CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

SELEXIPAG
(Uptravi — Actelion Pharmaceuticals Canada Inc.)
Indication: Pulmonary Arterial Hypertension

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that selexipag be reimbursed for long-term treatment of idiopathic pulmonary arterial hypertension (PAH), heritable HPAH, 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 to III to delay disease progression, if the following clinical criterion and conditions are met:

Clinical criterion:
- Inadequate control with a first- and second-line PAH therapy.

Conditions:
- Prescribed by a clinician with experience in the diagnosis and treatment of PAH
- Reduced price.

Reasons for the Recommendation:
1. One randomized controlled trial (RCT) (GRIPHON [N = 1,156]) demonstrated that selexipag is statistically and likely clinically significantly superior to placebo in delaying time to first morbidity or mortality event in patients with PAH on a heterogeneous background of PAH therapies or no PAH therapy.
2. Selexipag was compared only with placebo in the GRIPHON study. Therefore, the comparative clinical benefits and risks of selexipag with alternative drug treatment options for PAH are unknown.
3. At the marketed price of $64.1667 per tablet, the CADTH Common Drug Review (CDR) best estimate incremental cost-utility ratio (ICUR) for selexipag as an add-on to current therapy versus current therapy alone was approximately $485,000 per quality-adjusted life-year (QALY) for adult patients with WHO FC II to III PAH. Therefore, selexipag is not considered to be cost-effective at the submitted price.

Of Note:
1. CDEC noted that there may be variation in the way first-line PAH therapies are defined and reimbursed across the CDR-participating drug plans. The CADTH Therapeutic Review on

drugs for the management of PAH recommended that sildenafil and tadalafil be the preferred initial drug treatment for patients with FC II or III PAH.
2. CDEC noted that 80% of patients were receiving stable doses of one or two concomitant medications for PAH at baseline.
3. CDEC noted that although the GRIPHON study met its primary outcome, the total clinical benefit of selexipag is uncertain because limited or no evidence of improvement was observed for selexipag compared with placebo for patient-important outcomes such as overall deaths, PAH-related deaths, overall hospitalizations, WHO FC changes, health-related quality of life, symptoms of PAH, breathlessness, or dyspnea.
4. CDEC noted numerous important limitations with the manufacturer's pharmacoeconomic submission. The CDR revised analysis indicated that a price reduction of at least 42% is required for the use of selexipag in addition to current therapy, compared with current therapy alone, to be considered cost-effective when considering an ICUR of $50,000 per QALY.

Background:
Selexipag has a Health Canada indication for long-term treatment of idiopathic PAH, heritable PAH, PAH associated with connective tissue disorders, and PAH associated with congenital heart disease, in adult patients with WHO functional class (FC) II to III to delay disease progression. Selexipag is an oral, selective, prostacyclin pathway (prostacyclin [PGI_2] receptor) agonist. It is available as an oral tablet and the Health Canada–approved starting dose is 200 mcg given twice daily, with a maximum dose of 1,600 mcg twice daily.

Summary of CDEC Considerations:
The Committee considered the following information prepared by CDR: A systematic review of RCTs of selexipag, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information
Two patient groups, the Pulmonary Hypertension Association of Canada and the Scleroderma Society of Canada, jointly responded to the CDR call for patient input. Information was obtained through interviews and surveys of patients and caregivers, and through experience working in the PAH community. CDEC heard the following:

- Physical symptoms of PAH — such as difficulty breathing, fatigue, peripheral edema, fainting, and chest pain — can be substantial and often unpredictable. Low tolerance for physical exertion can impede activities of daily living and caring for children.
- Emotional and psychological symptoms are common and include depression, anxiety, and feelings of helplessness and hopelessness.
- Caregivers play an important role in supporting those living with PAH, as these patients may lose their ability to care for themselves and their children, and may be unable to work.
- Monotherapy with currently available treatments was often ineffective, especially for those with more advanced moderate to severe pulmonary hypertension (PH), and, as a result, patients were using combinations of more than one drug class. Patients noted that a significant number fail to achieve an adequate response to current therapies, and that an unmet need for more effective therapies exists.
- Patients reported difficulties in accessing PAH therapies due to lack of access to a PH specialist close to home; cost of supplies necessary to administer treatment; cost of treatments to manage adverse events; reliance on manufacturer's compassionate access

program; difficulties gaining approval for therapy; and unaffordable co-payments due to the high cost of treatments.
- Patients and caregivers stated that oral therapy with selexipag offers advantages over injectable treatments, and also indicated a willingness to tolerate serious adverse events (especially scleroderma patients) if selexipag slows disease progression or improves quality of life.

Clinical Trials

The systematic review included one randomized, double-blind, placebo-controlled, event-driven, group sequential trial in patients with symptomatic PAH (GRIPHON). No active comparator trials were identified for inclusion. A total of 1,156 patients, mainly classified as WHO FC II (46%) or III (53%), were randomized to selexipag or placebo (1:1) and titrated to the highest tolerated dose (range: 200 mcg to 1,600 mcg orally twice daily). Groups received study treatment as monotherapy or as add-on to stable single or double background PAH drugs (phosphodiesterase type 5 [PDE5] inhibitors and/or endothelin receptor antagonists [ERAs]).

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:
- Survival
- Hospitalization
- Clinical worsening (composite outcome referred to as “morbidity/mortality” in GRIPHON)
- Change in WHO FC
- Quality of life
- Six-minute walk distance (6MWD)
- Change in PH symptoms
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary outcome in GRIPHON was time to first Critical Event Committee (CEC)–confirmed morbidity or mortality event up to seven days after the last study drug intake. Secondary outcomes were subject to a hierarchical statistical testing procedure.

Efficacy

- The occurrence of death was higher in the selexipag group compared with placebo in certain analyses in GRIPHON. The analysis that counted all deaths up to study closure found approximately the same number of deaths in each treatment group (selexipag: 100 [17.4%]; and placebo: 105 [18.0%]) and no statistically significant difference between groups (hazard ratio [HR], 0.97 [99% confidence interval (CI), 0.68 to 1.39]). Based on this observation, selexipag did not appear to have an effect on mortality compared with placebo in the trial.
- The annualized number of hospitalizations per year for all causes was [redacted] for the selexipag group and [redacted] for the placebo group. There were no statistically significant differences in overall hospitalization rates or number of days spent in hospital after these rates were adjusted for cumulative time on study at the group level.
- Overall, 140 selexipag patients (24.4%) and 212 patients (36.4) had a clinical worsening (morbidity or mortality event; primary composite outcome). The results of the primary outcome were driven by hospitalization for PAH and disease progression. The HR for the primary outcome in the selexipag group was 0.61 (99% CI, 0.46 to 0.81), relative to placebo. This corresponds to a relative risk reduction of 39% and absolute risk reduction of 12%.

- Absence of worsening from baseline in WHO FC at week 26 was reported for 444 of 571 (77.8%) patients in the selexipag group and 430 of 574 (74.9%) patients in the placebo group (odds ratio, 1.16; 99% CI, 0.81 to 1.66). There was no statistically significant difference in absence of WHO FC worsening and, therefore, the hierarchical testing procedure was halted at this stage.
- The 6MWD was the first secondary end point in the hierarchy to be tested. There were statistically significant improvements in the 6MWD favouring selexipag compared with placebo (median difference of change 12 m), but this change is lower than the estimated minimal clinically important change of 33 m.
- The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) questionnaire was used in a subset of GRIPHON patients to assess PAH symptom changes, functioning, and quality of life. Only changes on the Symptoms and Breathlessness scales were analyzed in the trial. There were no statistically significant differences between selexipag and placebo in the CAMPHOR subscales.
- There were no statistically significant differences between selexipag and placebo in dyspnea score, as measured by the Borg dyspnea index.

Harms (Safety and Tolerability)

- Overall, [redacted] in the selexipag group and [redacted] in the placebo group discontinued their study regimen prematurely because of an adverse event. The most frequent adverse events leading to discontinuation in the selexipag group (events for which there was > 1% difference between the selexipag and placebo groups) were headache (3%), diarrhea (2%), and nausea (2%). Hyperthyroidism occurred in eight patients in the selexipag group and led to treatment discontinuation in one patient.
- Overall serious adverse event rates were similar between the selexipag (44%) and placebo (47%) groups. No serious adverse events were reported more frequently (i.e., at a rate > 1% higher) in the selexipag group than in the placebo group.
- The most frequent adverse events associated with prostacyclin use that were reported during the dose-adjustment and maintenance phases included headache, diarrhea, nausea, pain in jaw, myalgia, pain in extremity, vomiting, and flushing. Adverse events associated with prostacyclin occurred more frequently during the dose-adjustment phase.
- Patient input indicated that patients commonly report experiencing adverse events with other drug treatments for PAH, such as headaches, digestive problems, sleeping difficulties, nausea and/or stomach pain, stuffy nose, flushing, fainting, and dizziness. Patients stated that they are willing to accept adverse events associated with an oral prostacyclin therapy for PAH if there are advantages compared with parenteral administration. No data were available to compare adverse event rates of selexipag with parenteral prostacyclin therapies or with other oral drugs for PAH.

Cost and Cost-Effectiveness

At the currently marketed price of $64.1667 per tablet for all the available doses, the annual cost of selexipag is $46,842.

The manufacturer's submitted a cost-utility analysis from the perspective of a Canadian public payer, to determine the cost-effectiveness of selexipag when added on to current therapy (an ERA, a PDE5 inhibitor, both an ERA and a PDE5, or no treatment) compared with current therapy alone, in patients with PAH over a lifetime time horizon (of 30 years; mean patient age at model entry was between 42 and 54 years). Using a microsimulation modelling approach, the model simulated the progression of individual patients using data from the GRIPHON trial. Patients entered the model in one of eight subgroups at baseline, based on WHO FC (II or III),

and background treatment regimen. Transitions between WHO FC health states were driven by morbidity or mortality events captured in the GRIPHON trial. The manufacturer's base-case analysis was based on the simulation of 10 patients, where the ICUR was $187,418 per additional QALY for selexipag in addition to current therapy versus current therapy alone.

CDR identified four key limitations with the manufacturer's pharmacoeconomic submission:

- There was substantial uncertainty as to the generalizability of the data used for modelling from the GRIPHON trial to the use of selexipag in current Canadian clinical practice.
- Analyses comparing selexipag directly with an ERA and/or PDE5 inhibitors, or riociguat, should have been considered.
- The model results were based on the simulation of 10 patients, which is not a sufficient sample size to allow stability of the results. CDR noted that the model results were stable at 2,500 patients simulated.
- The modelling approach resulted in a mortality benefit for selexipag, which was not demonstrated in the GRIPHON trial.

The CDR base case incorporated revised patient baseline and background treatment characteristics and trial-based mortality results indicating no mortality benefit for selexipag; applied a discontinuation rate; included the option for patients to undergo heart or lung transplantation; and revised disutility values associated with treatment administration. Simulating 2,500 patients, the CDR base case resulted in an ICUR of $485,000 per QALY for selexipag in addition to current therapy versus current therapy alone. 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 was not able to appropriately assess patient subgroups by varying WHO FC and background therapy, due to the lack of data for these subgroups, and could not undertake analyses comparing selexipag directly with an ERA and/or a PDE5 inhibitor, and riociguat, due to a lack of clinical data.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

September 21, 2016 Meeting:

Regrets:
Three CDEC members were absent.

Conflicts of Interest:
None

About this Document:
CDEC provides formulary reimbursement recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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