Common Drug Review

Pharmacoeconomic Review Report

September 2017

Drug	selexipag (Uptravi)
Indication	Long-term treatment of idiopathic pulmonary arterial hypertension, heritable pulmonary arterial hypertension (HPAH), pulmonary arterial hypertension (PAH) associated with connective tissue disorders and PAH associated with congenital heart disease, in adult patients with WHO functional class (FC) II–III to delay disease progression.
Listing request	As per indication
Dosage form(s)	200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg, 1,600 mcg tablets for oral administration
NOC date	20 January 2016
Manufacturer	Actelion Pharmaceuticals Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in treating pulmonary arterial hypertension (PAH) who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

CDR	CADTH Common Drug Review
CUA	cost-utility analysis
ERA	endothelin receptor antagonist
FC	functional class
HR	hazard ratio
ICUR	incremental cost-utility ratio
LY	life-year
M/M	morbidity/mortality
PAH	peripheral arterial hypertension
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PSA	probabilistic sensitivity analysis
PDE5	phosphodiesterase type 5
PDE5i	phosphodiesterase type 5 inhibitor
QALY	quality-adjusted life-year
WHO	World Health Organization

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Selexipag (Uptravi) tablets (200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg, and 1,600 mcg) administered orally twice daily
Study Question	"To translate the clinical outcomes of GRIPHON comparing Uptravi to BSC [best supportive care] into a robust health economic analysis to determine the cost-effectiveness of Uptravi as compared with BSC (plus background therapy) for the treatment of patients with PAH [pulmonary arterial hypertension]"
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with PAH, consistent with the population indicated for the use of selexipag, per the population assessed by the GRIPHON pivotal trial, which included primarily patients in FC II or FC III disease (< 5% in FC I/FC IV) who were controlled on either existing current therapy (an ERA or PDE5 inhibitor alone or in combination) or no treatment.
Treatment	Selexipag (Uptravi) added on to current therapy: • ERA + PDE5 inhibitor, or • ERA only, or • PDE5 inhibitor only, or • No treatment
Outcome	QALYs
Comparators	Current therapy: • ERA + PDE5 inhibitor, or • ERA only, or • PDE5 inhibitor only, or • No treatment
Perspective	Canadian public payer perspective
Time Horizon	Lifetime (30 years)
Results for Base Case	The manufacturer's base-case analysis is representative of the simulation of 10 individual patients. ICUR = $187,418 per QALY for selexipag in addition to current therapy compared with current therapy alone
Key Limitations	• There is substantial uncertainty regarding the applicability and the generalizability of the clinical data (GRIPHON) on which the model has been undertaken to the Canadian setting. • Given the lack of active comparators in GRIPHON and the absence of an indirect treatment comparison, the relative clinical and cost-effectiveness of selexipag versus appropriate active comparators is unknown. • The manufacturer's base-case results cannot be considered at face value considering that only 10 patients were simulated, which was not enough to allow stability of the results. To ensure stability within a 5% difference between output values across runs, CDR simulated 2,500 patients for the reanalyses. • The model was not appropriately calibrated to reflect the results of the GRIPHON trial; and the extrapolation of the survival benefit of selexipag post-trial was overly optimistic. • The base-case results excluded treatment discontinuation and heart/lung transplantations. • Utility decrements associated with parenteral treatment options appear overestimated.

CDR Best Estimate	Correcting the limitations above that could be varied (better model stability — 2,500 simulated patients; revised population baseline characteristics; no mortality benefit over the model time horizon; inclusion of discontinuation and a transplantation health state; and revising disutility estimates for parenteral treatment), the CDR best estimate for selexipag as an add-on to current therapy is $486,421 per QALY compared with current therapy. CDR was not able to appropriately assess patient subgroups by varying both FC and background therapy due to the data applied to the model, and it could not undertake analyses comparing selexipag directly with relevant comparators (ERAs and/or PDE5 inhibitors, and riociguat) due to lack of clinical data.

BSC = best supportive care; CDR = CADTH Common Drug Review; ERA = endothelin receptor antagonist; FC = functional class; ICUR = incremental cost-utility ratio; PAH = peripheral arterial hypertension; PDE5 = phosphodiesterase type 5; QALY = quality-adjusted life-year.

EXECUTIVE SUMMARY

Background

Selexipag (Uptravi) is a prostacyclin (PGI_2) receptor (IP receptor) agonist indicated for the long-term treatment of idiopathic pulmonary arterial hypertension (PAH), heritable PAH, PAH associated with connective tissue disorders, and PAH associated with congenital heart disease in adult patients with World Health Organization (WHO) functional class (FC) II or III to delay disease progression.[1,2] Disease progression includes hospitalization for PAH, initiation of intravenous or subcutaneous prostanoids, or other disease progression events (decrease of six-minute walk distance [6MWD] associated with either worsened PAH symptoms or need for additional PAH-specific treatment).[1] Selexipag has been approved by Health Canada for use as monotherapy, dual therapy (with an endothelin receptor antagonist [ERA] or a phosphodiesterase 5 [PDE5] inhibitor), and triple therapy (with an ERA and a PDE5 inhibitor). The manufacturer requested listing selexipag as per the Health Canada indication.[3]

Selexipag is a film-coated tablet to be administered twice daily, available in the following doses: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg, and 1,600 mcg. The manufacturer submitted selexipag at a marketed price of $64.1667 per tablet, for all tablet strengths.

In 2015, CADTH published a Therapeutic Review to assess the comparative efficacy and safety and to determine the relative cost-effectiveness of pharmacologic treatments for adults with PAH.[4] Based on the Therapeutic Review and patient group input, the CADTH Canadian Drug Expert Committee (CDEC) recommended that sildenafil or tadalafil (both PDE5 inhibitors) be the preferred initial treatments for adult patients with FC II and III PAH; and that add-on therapy should be used in adult PAH patients who are unable to achieve disease control with a single drug.[5]

The manufacturer undertook a cost-utility analysis to determine the cost-effectiveness of selexipag when added on to current therapy (an ERA, a PDE5 inhibitor, both an ERA and PDE5, or no treatment) compared with current therapy alone, in patients with PAH over a lifetime time horizon (assumed to be 30 years). The model simulated individual patients based on patient characteristics and efficacy data from the pivotal, phase III GRIPHON trial, which enrolled PAH patients in WHO FC II or III who were treated with a stable dose of an ERA, a PDE5 inhibitor or both treatments in combination, or were not receiving current treatment. The two efficacy end points from the GRIPHON trial included in the model were the composite of morbidity/mortality (M/M; the primary end point) and mortality (secondary end point). A change in WHO FC is commonly used to determine the health of patients with PAH; this was used to justify the structure of the model, where patients transitioned between FC II, FC III, FC IV, and death (with the potential to consider transplantation in a scenario analysis). FC I (a symptomless state) was not included in the model. Patients entered the model in one of eight subgroups at baseline; they were either in FC II or III, and were being treated with an ERA, a PDE5 inhibitor, an ERA and a PDE5 inhibitor, or were receiving no treatment. Transitions between FC health states were driven by M/M events captured in the GRIPHON trial; the probability of transitioning was implemented using parametric functions that predicted the timing of future events based on data from the GRIPHON trial. Several assumptions were made by the manufacturer that affected the transitioning of patients through the model. First, although direct mortality data from the trial indicated there was no mortality benefit from selexipag, the manufacturer assumed that mortality was correlated to FC status based on published literature, with higher risks of death with higher FC. Further, patients' health could deteriorate (move to a higher FC) at any point in the model, but could only improve (move to a lower

FC) in the first three months after a new treatment was initiated. Next, patients did not cycle between different background therapies in the model.

The model, based on the simulation of 10 patients, reported an incremental cost-utility ratio (ICUR) of $187,418 per additional quality-adjusted life-year (QALY) for selexipag in addition to current therapy versus current therapy alone.

Summary of Identified Limitations

The CADTH Common Drug Review (CDR) identified four key limitations with the manufacturer's submitted base-case economic evaluation. First, there is substantial uncertainty as to the generalizability of the GRIPHON trial to the use of selexipag in current Canadian clinical practice. The patient population receiving treatment prior to add-on selexipag in GRIPHON may have been clinically stable at baseline, and thus there is uncertainty as to the value of adding on selexipag. Also, the efficacy data used in the model were not fully stratified by baseline background therapy in addition to by health state; this makes it unclear if selexipag is more effective as monotherapy, or as part of combination therapy. Second, the manufacturer did not consider all appropriate comparators. Selexipag may be used as monotherapy, dual, or triple therapy. An analysis comparing selexipag with an ERA and/or PDE5 inhibitor, or riociguat, should have been considered. Third, the results were based on 10 simulated patients, which is not a sufficient sample size to allow stability of the results (CDR simulated 2,500 patients per run for reanalyses). Finally, the manufacturer used predictive functions for M/M events leading health states' transitions based on the assumption that mortality was linked to FC, which resulted in an over-prediction of mortality benefit for patients receiving selexipag over the first three years of the model, which was not observed in GRIPHON, and assumed to continue for the lifetime (30-year) time horizon.

Other limitations with the base-case model included the exclusion of treatment discontinuation and heart/lung transplantation for severe patients, as well as overestimating the disutility values applied to parenteral treatment options.

Key Results and Conclusions

At the currently marketed price of $64.17 per tablet, the CDR best estimate ICUR for selexipag as an add-on to current therapy versus current therapy alone was approximately $485,000 per QALY when accounting for a greater number of simulated patients, revising baseline health status and background treatment proportions, assuming no mortality benefit over the lifetime (30 years) model's time horizon, including discontinuation and a transplantation health state, and revising parenteral treatment administration disutility values. This result suggests that selexipag is not cost-effective at conventionally accepted cost-effectiveness thresholds.

CDR notes, however, that there are substantial limitations with the manufacturer's economic model that cannot be assessed or tested and that the results reflect a mixed population of treatment experience. Also, the CDR best estimate may be an underestimate due to the potential need to titrate patients' dosing in the initial months.

Finally, there is no direct or indirect evidence available that assesses the comparative effectiveness of selexipag with riociguat, and ERAs and/or PDE5 inhibitors; thus, the comparative effectiveness of these treatments is unknown. Selexipag has a similar annual cost ($46,842) to riociguat ($46,811), a slightly higher annual cost compared with the ERAs ambrisentan ($44,720) and macitentan ($42,522), and a substantially higher annual cost compared with bosentan ($11,713), sildenafil ($12,544), and tadalafil ($7,390).

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer presented a cost-utility analysis (CUA) to determine the cost-effectiveness of selexipag as an add-on to current therapy — reported to be an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 (PDE5) inhibitor, both an ERA and PDE5 inhibitor, or no current treatment — compared with current therapy without additional selexipag, for patients with PAH from the perspective of a third-party payer in Canada.[1] Data from the pivotal GRIPHON trial were used to populate the model. The GRIPHON trial was a multi-centre, randomized, double-blind, parallel group, event-driven phase III study that compared selexipag with placebo in pulmonary arterial hypertension (PAH) patients primarily in World Health Organization (WHO) functional class (FC) II or III who were currently receiving a stable dose of an ERA, a PDE5 inhibitor, or both an ERA and PDE5 inhibitor, or were not receiving any current treatment.

The CUA was undertaken using a patient-level, micro-simulation approach that simulated disease progression and response to treatment for each patient individually over a lifetime time horizon (which was set as 30 years in the base case). The model was constructed using Microsoft Excel and used parametric functions to estimate patients' progression across FCs of disease severity and predicted the incidence of disease-attributable harmful events, including mortality. The manufacturer's base-case deterministic analysis simulated results based on a sample of 10 patients. Patients progressed though the model across a three-month cycle length, which was assumed appropriate to capture relevant events once per cycle, as well as physician visits. The manufacturer applied a half-cycle correction for mortality to adjust for the death occurring in the middle of the cycle; a half-cycle correction was not applied to other parameters in the model, as it was assumed that other outcomes and costs were accrued at the start of each cycle.

FC is the measure most commonly used to classify the health of PAH patients. The CUA observed patients in different health states based on FC and baseline therapy; the model assessed all baseline therapy uses concurrently (monotherapy, dual therapy, triple therapy) via probability values. Patients entered the model in one of eight subgroups at baseline, prior to receiving selexipag or no additional treatment (Table 2).

TABLE 2: BASELINE TREATMENT GROUPS

FC II, currently treated with an ERA	FC III, currently treated with an ERA
FC II, currently treated with a PDE5 inhibitor	FC III, currently treated with a PDE5 inhibitor
FC II, currently treated with a both an ERA and PDE5	FC III, currently treated with a both an ERA and PDE5
FC II, receiving no concurrent treatment	FC III, receiving no concurrent treatment

FC = functional class; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5.

At any time point in the model, the patient is in one of the following health states: FC II, FC III, FC IV, or dead (Figure 1). The manufacturer assumed that when patients experience a morbidity event, they would move to a higher FC (FC deterioration). Morbidity events considered from the GRIPHON study corresponded to hospitalization for PAH worsening; initiation of parenteral prostanoid or chronic oxygen therapy due to PAH worsening; and need for lung transplantation/atrial septostomy due to PAH

worsening. Patients' health could improve only in the first cycle following the initiation of a new treatment; or deteriorate (at any time) based on data from the GRIPHON trial applied with predictive functions. If patients progressed to FC IV, they were switched to an intravenous or subcutaneous prostacyclin. Heart or lung transplantation was not considered in the manufacturer's base-case model, but it was an option available in the model for FC IV patients. Patients could not improve from FC II to FC I in the model. The event rates in the model differed based on FC status, but do not appear to differ based on background treatment.

Patient characteristics at baseline were derived from a post-hoc analysis of data from the GRIPHON trial. Data on events and transition probabilities were also derived from the GRIPHON trial, except for the data related to FC IV patients, which were taken from published literature.[6-8] Adverse event (AE) data were sourced from the GRIPHON trial, and only severe AEs were included in the model. Utility values were sourced from a publication on an Australian PAH patient registry population treated with bosentan, which transformed quality-of-life data from the Short Form (36) Health Survey (SF-36) to utilities through the Short Form 6-Dimensions questionnaire (SF-6D).[9] Disutility values due to AEs and route of treatment administration were sourced from a variety of publications.[10-17] Drug costs were sourced from the Saskatchewan Drug Formulary, provided by the manufacturer, or estimated based on published literature.[4,5] Event and health-state costs were sourced from a variety of Canadian published literature.[4,5,18,19]

The manufacturer did not include discontinuations in its base-case analysis; however it did include an option in the model to apply all-cause discontinuation, based on data from the GRIPHON trial. Such discontinuation was allowed during the first cycle of treatment (three months) from treatment initiation.

2. MANUFACTURER'S BASE CASE

The results of the manufacturer's economic analysis (simulation of 10 patients) indicated that the ICUR for selexipag as an add-on to current therapy (an ERA, PDE5 inhibitor, ERA and PDE5 inhibitor, or no treatment) was $187,418 per additional quality-adjusted life-year (QALY) gained compared with current therapy alone (Table 3).

TABLE 3: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total costs	Incremental cost of selexipag	Total QALYs	Incremental QALYs of selexipag	Incremental cost per QALY
Current therapy	$261,447		3.1019		
Selexipag + current therapy	$499,818	$238,372	4.3738	1.2719	$187,418

QALY = quality-adjusted life-year.
Source: Manufacturer's Pharmacoeconomic submission.[1]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer tested the robustness of the model through deterministic one-way sensitivity analyses and a probabilistic sensitivity analysis (PSA). One-way sensitivity analyses were undertaken on all parameters using the deterministic base-case analysis (10 simulations). The PSA was carried out with 1,000 iterations. The manufacturer also undertook scenario analyses based on patient subgroups at treatment initiation.

One-way sensitivity analyses found that the model was most sensitive to varying utility values applied to FC, the discount rate applied, morbidity and mortality (M/M) hazard ratios (HRs) for selexipag, and intercept for mortality prediction. The PSA indicated the median ICUR was $263,399 per additional QALY gained.

The manufacturer's scenario analyses undertaken on the base-case deterministic results indicated that the lowest ICUR was when selexipag was used as monotherapy in patients with FC II/FC III ($87,022 per QALY), while the highest ICUR was when selexipag was used as triple therapy in patients with FC II/ FC III ($228,758).

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

The CADTH Common Drug Review (CDR) identified the following key limitations and sources of uncertainty with the manufacturer's submitted economic evaluation:

- **Substantial uncertainty regarding the applicability of the trial results to the Canadian setting:** The manufacturer's pivotal GRIPHON trial was undertaken in patients who may have been stable on background therapy; it is uncertain if this population is the one to receive selexipag in Canadian clinical practice. Additionally, the population in GRIPHON is highly heterogeneous, and there is uncertainty as to whether the treatment effect will differ based on patient's FC and background treatment at selexipag initiation.
- **No assessments of comparative effectiveness versus active comparators were provided:** The product monograph for selexipag indicates that it may be used as monotherapy, dual therapy or triple therapy. Thus, treatments such as ERAs and/or PDE5 inhibitors may be considered appropriate comparators. These treatments were included as background therapies in the GRIPHON trial, but no head-to-head analysis of comparative effectiveness has been provided, and the manufacturer did not attempt a network meta-analysis for these comparisons. Additionally, the Health Canada product monograph for riociguat includes the following text for the indication: "*for the treatment of* … [PAH (WHO Group 1)], *as monotherapy or in combination with* [ERAs] … *in adult patients (≥ 18 years of age) with WHO Functional Class II or III pulmonary hypertension,*"[20] which overlaps with the indication for selexipag. Riociguat was discussed previously by the CADTH Canadian Drug Expert Committee (CDEC) and received a recommendation of reimburse with clinical criteria and conditions.[21] Feedback from the CDR clinical expert suggested that riociguat is likely to be an appropriate comparator for selexipag, as both would be considered appropriate oral therapies, likely to be used in combination therapy (with an ERA and/or a PDE5 inhibitor). No justification for excluding riociguat was provided by the manufacturer. CDR undertook a search but could not identify any direct or indirect evidence comparing riociguat with selexipag (refer to the CDR Clinical Report); thus, the comparative effectiveness and cost-effectiveness of the drugs is uncertain, although the annual drug treatment costs appear to be similar (Table 5).
- **Substantial instability with the manufacturer base-case results:** The manufacturer's base-case results were based on the simulation of 10 patients. Such a small number of simulations for the number of variables included in the model does not allow for stability of the results. Best practice indicates that researchers running simulation models should ensure a stability within a 5% difference between output values across runs.[22] CDR undertook reanalyses of the manufacturer's base case to determine where the model's results stabilized. Based on these reanalyses, it was determined that the model stabilized at ICURs between $250,000 and $275,000 per QALY when testing between 500 and 2,500 simulations (Table 16). CDR's best estimate ran 2,500 simulations.

- **The base-case model outcomes do not reflect the trial results, the model structure lacks elements of the treatment pathway, and long-term benefits of treatment are overestimated:**
  - The model used a micro-simulation approach applying data from the GRIPHON trial for predictive functions for events and health states. The manufacturer's approach assumed a morbidity event resulted in a non-repairable deterioration in FC, and that mortality risk was linked to FC, which resulted in the model predicting a mortality benefit for patients receiving add-on treatment with selexipag over the within-trial time horizon (the initial three years of the model) and continued over the lifetime (30-year) time horizon of the model. However, CDR noted that the GRIPHON clinical trial did not demonstrate a mortality benefit for selexipag compared with placebo; this was not reflected in the model. Also, there are limited long-term data regarding the efficacy and safety of selexipag. The manufacturer's model included the opportunity to test a scenario analysis that used observed case data from the GRIPHON trial for the first three years of the model. The CDR best estimate considered the latter option but extended the lack of mortality benefit for the 30-year time horizon.
  - The manufacturer's base-case analysis did not include discontinuations from treatment or the potential for heart/lung transplantation for patients in FC IV. However, the manufacturer's model offered options for the inclusion of these features: including all-cause discontinuation from GRIPHON and a proportion of FC IV patients eligible for transplantation (20%). This was judged appropriate and included in the CDR best estimate.
- **Utility decrements for parenteral treatments appear to be overestimated:** Utility decrements for parenteral treatments (intravenous or subcutaneous prostacyclin) are based on literature for other conditions and have been judged by the CDR clinical expert to be overestimated. The CDR clinical expert indicated that patients reported lower quality of life with treatments administered subcutaneously compared with those administered intravenously due to administration-site pain. CDR best estimate used assumptions validated by the clinical expert for parenteral treatments disutility: CDR assumed a 0.10 disutility for treatments administered intravenously (base value = 0.362), and a 0.15 disutility for treatments administered subcutaneously (base value = 0.24).
- **The baseline characteristics and background treatment are not representative of Canadian clinical practice:** Feedback from the clinical expert consulted by CDR indicated that the proportion of patients in each of the FC subgroups at baseline in the model (50% FC II and 50% FC III) differed from what is expected in clinical practice (40% FC II and 60% FC III). Additional feedback suggested that the proportion of patients per current therapy at baseline differed from what is expected in Canadian clinical practice (refer to Table 4). Furthermore, the clinical expert indicated that the proportion of female patients reported by the manufacturer (80%) is higher than what is usually seen in Canadian practice (65%). Finally, the mean age of patients based on the GRIPHON trial (48 years) was judged appropriate to use across the eight baseline subgroups of the model. CDR best estimate considered these variations.

TABLE 4: REVISED PROPORTION OF PATIENTS ENTERING MODEL IN EACH BASELINE SUBGROUP

Subgroup	Manufacturer Assumptions (%)[a]	CDR Assumptions (%)[b]
FC II: ERA + PDE5i	16%	18%[c]
FC II: ERA	8%	10%[c]
FC II: PDE5i	16.5%	10%[c]
FC II: None	9.5%	2%[c]
FC II: Total	**50%**	**40%[c]**
FC III: ERA + PDE5i	16%	35%[d]
FC III: ERA	8%	12%[d]
FC III: PDE5i	16.5%	12%[d]
FC III: None	9.5%	1%[d]
FC III: Total	**50%**	**60%[d]**
Total population	**100%**	**100%**

FC = functional class; CDR = CADTH Common Drug Review; ERA = endothelin receptor antagonist; PDE5i = phosphodiesterase 5 inhibitor.

[a] Assumptions developed based on the proportions at baseline of the GRIPHON trial.

[b] Based on feedback from clinical expert.

[c] Approximately 50% of patients in FC II would be on either an ERA or PDE5i as background treatment, evenly split. 5% of patients in FC II (maybe less) would not be receiving treatment. The rest (just less than 50%) would already be on combination treatment with an ERA and PDE5i.

[d] Approximately 40% of patients in FC II would be on either an ERA or PDE5i as background treatment, evenly split. Much less than 5% of patients in FC II would not be receiving treatment. The rest (majority of patients) would already be on combination treatment with an ERA and PDE5i.

5. CADTH COMMON DRUG REVIEW REANALYSES

CDR undertook reanalyses based on the limitations as described above, which led to the CDR best estimate of $486,421 per QALY (Table 18). CDR reanalyses applying revised inputs individually based on the limitations identified are presented in Table 17. Based on the CDR best estimate, a price reduction of at least 42% is required for selexipag in addition to current therapy to be considered cost-effective when considering an ICUR of $50,000 per QALY compared with current therapy alone.

CDR emphasized that there are several limitations that could not be optimally tested, including the comparative effectiveness and cost-effectiveness of selexipag versus appropriate comparators such as ERAs and/or PDE5 inhibitors, and riociguat, and the cost-effectiveness of selexipag (as an add-on to current treatment) compared with current treatment alone in populations stratified by background treatment and FC.

6. ISSUES FOR CONSIDERATION

CDR noted that although the GRIPHON trial indicated a reduction in M/M events, during the trial there was higher mortality in the selexipag group than the placebo group; thus, the true benefit of selexipag is most likely assumed higher in the manufacturer's base-case model. These outcomes are discussed in depth in the CDR Clinical Report.

Feedback from the clinical expert consulted by CDR suggested that selexipag would not be considered as an alternative to parenteral therapy. Patients would receive selexipag if they aren't responding to their current therapies but do not yet require parenteral therapy or do require but are unable to tolerate or are contraindicated to parenteral therapy. The latter category may lead to selexipag being used off-label in FC

IV patients, as the parenteral prostacyclins are often used as last-line therapy in FC IV patients, although CDR notes that parenteral prostacyclins such as epoprostenol or treprostinil are indicated for use in FC III as well as FC IV.

Feedback from the clinical expert consulted by CDR suggested that the majority of patients are likely to receive selexipag as part of triple therapy with an ERA and a PDE5 inhibitor.

The flat pricing structure for selexipag could lead to a higher daily cost of treatment during the titration phase if patients use multiple lower-dose tablets to achieve daily dose, as dose is titrated by 200 mcg weekly to highest tolerated dose to a maximum of 1,600 mcg. Also, a substantial amount of wastage may occur in the titration phase. This would have a substantial impact on the incremental cost of treatment and ICUR.

7. PATIENT INPUT

Input was received from two patient groups: the Pulmonary Hypertension Association of Canada and the Scleroderma Society of Canada.

There are currently nine Health Canada–approved therapies available in Canada to treat PAH: six oral drugs (ambrisentan, bosentan, macitentan, sildenafil, tadalafil, and riociguat) and three intravenous infusions (epoprostenol, treprostinil, and thermostable epoprostenol). Patients reported that response to oral monotherapy is often limited, with many patients requiring two or more concurrent treatments for PAH, which is particularly the case for patients with more severe or advanced PAH, as supported by the clinical expert consulted by CDR. The majority of surveyed patients reported at least some benefit from current treatments in terms of symptoms and disease progression. However, current treatments are associated with adverse effects that affect quality of life. Quality of life was not reported in the GRIPHON trial and surrogate utility values were based on published literature, and the actual impact of selexipag on quality of life is therefore uncertain. Patients reported that expectations for selexipag are that oral treatments are preferred to non-oral treatments, and are hoping for less treatment-related AEs.

Finally, patients reported multiple barriers to accessing treatment for PAH: Access to a specialist close to home, out-of-pocket costs for treatment supplies (administration; treatment costs including co-payments; management of adverse effects), reliance on compassionate access programs, and difficulties getting approval for combination therapy.

8. CONCLUSIONS

At the currently marketed price of $64.1667 per tablet, the CDR best estimate ICUR for selexipag as an add-on to current therapy versus current therapy alone was approximately $485,000 per QALY. This may be an underestimate given the potential additional costs associated with drug titration for selexipag and the substantial uncertainty associated with the heterogeneous patient population considered — where appropriate stratified analyses have not be conducted. Based on the CDR best estimate, selexipag is not cost-effective at conventionally accepted cost-effectiveness thresholds.

No appropriate comparative clinical or cost-effectiveness evidence was provided by the manufacturer versus active comparators (ERAs and/or PDE5 inhibitors, and riociguat). The annual cost of selexipag ($46,842) is greater than ERAs ambrisentan ($44,720) and macitentan ($42,522), and substantially higher compared with bosentan ($11,713), sildenafil ($12,544), tadalafil ($7,390), and similar to riociguat ($46,811).

APPENDIX 1: COST COMPARISON

The treatment options presented in Table 5 have been deemed to be appropriate by a clinical expert for the treatment of patients with pulmonary arterial hypertension (PAH). Treatment options may be recommended (appropriate) practice, versus actual practice. Treatment options are not restricted to drugs, but may be devices or procedures. Existing Product Listing Agreements are not reflected in the table and, as such, the prices reported may not represent the actual costs to public drug plans.

TABLE 5: COST COMPARISON TABLE FOR TREATMENTS FOR PULMONARY ARTERIAL HYPERTENSION

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Selective IP Prostacyclin Receptor Agonist						
Selexipag (Uptravi)	**200 mcg 400 mcg 600 mcg 800 mcg 1,000 mcg 1,200 mcg 1,400 mcg 1,600 mcg**	**tablet**	**64.1667**[a]	**Initially 200 mcg every 12 hours, increasing in 200 mcg increments weekly to highest tolerated dose or to maximum 1,600 mcg**	**128.33**	**46,842**
Parenteral Prostanoids (Prostacyclins, Prostacyclin Analogues)						
Epoprostenol (Caripul)	0.5 mg/vial 1.5 mg/vial 50 mL diluent[b]	10 mL vial	17.1800 34.4500 6.8000	Titrated to tolerance, generally 40 to 60 ng/kg/min[c]	At final dose: 116.95 to 168.58[d]	First Year: 40,128 to 54,446[c] Thereafter: 42,570 to 61,363
Epoprostenol (Flolan)	0.5 mg/vial 1.5 mg/vial 50 mL diluent[b]	10 mL vial	18.6400 37.2700 10.6500	Titrated to tolerance, generally 40 to 60 ng/kg/min[c]	At final dose: 133.11 to 188.42[d]	First Year: 45,759 to 61,092[c] Thereafter: 48,452 to 68,585
Treprostinil (Remodulin)	1 mg/mL 2.5 mg/mL 5 mg/mL 10 mg/mL	20 mL multi-use vial[e]	45.0000 114.2500 225.0000 450.0000	Titrated to tolerance, generally 20 to 40 ng/kg/min[c]	At final dose: 113.08 to 188.08[f]	First Year: 39,983 to 64,121[c] Thereafter: 41,162 to 68,462
ERAs						
Ambrisentan (Volibris)	5 mg 10 mg	tablet	122.5200	5 to 10 mg once daily	122.52	44,720
Bosentan (generics)	62.5 mg 125 mg	tablet	16.0447[g]	62.5 mg twice daily for four weeks then 125 mg twice daily	32.09	11,713
Macitentan (Opsumit)	10 mg	tablet	116.5000[h]	10 mg once daily	116.50	42,522
PDE5i						
Sildenafil (Revatio, generics)	20 mg 25 mg	tablet	11.4557 6.4692[i]	20 mg three times daily	34.37	12,544

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Tadalafil (generic)	20 mg	tablet	10.1228[j]	40 mg once daily	20.25	7,390
Stimulators of sGC						
Riociguat (Adempas)	0.5 mg 1.0 mg 1.5 mg 2.0 mg 2.5 mg	tablet	42.7500	1 to 2.5 mg three times daily	128.25	46,811

ERA = endothelin receptor antagonist; IP = prostacyclin (PGI_2); PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase 5 inhibitor; sGC = soluble guanylate cyclase.
Note: All prices are from the Saskatchewan Drug Benefit Formulary (accessed April 2016), unless otherwise indicated. Administration fees, dispensing fees, drug delivery system costs, and markups are not included. The Saskatchewan Drug Benefit Formulary allows $46.00 per diem for supplies for infused products, which is not included in the table.
[a] Current market price as submitted by manufacturer.
[b] Two vials of diluent for epoprostenol are assumed to be used each 24-hour period, as per product monograph, and are included in the average daily and annual drug cost.
[c] Recommended dose based on feedback from clinical expert: titration is assumed to occur in hospital, starting at 2 ng/kg/min, increasing to 15 ng/kg/min after 2 weeks and continuing to be increased by 2 ng/kg/min every 4 days until maximum tolerated dose is reached.
[d] Based on a 70 kg patient, the final daily dose would range from 4.032 mg to 6.048 mg per day. Wastage assumed, although this is a conservative assumption as, in practice, physicians likely round down to avoid the substantial wastage.
[e] Stable 30 days after the initial puncture of the rubber stopper.
[f] Based on a 70 kg patient, the final daily dose would be 2.016 to 4.032 mg per day. No wastage assumed due to multi-dose vials.
[g] Tracleer brand bosentan is listed at $64.1800 per tablet and is interchangeable with the generic brands.
[h] Régie de l'assurance maladie Québec list of medications (accessed April 2016).
[i] The British Columbia Drug Benefit Formulary (accessed April 2016) reimburses 25 mg generic sildenafil for the treatment of PAH, presumably 3 times daily. Note that only the 20 mg dosage strength is indicated for PAH.
[j] Adcirca brand tadalafil is listed at $13.4970 per tablet and is interchangeable with the generic brand.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS SELEXIPAG AS AN ADD-ON TO CURRENT THERAPY COMPARED WITH CURRENT THERAPY ALONE?

Selexipag Add-On to Current Therapy vs. Current Therapy Alone	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$486,421 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.
Note: Based on the CADTH Common Drug Review reanalysis.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 7: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	The manufacturer's model lacks transparency and flexibility. Varying some model components had counter-intuitive impacts on other components, which could not be examined further by CDR based on the model's lack of transparency and reduced the model credibility.		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was information easy to locate?		X	
Comments	The manufacturer provided subsequent information on the analysis upon request.		

CDR = CADTH Common Drug Review.

TABLE 8: AUTHORS' INFORMATION

Authors of the pharmacoeconomic evaluation submitted to CDR			
☐ Adaptation of global model/Canadian model done by the manufacturer ☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

CDR = CADTH Common Drug Review.

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

Selexipag was recently reviewed for the treatment of pulmonary arterial hypertension (PAH) by the Pharmaceutical Benefits Advisory Committee (PBAC) for the Australian Pharmaceutical Benefits Scheme.[23] The PBAC did not recommend the listing of selexipag for the treatment of PAH. The PBAC considered the magnitude of clinical benefit for selexipag to be unclear and the cost-effectiveness estimate in the manufacturer's submission to be difficult to interpret. The incremental cost-effectiveness ratio presented was high, especially in the context of the outcome presented — number of morbidity/mortality events avoided — which the PBAC considered to be of uncertain clinical significance. Overall, the PBAC concluded that for every 100 patients treated with selexipag plus background therapy, compared with placebo plus background therapy, approximately 15 fewer patients would have a morbidity/mortality event in the first 64 weeks of treatment, while approximately seven patients would discontinue treatment due to an adverse event (AE) not classified as PAH progression, and approximately eight patients would discontinue treatment due to a prostacyclin-associated AE over a median exposure duration of 64 to 71 weeks.[23] The economic portion of the Australian submission differs substantially from that submitted to the CADTH Common Drug Review (CDR). Table 9 outlines the PBAC assessment of selexipag.

TABLE 9: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	PBAC (March 2016)[24]
Treatment	Selexipag (Uptravi) tablets: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg, and 1,600 mcg.
Indication	The submission requested listing for selexipag as "add-on therapy in patients (with PAH in FC III or FC IV) stabilized on background therapy with an ERA and/or a PDE5 inhibitor but who have not achieved physician-directed treatment targets," allowing a new patient to be commenced on dual therapy. The restriction does not specify that patients must have had inadequate response to stabilized ERA or PDE5 inhibitor therapy to be eligible for selexipag, nor does it define what constitutes an inadequate response. In the absence of such criteria, PBAC noted there would be considerable potential for use outside the intended patient population. The requested restriction is not consistent with the Therapeutic Goods Administration indication, which includes use as monotherapy.
Comparator	PBAC noted differences between Pharmaceutical Benefits Scheme listing criteria and current clinical practice; defining the appropriate comparator(s) was difficult. The submission nominated placebo (as add-on to current therapy) as the comparator, which PBAC accepted, considering that selexipag is likely to expand the current market for combination therapy.
Price	Price was redacted.
Similarities with CDR submission	The manufacturer submitted model was based on data from the GRIPHON trial.
Differences with CDR submission	Manufacturer submitted a trial-based cost-effectiveness analysis, in which the ICER was the incremental cost per unit reduction in the number of first M/M events per person-year. PAH is a chronic condition; long-term effectiveness and costs were not captured.
Manufacturer's results	Manufacturer's results were redacted. PBAC reported that the estimated ICER for selexipag when used as add-on therapy in patients with WHO FC III/IV PAH was approximately $105,000 to $200,000 per first M/M

	PBAC (March 2016)[24]
	event per person-year avoided, based on the proposed price.
Issues noted by the review group	Population: Results for the subgroup of PAH patients per the listing request (WHO FC III/IV patients who were receiving PAH-specific therapy at baseline) were not provided. However, PBAC felt that the WHO FC and background therapy did not appear to significantly affect the HR for the primary outcome. Efficacy claim: Submission claimed selexipag was superior to placebo in terms of comparative effectiveness and inferior in terms of comparative safety. PBAC felt the safety claim was reasonable. PBAC noted uncertainty in terms of the comparative effectiveness given the difference in population between the indication and requested listing. PBAC also had concerns with the data, including lack of data for FC IV patients, lack of subgroup data provided, no difference in the primary outcome for patients on ERA monotherapy at baseline, no evidence that selexipag ± background therapy had an effect on overall survival, and use of a composite where death has the same clinical relevance as hospitalization is not informative. PBAC considered that the clinical data were likely to be biased in favour of selexipag. Comparative effectiveness: PBAC noted the submission did not present any evidence for comparative effectiveness and safety of selexipag, when used as add-on therapy, versus other PAH agents (non-PBS subsidized) that are currently being used for this purpose in clinical practice. The health outcome used in the economic evaluation (M/M events) also did not capture subsequent M/M events in patients experiencing non-fatal first M/M events. Model uncertainty: PBAC noted that the population in the model was not representative of the population in the listing request. Also, the submission did provide a frame of reference for the acceptability of the ICER, by providing the incremental cost per incremental reduction in the rate of first M/M event; a formal cost-utility analysis would have been informative. PBAC noted that the comparator of selexipag in the cost-effectiveness assessment (macitentan) was not appropriate or informative; and that other potentially relevant active comparators (including sildenafil, iloprost and epoprostenol) were not considered.
Results of reanalyses by the review group	Not presented.
Recommendation	PBAC did not recommend listing selexipag on the PBS for PAH. PBAC considered that the magnitude of clinical benefit was unclear, and the estimate of cost-effectiveness as presented in the submission was difficult to interpret. PBAC considered the ICER presented in the submission was high, especially in the context of an outcome of unclear clinical importance (M/M events avoided).
There are differences in the listing criteria between PAH treatments, including selexipag, in Australia and Canada, which makes the interpretation and generalizability of the PBAC recommendation to the Canadian context difficult. Even with the differences in submitted models, PBAC noted several of the same issues with the clinical data that have been identified by CDR.	

CDR = CADTH Common Drug Review; ERA = endothelin receptor antagonist; FC = functional class; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; M/M = morbidity/mortality; PAH = peripheral arterial hypertension; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PDE5 = phosphodiesterase type 5; WHO = World Health Organization.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer's cost-utility analysis (CUA) assessed selexipag as an add-on to current therapy – reported to be an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 (PDE5) inhibitor, both an ERA and PDE5 inhibitor, or no current treatment in patients with pulmonary arterial hypertension (PAH) from the perspective of a third-party payer in Canada.[1] The model was developed as a patient-level micro-simulation, based on the multi-centre, randomized, double-blind, parallel group, placebo-controlled and event-driven phase III GRIPHON trial, which enrolled PAH patients in World Health Organization (WHO) functional class (FC) II or III who were being treated with a stable dose of an ERA, a PDE5 inhibitor, or both treatments in combination, or were not receiving current treatment. A lifetime (30-year) time horizon was used. The two efficacy end points from the GRIPHON trial included in the model were the composite of morbidity/mortality (M/M; the primary end point) and mortality (secondary end point). Individual patient disease progression and event risks were calculated over three-month cycles in accordance with the severity of the disease, considering morbidity and mortality disease-related events. A three-month cycle length was selected as it was aligned with physician visits, and deemed short enough that specific events related to PAH will occur at most once per cycle. A half-cycle correction was applied for mortality; that is, it was assumed that when a patient dies, the death occurs in the middle of the cycle. A half-cycle correction was not applied to other parameters in the model, as it was assumed that other outcomes and costs were accrued at the start of each cycle.

The model used the morbidity and mortality event rates observed in the GRIPHON trial to predict, using parametric functions, patients' disease progression and death. A "morbidity event" is associated with disease progression (i.e., non-fatal morbidity event), whereas a "mortality event" indicated death occurring with or without a prior morbidity event. In the model, the manufacturer assumed that when a patient has a morbidity event, this leads to deterioration in the health of the patient, which affects the disease severity FC classification, the risk of future events, and the utility values, and may lead to the addition or modification of treatment.

FC is the measure most commonly used to classify the health of PAH patients; however, this information was not always available for patients in the GRIPHON trial, due to the study design; patients were not followed after the composite primary M/M end point was reached, and information on subsequent FC status was thus not available. Given this limitation, it was assumed that a morbidity event would lead to FC deterioration in the model base case. From the GRIPHON study, the following components of the M/M events were used to reflect deterioration in FC:

- Hospitalization for PAH worsening
- Initiation of parenteral prostanoid or chronic oxygen therapy due to PAH worsening
- Need for lung transplantation/atrial septostomy due to PAH worsening.

The model compared selexipag as an add-on to current therapy — reported to be an ERA, a PDE5 inhibitor, both an ERA and PDE5 inhibitor, or no current treatment — with current therapy without additional selexipag. Riociguat was not included in the manufacturer's model. No justification was provided. The treatment combinations were stratified by FC status. Patients entered the model in one of eight subgroups at baseline (Table 10).

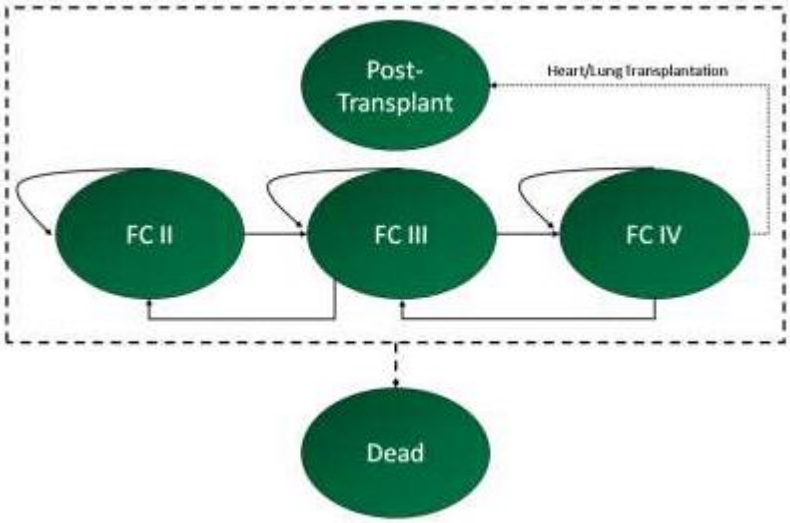
TABLE 10: BASELINE SUBGROUPS

FC II, currently treated with an ERA	FC III, currently treated with an ERA
FC II, currently treated with a PDE5 inhibitor	FC III, currently treated with a PDE5 inhibitor
FC II, currently treated with a both an ERA and PDE5 inhibitor	FC III, currently treated with a both an ERA and PDE5 inhibitor
FC II, receiving no concurrent treatment	FC III, receiving no concurrent treatment

ERA = endothelin receptor antagonist; FC = functional class; PDE5 = phosphodiesterase type 5.

At any time point in the model, a PAH patient is classified as being in one of the following health states: FC II, FC III, FC IV, or dead. FC I was reported to be a symptomless state for which there were no treatments indicated, and it was therefore not included in the model. Any FC improvement takes place only in the first cycle following the initiation of a new treatment. The manufacturer made the assumption that patients cannot improve from FC II to FC I in the model. If patients deteriorate to FC IV, they may receive parenteral prostacyclin. Heart or lung transplantation was not considered in the manufacturer's base-case analysis, but in a possible scenario analysis, the assumption was made that only patients in FC IV were assumed to be eligible to receive heart/lung transplants, and upon successful heart/lung transplantation, the patient was assumed to no longer suffer from PAH. Options allowed for user-definable hospitalization and mortality rates post-transplantation. The model structure is reported in Figure 1.

FIGURE 1: MODEL STRUCTURE: TRANSITIONS BETWEEN FC AND DEATH



FC = functional class.
Source: Manufacturer's Pharmacoeconomic Submission.[1]

Patient outcomes due to the progression of disease were simulated over a lifetime (i.e., until death); the manufacturer set this "lifetime" as a maximum of 30 years in the base case. Other time horizons were tested in sensitivity analyses.

Transition probabilities for M/M events for selexipag and the comparator arm were based on parametric survival estimates from GRIPHON; transition probabilities for the efficacy of no additional treatment were calculated from parametric models and treatment-specific hazard ratios (HRs) from GRIPHON were applied for the efficacy of additional selexipag. The manufacturer used the Akaike information criterion,

Bayesian information criterion and visual inspection to compare the fit of the distributions to the observed trial data, and decided to use an exponential distribution for both time to first M/M event and time to mortality. For validation, the model-predicted survival curve was compared with observed survival curves from two major registries.[25,26] As patients in the GRIPHON trial were censored once they moved to FC IV, data for patients in this subgroup of patients were based on published data.

The manufacturer included the option of a scenario analysis ("Trial Module") in the model, which incorporated morbidity and mortality events directly from the GRIPHON trial, which applies to the first three years in the model. This module does not rely on FC to derive a mortality risk, but uses treatment-dependent mortality risks as reported in the GRIPHON trial. Constant per cycle rates are used over the "Trial Module," after which the model uses FC as a predictor of mortality.

The model used Visual Basic for Applications macros to run the simulations, creating random number tables to determine, along with the probability derived from the trial, whether the simulated patient had the event during each cycle of the model. For the base-case results, the manufacturer relied on a simulation of 10 patients.

The data sources used and key assumptions made by the manufacturer are reported in Table 11 and Table 12, respectively.

TABLE 11: DATA SOURCES

Data Input	Description of Data Sources	Comment
Efficacy	The main efficacy variables used in the model are expressed in improvement in FC and the risk of M/M events. Data from the GRIPHON trial were used to inform the efficacy variables.	Given the model structure, it is appropriate that data for modelling were from GRIPHON, although CDR noted limitations with the model structure. Additionally, GRIPHON data were used for the development of predictive parametric functions, which led to some uncertainty compared with using observed case data from the trial. The model offers the option to use directly collected data from GRIPHON for the first 3 years of the model. Pharmacoeconomic end points including hospitalization were captured in the GRIPHON trial, but not included in the submitted economic model. Efficacy data were stratified by FC, but not by background treatment; the efficacy data for the population modelled is heterogeneous.
Patient characteristics	Post-hoc subgroup analysis of data from the GRIPHON trial	Age at treatment initiation appeared to vary substantially based on FC and treatment subgroup. Generalizability to the Canadian population is uncertain.
Discontinuation rate	Actelion data on file Publications[10,27]	Not included in base case, but the model allows for the option of considering discontinuation.
Health state utilities	Keogh et al. 2007[9]	Appears to be the most appropriate data available.

Data Input	Description of Data Sources	Comment
Disutility due to route of administration	Publications[15,17,28]	Disutilities for route of administration were based on studies in AIDS patients and iron chelation therapy for iron-deficient patients; generalizability of these data to PAH is questionable.
Disutility due to AE	Publications[10-14,16]	Disutilities for AEs were based on studies in various conditions; thus, generalizability is uncertain.
Resource use	Drug utilization based on treatment product monographs, GRIPHON trial and assumptions	Feedback from the CDR clinical expert suggested the breakdown of treatment utilization within class differs in practice from proportions used in model.
AEs[a]	Only severe AEs are included in the model. Data for selexipag, no additional treatment and background treatments were sourced from a post-hoc analysis of the GRIPHON trial. Data for the parenteral prostacyclins were sourced from US prescribing information (2014, 2015) and French prescribing information (2013).	Feedback from the CDR clinical expert suggested the assumptions based on data from the GRIPHON were appropriate. CDR was not able to validate the AE rates reported for the parenteral prostacyclins. Testing this parameter did not affect the manufacturer's results.
Mortality	Odds multiplier for M/M events for FC IV compared with FC III were based on a publication (McLaughlin et al. 2002).[8] Background mortality was based on data from Statistics Canada.[29]	The manufacturer reported two other odds multiplier values.[6,7] The manufacturer's justification that the value chosen appears representative appears to be questionable, as the values from Sitbon et al. 2002 and Benza et al. 2011 are aligned and much lower.
Costs		
Drug (selexipag)	Manufacturer	Appropriate
Oral comparators	Saskatchewan Drug Formulary	Appropriate
Parenteral prostacyclins	CADTH Therapeutic Review[4,5] WHO DDD[30] Saskatchewan Drug Formulary	Alternative costs are available. However, the model results are not sensitive to varying these values.
FC per day	CADTH Therapeutic Review[b]	Appropriate
AEs	CADTH Therapeutic Review[b] Ontario Schedule of Benefits and Physician Benefits	Appropriate
Hospitalization (for morbidity event, AEs)	CIHI PCE[b] (unreferenced)	While likely an appropriate source, the lack of granularity in the disease category for hospital costs does leave some uncertainty in the costs used.

AE = adverse event; CDR = CADTH Common Drug Review; CIHI = Canadian Institute for Health Information; DDD = daily drug dose; FC = functional class; M/M = morbidity/mortality; PCE = patient cost estimator; WHO = World Health Organization.
[a] Only severe AEs included: headache, diarrhea, nausea, jaw pain, vomiting, pain in extremity, myalgia, edema, abdominal pain, syncope, pneumonia, sepsis, cellulitis.
[b] Values were adjusted for inflation.

TABLE 12: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
GRIPHON trial's population is representative of the patient population that will receive selexipag in Canada.	Uncertain. The trial was conducted in patients who were receiving a stable dose of an ERA, a PDE5 inhibitor, or a combination of an ERA and PDE5 inhibitor, or were not receiving treatment. There is some uncertainty as to why selexipag would be added in patients who are stable on current therapy.
GRIPHON trial did not show a mortality benefit for selexipag, despite a reduction in M/M events, yet the base case assumes that during the first 3 years of the model and beyond, mortality is linked to FC status.	In the base case, M/M data from GRIPHON were used to inform parametric functions to predict patient's evolution and the incidence of morbidity and mortality. This approach was associated with uncertainty compared with using observed case data from GRIPHON directly for modelling. The manufacturer included an option in the model to use GRIPHON data for the first 3 years of the model, and then rely on predictive functions linking morbidity, FCs, and mortality. The assumption of long-term mortality benefit is also uncertain given the absence of long-term data for selexipag indicating any mortality benefit.
The parametric model distribution chosen by the manufacturer was appropriate given long-term model-fit, despite its limitations based on AIC and BIC.	There is some uncertainty as to the appropriateness of the choice of model distribution. The distribution type appears to have an impact on the manufacturer's base-case analysis.
A patient can improve by only one FC when a new treatment is initiated. Any FC improvement occurs only in the first cycle following initiation of a new treatment.	Feedback from the clinical expert consulted by CDR suggested that this was questionable, as patients can move back and forth between FCs during the course of the disease, sometimes in relation to morbidity events and treatment variations. The example given was that a patient might be in FC II, but then have an infection and move to FC IV; however, once the infection is dealt with, the patient may improve back to FC II.
A morbidity event (as classified in GRIPHON) would lead to FC deterioration.	Feedback from the clinical expert consulted by CDR suggested that this may be questionable, as the initial FC status and the severity of the morbidity event have an impact on whether the patient's FC has worsened. The patient may remain in the same health state, or move two health states.
Only patients in FC III and FC IV are able to improve their functional class; no PAH treatments are indicated for FC I patients and few patients improved to FC I during GRIPHON trial. The lack of observed improvement from FC II to FC I reflects that FC I is a symptomless state, and it is unlikely that treated-patients would become symptomless following improvement.	Questionable, but given the available trial data, may be reasonable in the context of the manufacturer's model structure.
QoL and morbidity event risks are associated with FC.	Feedback from the CDR clinical expert suggests this is reasonable.
Background treatment is unchanging and will not lead to any FC improvement or result in severe AE.	This may not be appropriate. As noted earlier, feedback from the CDR clinical expert indicated that patients can oscillate between FCs. The implication being that a patient may then improve or deteriorate at a point in time other than the first treatment cycle. CDR also noted that there is a lack of data regarding the interaction of selexipag with background therapies; the placebo results from

Assumption	Comment
	GRIPHON may provide an insight into the impact of background treatments on patient FC changes and AE rates though population heterogeneity is a problem associated with the study. Additionally, it is likely that patients on no or one background therapy who experience PAH worsening would initiate another background therapy, which might lead to FC improvements or adverse events not accounted for in the model.
Treatment discontinuation is not included in the base case, but there is the option with the model to consider all-cause discontinuation during the first cycle of treatment (3 months) with the first new therapy.	Feedback from the clinical expert consulted by CDR suggested that it was appropriate to assume that treatment discontinuation generally occurs within the first 3 months, and that discontinuation would likely be due to AE.
Patient cannot have FC improvement in the same cycle they discontinue treatment.	Feedback from the CDR clinical expert suggests this is reasonable.
Riociguat, ERAs, and PDE5 inhibitors were not considered direct comparators for selexipag.	Highly questionable. The Health Canada product monograph states that riociguat is indicated for the treatment of PAH (WHO Group 1), as monotherapy or in combination with ERAs in adult patients (≥ 18 years of age) with WHO FC II or III pulmonary hypertension. The CDR clinical review did not identify any data directly or indirectly comparing riociguat to selexipag. The product monograph for selexipag indicates its use as monotherapy or in combination therapy; therefore, selexipag may be used in place of an ERA or PDE5 inhibitor. Thus, appropriate analyses considering selexipag compared with an ERA and/or with a PDE5 inhibitor should have been undertaken.
Application of a half-cycle correction for mortality only	A half-cycle correction was applied to mortality, but not to other outcomes (e.g., QALYs) or costs. It is unclear how appropriate it is without further details of the trial data.

AIC = Akaike information criterion; BIC = Bayesian information criterion; CDR = CADTH Common Drug Review; AE = adverse event; ERA = endothelin receptor antagonist; FC = functional class; M/M = morbidity/mortality; PAH = peripheral arterial hypertension; PDE5 = phosphodiesterase type 5; QALY = quality-adjusted life-year; QoL = quality of life; WHO = World Health Organization.

Validation

Data from the GRIPHON trial were validated and supplemented with information from advisory board discussions to improve the structure, assumptions, and the inputs of the model. Literature was searched to validate mortality rate and procure data for utilities and information on costs related to the management of adverse events and health state specific costs. A group of Canadian specialists who treat PAH patients was interviewed to validate the methodology of the model to suit the Canadian clinical setting and to procure expert opinion where gaps in data exist. In addition, the model structure was reviewed and validated with global experts. As a final step, all model aspects and inputs were compared with the economic evaluation completed by CADTH as part of the PAH Therapeutic Review. Where possible, inputs from that analysis were included in this economic evaluation.

Manufacturer's Results

Over the 30-year model time horizon, patients receiving selexipag in addition to their current therapy accrued 4.38 quality-adjusted life-years (QALYs) and 7.31 life-years (LYs) compared with patients who did not receive selexipag, who accrued 3.10 QALYs and 5.72 LYs. During this period, the total cost for the

selexipag arm was $499,818 compared with $261,447 for the comparator arm. Treatment-specific costs were 85% for selexipag and 60% for the comparator arm.

The incremental cost-utility ratio (ICUR) for add-on treatment with selexipag was $187,418 per additional QALY gained (Table 13).

TABLE 13: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total Costs ($)	Incremental Cost of Selexipag ($)	Total QALYs	Incremental QALYs of Selexipag	Incremental Cost per QALY
Current therapy	261,447		3.1019		
Selexipag plus current therapy	499,818	238,372	4.3738	1.2719	$187,418

QALY = quality-adjusted life-year.

Sensitivity Analyses

The manufacturer tested the robustness of the model through both deterministic sensitivity analysis and probabilistic sensitivity analysis (PSA). One-way sensitivity analyses were undertaken on all parameters (Table 14).

TABLE 14: PARAMETERS TESTED IN MANUFACTURER'S DETERMINISTIC ONE-WAY SENSITIVITY ANALYSES

Discount rate	M/M event cost (hospitalization)
Utilities	PAH management cost (all FCs)
M/M risk in FC IV	Non-oral treatment initiation costs
Mean age	Cost of consumables
% female	AE costs
FC improvement rate	AE disutilities
RR of FC improvement for selexipag	Mortality HR selexipag
RR of FC improvement for IV epoprostenol	Mortality HR IV epoprostenol
Proportion of FC II/III requiring hospitalization	Disutility for IV
Proportion of FC IV requiring hospitalization	M/M model intercept

AE = adverse event; FC = functional class; HR = hazard ratio; IV = intravenous; M/M = morbidity/mortality; PAH = peripheral arterial hypertension; QALY = quality-adjusted life-year; RR = relative risk.

The one-way sensitivity analyses found that the morbidity/mortality (M/M) hazard ratio (HR) for selexipag, M/M model intercept value, discount rate for costs and benefits, mean age, and the base utility values had the largest impact on the ICUR. When testing these parameters, the ICUR ranged from a low of $104,000 per QALY (discount rate for LYs/QALYs set at 0%) to a high of $872,000 per QALY (M/M model intercept upper confidence interval [CI] value).

The manufacturer also undertook a multivariate PSA, running 1,000 iterations to test the robustness of the model. The median ICUR from the 1,000 iterations was $263,399 per additional QALY gained.

The manufacturer also undertook scenario analyses for some patient subgroups at treatment initiation:

- FC II only
- FC III only
- FC II/III — triple therapy only

- FC II/III — monotherapy only
- Subcutaneous prostacyclin (treprostinil) therapy when patients reach FC IV, instead of infusion therapy (epoprostenol)

The results of the manufacturer's analyses indicated that patient FC status and concurrent therapy have a substantial impact on the results (Table 15). Results for the dual therapy (with an ERA or PDE5 inhibitor) were not reported by the manufacturer.

TABLE 15: MANUFACTURER'S SCENARIO ANALYSES (SELEXIPAG ADD-ON VERSUS NO SELEXIPAG ADD-ON)

Parameter	FC II Only	FC III Only	FC II/III — Monotherapy	FC II/III – Triple Therapy	Subcutaneous Once FC IV, Instead of Intravenous Infusion
ICUR (per QALY)	$114,467	$181,189	$87,022	$228,758	$150,992

FC = functional class; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years; SC = subcutaneous.

CADTH Common Drug Review Reanalyses

The CADTH Common Drug Review (CDR) identified several limitations and parameters that were associated with uncertainty from the manufacturer's economic model. These have been discussed earlier. Additional limitations and reanalyses have been noted below.

CDR initially undertook an exercise to test the stability of the model. A brief summary of some of these tests are presented in Table 16. The model appeared to stabilize to an appropriate level once 2,500 simulated patients were used; thus, the CDR reanalyses were undertaken based on this cohort.

TABLE 16: CADTH COMMON DRUG REVIEW EXERCISE TO DETERMINE MODEL STABILITY

Parameter (Results Reported as Selexipag vs. Comparator)	Incremental Cost	Incremental QALY	ICUR (per QALY)
Manufacturer's base case (10 simulated patients, seed of 9)	**$238,372**	**1.2719**	**$187,418**
Model stability tests:			
• Simulated patients = 10, Seed = 2	$174,189	1.1062	$157,460
• Simulated patients = 10, Seed = 5	$111,234	1.0986	$101,249
• Simulated patients = 10, Seed = 8	$165,313	0.7174	$230,425
• Simulated patients = 500, Seed = 20	$223,044	0.8084	$275,907
• Simulated patients = 500, Seed = 250	$208,920	0.8102	$257,870
• Simulated patients = 1,000, Seed = 50	$222,327	0.8577	$259,213
• Simulated patients = 1,000, Seed = 200	$219,908	0.8758	$251,106
• Simulated patients = 1,000, Seed = 850	$224,190	0.9194	$243,853
• Simulated patients = 2,500, Seed = 9	$224,754	0.8861	$253,655
• Simulated patients = 2,500, Seed = 100	$223,908	0.8849	$253,042
• Simulated patients = 2,500, Seed = 400	$225,490	0.9069	$248,649
• Simulated patients = 2,500, Seed = 1,500	$221,452	0.8794	$251,830

ICUR = incremental cost-utility analysis; QALY = quality-adjusted life-year; vs. = versus.

One-Way Scenario Analyses

The results of the one-way scenario analyses that CDR undertook on the manufacturer's base-case analysis (revised using the aforementioned 2,500 simulated patients) are reported in Table 17.

TABLE 17: CADTH COMMON DRUG REVIEW SINGLE-PARAMETER REANALYSES OF THE MANUFACTURER'S BASE-CASE ANALYSIS

Parameter (Results Reported as Selexipag vs. Comparator)	Incremental Cost	Incremental QALY	ICUR (per QALY)
Manufacturer's Base Case	**$223,908**	**0.8849**	**$253,042**
Baseline Characteristics:			
• Patient status at model entry per clinical expert feedback	$242,608	0.9226	$262,962
• Mean age of patients 48 years old for all subgroups	$225,156	0.8966	$251,131
• Proportion of female patients = 65%	$222,024	0.8716	$254,729
Model Structure and Inputs:			
• Trial-based mortality data (no benefit) assumed for the model lifetime time horizon (30 years)	$189,519	0.4318	$438,892
• Including a discontinuation rate[a]	$207,886	0.8348	$249,012
• Including the potential for transplantation of patients	$224,275	0.8807	$254,658
Uncertainty Associated With Utility Decrements:			
• Revised disutility values for administration	$223,908	0.8048	$278,211

ICUR = incremental cost-utility analysis; QALY = quality-adjusted life-year; RR = relative risk.
[a] RR of discontinuation for other drugs applied based on discontinuation rate for placebo from GRIPHON. RR for selexipag compared with placebo changed based on data reported in Table 10-2 of the GRIPHON Clinical Study Report.

CADTH Common Drug Review Best Estimate Analysis

CDR combined the following analyses to form the CDR best estimate:

- CDR undertook the reanalysis using 2,500 simulations, with a seed of 100.
- Revised assumptions regarding background characteristics for patients (including revised proportions of patients in FC II and FC III, background treatments patients were receiving, and female patients, as well as having the age set across all patient backgrounds).
- No mortality benefit over the model lifetime time horizon (30 years).
- Assumptions regarding discontinuation and transplantation were included.
- Revised disutility values associated with route of administration.

The results of these reanalyses are reported in Table 18.

TABLE 18: CADTH COMMON DRUG REVIEW BEST ESTIMATE

Parameter (Results Reported as Selexipag vs. Comparator)	Incremental Cost	Incremental QALY	ICUR (per QALY)
CDR best estimate	$113,778	0.2339	$486,421

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility analysis; QALY = quality-adjusted life-year; vs. = versus.

REFERENCES

1. Pharmacoeconomic evaluation. In: CDR submission: Uptravi (selexipag), 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg film-coated tablets; oral. Actelion Pharmaceuticals Canada, Inc. [**CONFIDENTIAL** manufacturer's submission]. Laval (QC): Actelion Pharmaceuticals Canada, Inc.; 2016 Mar.
2. [Pr] Uptravi (selexipag): 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg film-coated tablets; oral [product monograph]. Laval (QC): Actelion Pharmaceuticals Canada, Inc.; 2016 Jan 19.
3. CDR submission: Uptravi (selexipag), 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg film-coated tablets; oral. Actelion Pharmaceuticals Canada, Inc. [**CONFIDENTIAL** manufacturer's submission]. Laval (QC): Actelion Pharmaceuticals Canada, Inc.; 2016 Mar 30.
4. Drugs for pulmonary arterial hypertension: comparative efficacy, safety, and cost-effectiveness [Internet]. Ottawa: CADTH; 2015. [cited 2016 Jun 1]. (CADTH therapeutic review report). Available from: https://www.cadth.ca/media/pdf/TR0006_PAH_ScienceReport.pdf
5. Drugs for pulmonary arterial hypertension: comparative efficacy, safety, and cost-effectiveness - recommendations report [Internet]. Ottawa: CADTH; 2015. [cited 2016 Jun 1]. (CADTH therapeutic review report). Available from: https://www.cadth.ca/sites/default/files/pdf/TR0006_PAH_Recs_Report.pdf
6. Benza RL, Gomberg-Maitland M, Naeije R, Arneson CP, Lang IM. Prognostic factors associated with increased survival in patients with pulmonary arterial hypertension treated with subcutaneous treprostinil in randomized, placebo-controlled trials. J Heart Lung Transplant. 2011 Sep;30(9):982-9.
7. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol. 2002 Aug 21;40(4):780-8.
8. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation. 2002 Sep 17;106(12):1477-82.
9. Keogh AM, McNeil KD, Wlodarczyk J, Gabbay E, Williams TJ. Quality of life in pulmonary arterial hypertension: improvement and maintenance with bosentan. J Heart Lung Transplant. 2007 Feb;26(2):181-7.
10. Smith KJ, Wateska A, Nowalk MP, Raymund M, Lee BY, Zimmerman RK, et al. Cost-effectiveness of procalcitonin-guided antibiotic use in community acquired pneumonia. J Gen Intern Med [Internet]. 2013 Sep;28(9):1157-64. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3744292
11. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes [Internet]. 2008;6:84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2579282
12. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer. 2008 Dec;62(3):374-80.
13. Hutton J, Brown R, Borowitz M, Abrams K, Rothman M, Shakespeare A. A new decision model for cost-utility comparisons of chemotherapy in recurrent metastatic breast cancer. Pharmacoeconomics. 1996;9 Suppl 2:8-22.
14. Lipsky BA, Moran GJ, Napolitano LM, Vo L, Nicholson S, Kim M. A prospective, multicenter, observational study of complicated skin and soft tissue infections in hospitalized patients: clinical

characteristics, medical treatment, and outcomes. BMC Infect Dis [Internet]. 2012;12:227. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3524462

15. Osborne RH, De Abreu Lourenco R, Dalton A, Houltram J, Dowton D, Joshua DE, et al. Quality of life related to oral versus subcutaneous iron chelation: a time trade-off study. Value Health. 2007 Nov;10(6):451-6.
16. Rose MS, Koshman ML, Spreng S, Sheldon R. The relationship between health-related quality of life and frequency of spells in patients with syncope. J Clin Epidemiol. 2000 Dec;53(12):1209-16.
17. Johnson ES, Sullivan SD, Mozaffari E, Langley PC, Bodsworth NJ. A utility assessment of oral and intravenous ganciclovir for the maintenance treatment of AIDS-related cytomegalovirus retinitis. Pharmacoeconomics. 1996 Dec;10(6):623-9.
18. Schedule of benefits for physician services under the Health Insurance Act [Internet]. Toronto: Ministry of Health and Long-Term Care; 2016. [cited 2016 Jun 14]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html
19. Patient cost estimator [Internet]. Ottawa: Canadian Institute for Health Information; 2016. [cited 2016 Jun 14]. Available from: https://www.cihi.ca/en/spending-and-health-workforce/spending/patient-cost-estimator
20. [Pr]Adempas® (riociguat): film-coated tablet 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg [product monograph]. Toronto (ON): Bayer Inc.; 2014 Mar 4.
21. Riociguat (Adempas). CADTH Canadian Drug Expert Review Committee final recommendation [Internet]. Ottawa: CADTH; 2015 Dec 17. [cited 2016 Jul 13]. (Common drug review). Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0438_complete_Adempas-Dec-21-15_e.pdf
22. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Moller J, et al. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--4. Value Health. 2012 Sep;15(6):821-7.
23. 1st time decisions not to recommend [Internet]. Canberra (Australia): Pharmacueutical Benefits Scheme (PBS); 2016 Mar. [cited 2016 Jun 27]. (PBAC outcomes). Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2016-03/first-time-decisions-not-to-recommend-2016-03.docx
24. Selexipag, tablet 200, 400, 600, 800, 1000, 1200, 1400 and 1600 micrograms. Public summary document [Internet]. Canberra (Australia): Pharmaceutical Benefits Scheme (PBS); 2016 Mar. [cited 2016 Jul 25]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/selexipag-psd-march-2016.pdf
25. Ling Y, Johnson MK, Kiely DG, Condliffe R, Elliot CA, Gibbs JS, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med [Internet]. 2012 Oct 15 [cited 2016 Jun 14];186(8):790-6. Available from: http://www.atsjournals.org/doi/pdf/10.1164/rccm.201203-0383OC
26. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest. 2012 Aug;142(2):448-56.
27. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002 Mar 15;165(6):800-4.

28. Higgins A, Barnett J, Meads C, Singh J, Longworth L. Does convenience matter in health care delivery? A systematic review of convenience-based aspects of process utility. Value Health. 2014 Dec;17(8):877-87.

29. Statistics Canada [Internet]. Ottawa: Government of Canada. 2016 [cited 2016 Jun 14]. Available from: http://www.statcan.gc.ca/start-debut-eng.html

30. ATC/DDD index 2016 [Internet]. Geneva: World Health Organization; 2016. [cited 2016 Jun 1]. Available from: http://www.whocc.no/atc_ddd_index/