CADTH reports using an assumed lower price as the published CEA results depend on the submitted price. However, a lower submitted price will mean a lower price reduction is required to produce the same PEP.)

Interpretation of results

- The range in PEP price estimates (from $55.25 per mg through to $29.36 per mg) given the lack of a base case re-analysis from CADTH again shows how uncertain a price based on the PEP alone may be. However, in all scenarios examined here, the PEP estimate is above the submitted price.
- In this case study, the Reduction Floor has no influence on the estimate of the MRP.
- Price reductions become likely at revenue of $125M and beyond but are relatively modest.

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

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 - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		4	1
Incremental costs (c)		622,746	422,874
Treatment costs (d)		498,197	338,299
Submitted public price (e) - $/mg		5.98	5.98
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial		7.53	1.02
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial		5.28	0.39
MRP as percent reduction of submitted price with floor test			
If TCL 1		0%	20%
If TCL 2		12%	30%
If TCL 3		12%	40%
If TCL 4		12%	50%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		0%	10%
Where revenue $25M and TCL 2		6%	16%
Where revenue $25M and TCL 3		6%	21%
Where revenue $25M and TCL 4		6%	26%
Where revenue $125M and TCL 1		16%	27%
Where revenue $125M and TCL 2		23%	33%
Where revenue $125M and TCL 3		23%	39%
Where revenue $125M and TCL 4		23%	45%

In combination with bortezomib and dexamethasone

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		2	1
Incremental costs (c)		189,690	178,583
Treatment costs (d)		151,752	142,866
Submitted public price (e) - $/mg		5.98	5.98
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial		12.06	6.12
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial		8.67	4.22
MRP as percent reduction of submitted price with floor test			
If TCL 1		0%	0%
If TCL 2		0%	29%
If TCL 3		0%	29%
If TCL 4		0%	29%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		0%	0%
Where revenue $25M and TCL 2		0%	15%
Where revenue $25M and TCL 3		0%	15%
Where revenue $25M and TCL 4		0%	15%
Where revenue $125M and TCL 1		16%	16%
Where revenue $125M and TCL 2		16%	33%
Where revenue $125M and TCL 3		16%	33%
Where revenue $125M and TCL 4		16%	33%

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.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP.

Interpretation of results

- The range in PEP price estimates (from $12.06 per mg through to 39c per mg – a 93% price reduction) given the lack of a base case re-analysis from CADTH shows how uncertain a price based on the PEP alone may be.
- The Reduction Floor reduces this possible variation substantially resulting in prices ranging from no reduction relative to the submitted price (assumed to be the MLP) to a 50% reduction.
- Given the first $12M of revenue may be earned at the MLP, the market size adjustment also significantly attenuates the possible range of required price reductions from none through to a worst case of 15% -26% at revenue of $25M (depending on the comparator) and a worst case of 33% to 45% at revenue of $125M (depending on the comparator).

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

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 - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		1	0
Incremental costs (c)		158,224	158,270
Treatment costs (d)		154,919	154,964
Submitted public price (e) - $/vial		2,987.26	2,987.26
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial		2,674.42	553.14
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial		1,989.88	398.92
MRP as percent reduction of submitted price with floor test			
If TCL 1		10%	20%
If TCL 2		30%	30%
If TCL 3		33%	40%
If TCL 4		33%	50%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		5%	10%
Where revenue $25M and TCL 2		16%	16%
Where revenue $25M and TCL 3		17%	21%
Where revenue $25M and TCL 4		17%	26%
Where revenue $125M and TCL 1		22%	27%
Where revenue $125M and TCL 2		33%	33%
Where revenue $125M and TCL 3		35%	39%
Where revenue $125M and TCL 4		35%	45%

Assumptions:

- Estimation of MRP would be determined from the adult indication given its likely greater prevalence.
- 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.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP. (Note that the submitted price may be lower with the implementation of the draft Guidelines but the PEP cannot be calculated from the CADTH reports using an assumed lower price as the published CEA results depend on the submitted price. However, a lower submitted price will mean a lower price reduction is required to produce the same PEP.)

Interpretation of results

- The range in PEP price estimates (from $2,674.42 through to $398.92 per vial – an 87% price reduction) given the lack of a base case re-analysis from CADTH shows how uncertain a price based on the PEP alone may be.
- The Reduction Floor reduces this possible variation significantly resulting in prices ranging from 10% reduction relative to the submitted price (assumed to be the MLP) to a 50% reduction.
- Given the first $12M of revenue may be earned at the MLP, the market size adjustment also significantly attenuates the possible range of required price reductions from 5% through to 26% (at revenue of $25M) and 22% to 45% (at revenue of $125M).
- The results also indicate that the potential price reduction required is significantly affected the TCL classification of the drug.

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

The degree of variation in price reductions likely as a result of the TCL determination and the level of unknowns surrounding this determination in the short term would, however, likely introduce a significant level of uncertainty that could lead to decisions not to, or delay, launch.

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 - TCL 1 (a1)	200,000		
ICER threshold - TCL 2, 3 and 4 (a2)	150,000		
Incremental QALYs (b)	5		
Incremental costs (c)	347,793		
Treatment costs (d)	313,014		
Submitted public price (e) - $/vial	12,850.00		
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial	37,490.01		
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial	27,760.56		
MRP as percent reduction of submitted price with floor test		NOT AVAILABLE	NOT AVAILABLE
If TCL 1	0%		
If TCL 2	0%		
If TCL 3	0%		
If TCL 4	0%		
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4	0%		
Where revenue $25M and TCL 1	0%		
Where revenue $25M and TCL 2	0%		
Where revenue $25M and TCL 3	0%		
Where revenue $25M and TCL 4	0%		
Where revenue $125M and TCL 1	16%		
Where revenue $125M and TCL 2	16%		
Where revenue $125M and TCL 3	16%		
Where revenue $125M and TCL 4	16%		

Assumptions:

- 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.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP. (Note that the submitted price may be lower with the implementation of the draft Guidelines but the PEP cannot be calculated from the CADTH reports using an assumed lower price as the published CEA results depend on the submitted price. However, a lower submitted price will mean a lower price reduction is required to produce the same PEP.)

Interpretation of results

- The range in PEP price estimates (from $27,761 through to $37,490 per vial) shows the level of variation possible from TCL classification is non-trivial. However, in both scenarios examined here, the PEP estimate is above the submitted price.
- In this case study, the Reduction Floor has no influence on the estimate of the MRP.

- Price reductions become likely at revenue of $125M and beyond but are relatively modest.

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

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 - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		0	0
Incremental costs (c)		142,401	141,598
Treatment costs (d)		131,147	130,408
Submitted public price (e) - $/mg		3.68	3.68
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/mg		2.32	1.94
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/mg		1.66	1.38
MRP as percent reduction of submitted price with floor test			
If TCL 1		20%	20%
If TCL 2		30%	30%
If TCL 3		40%	40%
If TCL 4		50%	50%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		10%	10%
Where revenue $25M and TCL 2		16%	16%
Where revenue $25M and TCL 3		21%	21%
Where revenue $25M and TCL 4		26%	26%
Where revenue $125M and TCL 1		27%	27%
Where revenue $125M and TCL 2		33%	33%
Where revenue $125M and TCL 3		39%	39%
Where revenue $125M and TCL 4		45%	45%

Compared with ofatinib

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		0	0
Incremental costs (c)		138,459	137,686
Treatment costs (d)		130,882	130,152
Submitted public price (e) - $/mg		3.68	3.68
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/mg		2.26	1.88
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/mg		1.64	1.36
MRP as percent reduction of submitted price with floor test			
If TCL 1	NOT AVAILABLE	20%	20%
If TCL 2		30%	30%
If TCL 3		40%	40%
If TCL 4		50%	50%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		10%	10%
Where revenue $25M and TCL 2		16%	16%
Where revenue $25M and TCL 3		21%	21%
Where revenue $25M and TCL 4		26%	26%
Where revenue $125M and TCL 1		27%	27%
Where revenue $125M and TCL 2		33%	33%
Where revenue $125M and TCL 3		39%	39%
Where revenue $125M and TCL 4		45%	45%

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.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP. (Note that the submitted price may be lower with the implementation of the draft Guidelines but the PEP cannot be calculated from the CADTH reports using an assumed lower price as the published CEA results depend on the submitted price. However, a lower submitted price will mean a lower price reduction is required to produce the same PEP.)

Interpretation of results

- The range in PEP price estimates (from $2.32 through to $1.36 per mg) given the lack of a base case re-analysis from CADTH again shows how uncertain a price based on the PEP alone may be.
- The Reduction Floor reduces this possible variation substantially resulting in prices ranging from a 20% reduction relative to the submitted price (assumed to be the MLP) to a 50% reduction.
- Given the first $12M of revenue may be earned at the MLP, the market size adjustment also significantly attenuates the possible range of required price reductions from none through to 26% (at revenue of $25M) and 45% (at revenue of $125M).
- The results also indicate that the potential price reduction required is significantly affected the TCL classification of the drug.

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

The degree of variation in price reductions likely as a result of the TCL determination and the level of unknowns surrounding this determination in the short term would, however, likely introduce a significant level of uncertainty that could lead to decisions not to, or delay, launch.

Other observations

- The 2020 draft Guidelines use ICER thresholds that bear no relationship with those implicitly used by CADTH. It is widely accepted anecdotally that CADTH uses a threshold of $100,000 for oncology drugs and $50,000 for other technologies when proclaiming the price of a technology is not at a level considered cost effective. It is odd, therefore, that in the process of proposing new draft Guidelines that the ICER thresholds used across the Canadian health system are not proposed to be congruent with one another.

- This analysis did not try to determine into which TCL the drug under analysis would fall. The reason for this is that the definitions of the TCL are open to significant variation in interpretation. For example:

  TCL 1 includes ". . . is the first medicine . . . that effectively treats a particular illness or effectively addresses a particular indication in a clinically impactful manner . . . " and, therefore, leaves a question mark over impactful treatments that are used in an indication for a sub-group of patients (defined, potentially, by a genetic marker) that gain no benefit from treatments already available for the indication.

  TCL 1 notes that "A high QALY gain is normally associated with medicines at this level." TCL 2 also notes "A high QALY gain is normally associated with medicines at this level." But how high in each case?

  The difference in ICER threshold between TCL 1 and 2 is significant and can result in non-trivial differences in PEP estimates.

- The creation of different TCLs will create a great deal of uncertainty over how the PMPRB will classify drugs as, for the short term at least, there will be no history on which stakeholders may base their judgements. Key stakeholders needing to understand this judgement include both manufacturers making decisions to bring products to market and the pCPA (or payer negotiators) who must attempt to make pricing decisions that in the medium term are not higher than those established on PMPRB review. The pCPA may address this uncertainty through two means: either delaying its negotiations where it has the greatest uncertainty or by negotiating higher price reductions than it might have otherwise. Either way, the uncertainty introduced in the short term may manifest itself as private decisions by manufacturers to not launch in the Canadian market.