CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Pitolisant hydrochloride (Wakix)

Indication: The treatment of excessive daytime sleepiness or cataplexy in adult patients with narcolepsy

Sponsor: Paladin Labs Inc.

Recommendation: Do Not Reimburse

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Single Technology

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that pitolisant hydrochloride not be reimbursed for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy.

Rationale for the Recommendation

Evidence was identified from three 7 to 8-week double-blind, randomized, controlled trials in adults with narcolepsy with or without cataplexy comparing pitolisant hydrochloride to modafinil and placebo (HARMONY I, HARMONY Ibis) or placebo only (HARMONY CTP). Because of the availability of other safe and effective drugs such as psychostimulants and anticataplectics, CDEC did not identify an unmet need whereby patients would have no therapeutic option. Hence, comparison of the drug to standard of care was considered most relevant. Pitolisant hydrochloride did not meet criteria for non-inferiority to modafinil in the HARMONY I and HARMONY Ibis trials in terms of EDS, and there was no comparison to available drugs in HARMONY CTP, which focused on outcomes reflecting symptoms of cataplexy. No other direct or indirect evidence was identified. As a result, the comparative efficacy of pitolisant hydrochloride for the treatment of EDS or cataplexy remains unknown and the drug may not offer additional benefits over standard treatments.

Patients expressed a need for medications that are more reliable and effective in controlling narcolepsy symptoms, are better tolerated, easier to take and need to be taken less frequently. CDEC concluded that there was insufficient evidence to demonstrate that these needs were met by pitolisant hydrochloride relative to standard treatment.

Discussion Points

- Clinical experts indicated that patients who experience both EDS and cataplexy would benefit from a single agent that is able to provide a effective and safe option for both symptom domains. However, no single trial reached statistically significant conclusions for EDS and cataplexy outcomes in the same population. It is therefore not possible to determine with certainty that patients with both EDS and cataplexy can derive a full range of symptomatic relief from monotherapy with pitolisant hydrochloride.
- CDEC noted the lack of other direct and indirect comparative evidence available for this review given that other treatments for narcolepsy are currently available. Therefore, CDEC was unable to determine whether pitolisant hydrochloride provided any additional clinical benefit over other currently reimbursed treatment options.
- CDEC noted the challenge in accurately diagnosing narcolepsy, which was notably undefined in the inclusion criteria of the HARMONY trials. A similar challenge is present in clearly defining response to treatment in clinical practice.
- CDEC noted the small sample sizes and short trial durations reduced the certainty in results. For a condition that is chronic and not rare, CDEC discussed the need for longer, larger trials that compare the new drug to standard medications.

Background

Narcolepsy is a chronic neurologic condition that is caused by an imbalanced sleep wake cycle or sleep wake instability. It is characterized by chronic, excessive attacks of drowsiness during the day, also known as excessive daytime sleepiness (EDS). Type 1 narcolepsy is classified as EDS with cataplexy, while Type 2 consists of EDS alone. Cataplexy is defined as a sudden episode of partial or complete paralysis of voluntary muscles, triggered by strong emotion. Approximately 60% to 70% of patients with narcolepsy have cataplexy (Type 1 disease). There is no standard diagnostic criteria for narcolepsy. Approximately 1 in 2,000 individuals in Canada are affected by narcolepsy. This prevalence is considered underestimated due to misdiagnosis and limited availability of healthcare providers with experience in narcolepsy.

Narcolepsy can affect all aspect of life in work and social settings, and affect patient's day-to-day functioning and their health- related quality of life and productivity Patients can experience EDS during common situations during the day such as work or driving, often while the patient is sedentary. Narcolepsy is also associated with an increased risk for comorbid conditions, including depression, anxiety, obesity, cardiovascular disease and an increased overall mortality risk. In Canada, the current treatment standard for excessive daytime sleepiness in narcolepsy is modafinil, thought to improve wakefulness by reducing dopamine reuptake.

Pitolisant hydrochloride is an inverse agonist/antagonist of the histamine 3 (H_3) receptor. The human H_3 receptor functions as a presynaptic autoreceptor on histamine-containing neurons. H3 antagonists promote wakefulness by increasing histamine synthesis and release. By binding competitively to H3 autoreceptors on presynaptic histaminergic neurons, pitolisant hydrochloride blocks the normal negative feedback mechanisms for histamine release, increasing histaminergic transmission and resulting in enhanced histamine synthesis and release. Pitolisant hydrochloride is administered orally up to 40 mg daily with 5 mg and 20 mg tablets. It is indicated for the treatment of excessive daytime sleepiness or cataplexy in adult patients with narcolepsy. It received NOC on May 25, 2021 after undergoing standard review. The reimbursement request is per indication.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of the 3 of RCTs in patients with narcolepsy with or without cataplexy
- Patients perspectives gathered by 1 patient group, Wake Up Narcolepsy, Inc.
- Input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with narcolepsy
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

One patient group, Wake Up Narcolepsy, Inc. (WUN), submitted patient input for this review. WUN is a patient advocacy non-profit organization established in 2008 that aims to accelerate research and increase awareness of narcolepsy as well as provide supportive services to patients. The input was based on a survey of 19 patients in Canada who have a narcolepsy diagnosis or are undiagnosed but living with narcolepsy symptoms. Most patients were between 18 to 34 years of age (66%), female (72%), and none had experience with the treatment under review.

Respondents reported excessive daytime sleepiness (EDS) to be the most troubling symptom of narcolepsy with 39% of respondents giving it a rating of 6 on a scale of 1 ("not at all bothersome") to 7 ("completely bothersome"). The second most troublesome symptom was disturbed nocturnal sleep (DNS), followed by hallucinations when falling asleep or waking up, cataplexy, and sleep paralysis. Negative impacts of narcolepsy on respondents' lives include experiencing mental health and emotional symptoms (mood swings, anger, depression, and anxiety), missing out on social activities, difficulty managing career and job tasks, depending on others for support for daily activities, and difficulty maintaining physical health and wellness (weight gain). Current treatments that respondents noted using for their narcolepsy include stimulants (56%), antidepressants (33%), sodium oxybate (13%), and modafinil/armodafinil (13%). Some respondents reported that the physical side effects (28%) and mental side effects (39%) of their current treatment options were moderately or extremely challenging.

Respondents would like a new drug or treatment to be more effective in treating symptoms of sleepiness, cataplexy, and DNS. Respondents indicated a desire to have a treatment that is easy to swallow, does not cause nausea, weight gain, or affect their mood/personality. Respondents also want a treatment with an extended release which allows them to stay awake longer in the day without having to take additional doses.

Clinician input

Input from clinical experts consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of narcolepsy.

Diagnosis is extremely challenging, due to a number of factors. Patients often first come to family doctors, or pediatricians who are generally not well trained at recognizing this condition. Patients frequently are misdiagnosed and over 70% of patients with narcolepsy are undiagnosed. While existing medications treat the underlying symptoms of narcolepsy including primarily daytime sleepiness or cataplexy, it is believed that none of the above-mentioned treatment options address the fundamental underlying neurochemical abnormality of loss of hypocretin cells and secondary absence/reduction of available CNS hypocretin associated with narcolepsy.

Several problems persist with existing treatment options. For SSRI/SNRI/TCAs, not all patients respond to treatment and/or become tolerant to treatment. Tolerance to REM suppressing effects of SSRI/SNRI/TCA medications frequently occurs, leading to persistent cataplexy. Side effects can be problematic including stomach upset, night sweats, sexual side effects, headaches, and others. Some can be excessive sedating in the day, which can be a problem despite anti cataplectic effects. For stimulants, daytime sleepiness may not be fully resolved and/or drugs may or may not wear off and inopportune times leading to excess daytime sleepiness in the evenings and/or insomnia difficulties at night. Side effects can be problematic including appetite suppression, anxiety, increased blood pressure, cardiac effects, allergic reaction, reduced seizure threshold, fetal defects, inactivation of birth control, or hair loss. There can be abuse/sequestration potential; usually patients with narcolepsy themselves have low abuse potential even though they may require high doses, but there could be temptation to sequester for others.

The consistent use of ongoing anticataplectic treatments while also using pitolisant hydrochloride may mask and/or minimize potential benefits pitolisant might have for cataplexy. On the other hand, if pitolisant hydrochloride has minimal benefits for cataplexy, then this would also be difficult to assess. In short, it will be difficult to properly assess potential benefits of pitolisant hydrochloride against cataplexy with use of ongoing anticataplectic treatments.

Based on its efficacy in early studies, its novel mechanism of action as a histamine three (H3) antagonist/inverse agonist, and relatively favorable side effect profile, it is likely to be placed as an early treatment option. It has a strong recommendation statement from the American Academy of Sleep Medicine (AASM) in their most recent (2021) guidelines for the treatment of hypersomnolence disorders.[12] It will be an early agent to consider for treatment of narcolepsy. It may also find a niche as an adjunct treatment to be combined with other agents to boost their efficacy. It may also become an agent of choice for patients in whom stimulant and/or other therapies are contraindicated, such as no effect on birth control efficacy (unlike modafinil), no significant known cardiovascular effects (like other stimulants). Patients most in need of intervention include: patients who cannot tolerate stimulant therapies, patients who are concerned about getting pregnant, and patients with a history of drug abuse. Jurisdictions should continue to provide coverage to prior therapies that are currently considered SOC in combination with pitolisant hydrochloride, because the mechanism of action of pitolisant hydrochloride is quite different than any current available agent, which represents an exciting prospect for patients suffering from this debilitating condition.

According to the clinical experts consulted on this report, treatment goals are primarily to improve quality of life. While narcolepsy is not lethal, symptoms of excessive daytime sleepiness and cataplexy can be debilitating if left uncontrolled. In severe circumstances, sleep attacks can occur while eating, or even talking to someone. Uncontrolled, these symptoms limit abilities to do basic daily activities such as driving, working, interacting with people. Cataplexy (which occurs in 60-70% of patients with narcolepsy) is equally if not more debilitating when left uncontrolled. Patients cannot drive or walk outside safely since surprises could trigger a cataplectic attack. Basic daily activities such as showering/bathing, dressing, eating can be dangerous and/or challenging when untreated. Without treatment, most patients have very limited if any work options, and may not be able to attend school. These symptoms can lead to isolation, anxiety and depression. Treatment is aimed at reducing excessive daytime sleepiness and cataplexy potential, so that patients are not dependent on caregivers for support and can interact and be functional members of society. Treatment can significantly improve alertness and daytime abilities to be functional members of society. Diagnosis is often delayed, often occurring 10 years or longer after symptom onset, potentially leading to significant suffering, but if appropriate treatment is initiated, tolerated and maintained, up to 80% of functional capacity could be retained.

The primary outcomes(s) in clinical practice will likely be the degree to which excessive daytime sleepiness is reduced, as well as the frequency, intensity and duration, and predictability of cataplexy episodes. Clinically meaningful responses to treatment include the reduction in frequency, severity, intensity of cataplexy episodes. While frequency is easier to assess systematically, the intensity and severity of spells, as well as perceived predictability control of episodes is more of a clinical assessment. For example, patients describing certain emotions no longer trigger episodes like they had experienced before. Other parameters that may be used probably would include reduction of other REM intrusion phenomena if present, and the degree to which patients can resume normal function and return to daily activities.

Outcomes typically assessed in most clinical trials include degree of reduction of excessive daytime sleepiness and possibly reduction in frequency of cataplexy spells. The use of ESS scores in clinical practice for coverage of pitolisant may not be ideal. ESS is very subjective and could easily manipulate their scores. There can be significant differences also between men and women and how they score their results, further skewing potential for coverage. In research trials it's ideal if patients are blinded to what they are being offered, and there is no incentive for better/worse scores. A score of 10 or lower on the ESS would be ideal with no different sleepiness compared to the normal population. As a comparison, patients with narcolepsy typically score >18/24 on the ESS (severe sleepiness), 15-17 is considered moderate sleepiness, and 11-14 is mild sleepiness.

There is very little data on defining "what is effective reduction of cataplexy". Trials on sodium oxybate demonstrated >90% reduction in cataplexy episodes. For driving, driving is not recommended if there has been cataplexy in the last year. A minimum of a 50% reduction in cataplexy episodes would be meaningful. Depending on severity and frequency, less than once per week would be a reasonable standard.

At this time, patients who wish to get pregnant or breastfeeding patients may not be suitable. There should be more caution/concern for children or the elderly to use this due to lack of data. Patients who are on multiple medications (more potential for drug interactions, particularly those affecting QTc interval, or drugs that are significant 2D6 inhibitors), patients who have a history of significant kidney/liver failure also may not be ideal (difficult to predict metabolism). Patients who have had adverse reactions to opioids that include hives might be predisposed to some allergic reaction to pitolisant hydrochloride, or a history of some kind of urticarial/skin condition. Ongoing treatment will be determined either by lack of response and/or excess adverse side effects, like most medications. Whether it will continue to be used as an adjunct if abandoned as a single agent is unclear. Excess adverse side effects or drug interaction may necessitate withdrawal. Similarly, if a patient wishes to become pregnant, this may also necessitate withdrawal.

As with other agents for narcolepsy, there should be close follow up in the first month and subsequent months of therapy. The first follow up 1 month after starting the agent, then every 1-2 months for the next several months, and then intermittent follow up after that, with probably at a minimum at least yearly follow up long term. Medical supervision in an outpatient sleep medicine setting with physician trained in sleep medicine would be appropriate for treatment with pitolisant hydrochloride for narcolepsy. In the future, psychiatrists will become interested in using this medication for conditions/symptoms outside of narcolepsy. At this time, since the indication for pitolisant hydrochloride is only for narcolepsy, with a conditional recommendation for idiopathic hypersomnia, prescribing should probably be limited to those with specialty

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for pitolisant hydrochloride:

- Considerations for initiation of therapy
- Considerations for continuation or renewal of therapy
- Considerations for discontinuation of therapy
- Considerations for prescribing of therapy

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

Three double-blind (DB), phase III, placebo-controlled RCTs met the inclusion criteria for the systematic review[13-15] [13,14]. In all 3 trials, patients were included if they had narcolepsy with cataplexy. HARMONY I and HARMONY I bis also included patients without cataplexy (narcolepsy Type 2). HARMONY I and HARMONY I bis required patients to have an Epworth Sleepiness Scale score ≥ 14/24 during the baseline period, whereas HARMONY CTP required an ESS score of ≥ 12/24. HARMONY CTP included patients with at least 3 weekly cataplexy attacks. In all trials, patients with severe cataplexy were permitted stable doses of anticataplectic medications, except tricyclic antidepressants, that were administrated for at least 1 month prior to the trial.

HARMONY I and HARMONY I bis were 8-week trials that assessed superiority of pitolisant hydrochloride compared to placebo with regard to EDS in narcoleptic patients. An additional efficacy objective was a non-inferiority comparison of pitolisant hydrochloride with modafinil. Harmony-CTP was a 7-week randomized, double-blind placebo-controlled study comparing pitolisant hydrochloride to placebo. It focused on the safety and efficacy of pitolisant hydrochloride in decreasing frequency of cataplexy attacks in patients who had narcolepsy with cataplexy. The maximum dosages for pitolisant hydrochloride were 20 mg daily for HARMONY I bis, while HARMONY I and HARMONY CTP had a maximum daily dosage of 40 mg. Titration of study drug was at the discretion of the study investigators, which could affect efficacy and potentially threatened blinding to treatment arms. Patients on anticataplectic medications represented 35% of all patients in HARMONY I, [redacted] of all patients in HARMONY I bis, and 10% of all patients in HARMONY CTP.

Efficacy Results

Excessive Daytime Sleepiness

In HARMONY I, the adjusted mean difference in the final ESS score for pitolisant hydrochloride compared with placebo was -3.10 (95% CI: -5.73 to-0.46), p = 0.022. Sensitivity analyses on the PP population and without accounting for the centre effect showed similar results. Since the superiority of pitolisant hydrochloride over placebo for EDS was demonstrated at the a priori α = 0.025, the non-inferiority of pitolisant hydrochloride to modafinil was tested. The adjusted mean difference in the final ESS score between pitolisant hydrochloride and modafinil was 0.09 (95%: CI -(2.31 to 2.30); thus, pitolisant hydrochloride was judged to not be non-inferior to modafinil at the pre-specified non-inferiority margin of 2. A patient was considered a responder when final ESS was <10. Based on this consideration, the responder rates were 13.3% in the placebo group, 45.2% in the pitolisant hydrochloride group and 45.3% in the modafinil group. The adjusted OR of response for pitolisant hydrochloride compared with placebo was 7.86 (95% CI: 1.59 to 38.86). The adjusted OR of response for pitolisant hydrochloride compared with modafinil was 1.09 (95% CI: 0.31 to 3.81).

In HARMONY I bis, the mean ESS score reductions from baseline (SD) were [redacted] in the placebo group, [redacted] in the pitolisant hydrochloride group and [redacted] in the modafinil group. The adjusted mean difference in the final ESS score for pitolisant hydrochloride compared with placebo was -2.19 (95% CI: -4.17 to -0.22), p=0.030). Sensitivity analyses without reallocation by centre, and without adjustment for baseline ESS, or by adjusting for baseline following the mean change, and the mean change over baseline methods showed similar results. Since the superiority of pitolisant hydrochloride over placebo for EDS was demonstrated at the a priori α = 0.05, the non-inferiority of pitolisant hydrochloride to modafinil was tested. The adjusted mean difference in the final ESS score between pitolisant hydrochloride compared with modafinil was 2.75 (95% CI: 1.02 to 4.48); thus, pitolisant hydrochloride was judged to not be non-inferior to modafinil at the pre-specified non-inferiority margin of 2. A patient was considered a responder when the final ESS was ≤10 or the change from baseline was ≥3. The response proportions were [redacted], [redacted] and [redacted] for placebo, pitolisant hydrochloride, and modafinil groups, respectively. The adjusted RR for the difference between pitolisant hydrochloride and placebo [redacted]. The adjusted RR for the difference between pitolisant hydrochloride and placebo was [redacted].

In HARMONY CTP, the observed mean changes in ESS over baseline were -1.9 (SD: 4.3) and -5.4 (SD: 4.3) in the placebo and pitolisant arms, respectively. The adjusted mean difference in the change from baseline for pitolisant hydrochloride compared with placebo was -3.42 (95% CI: -4.96 to -1.87). Sensitivity analyses using the LOCF, BOCF, and the PP population were consistent with the main analysis. A patient was considered a responder when the final ESS was ≤10 or the change from baseline was ≥3. The response proportions were 34.0% and 68.6% for placebo, pitolisant hydrochloride, respectively. The adjusted OR for the difference between pitolisant hydrochloride and placebo 4.26 (95% CI: 1.72 to 10.52).

Maintenance of Wakefulness Test

In HARMONY I, the adjusted mean difference in final score between placebo and pitolisant hydrochloride was 1.47 (95% CI:1.01 to 2.14) and the adjusted mean difference in final score between pitolisant hydrochloride and modafinil was 0.77 (95% CI: 0.52 to 1.13). This was consistent with the findings of HARMONY I bis, where the adjusted mean difference between placebo and pitolisant hydrochloride was 1.46 (95% CI: 1.06, 2.01). The adjusted mean difference in final score between pitolisant hydrochloride and modafinil was [redacted]. In HARMONY CTP, the geometric mean of ratios (final/baseline) was 1.78 (95% CI: 1.22 to 2.60). Sensitivity analyses for all trials using the PP population were consistent with the main analysis.

Sustained Attention to Response Task

In HARMONY I, the adjusted mean difference between the pitolisant hydrochloride and placebo treatment arms was 0.82 (95% CI: 0.67 to 0.99) for NOGO, 0.80 (95% CI: 0.57 to 1.13) for GO, and 0.79 (95% CI: 0.64 to 0.99) for TOTAL scores. The adjusted mean difference between the pitolisant hydrochloride and modafinil treatment arms was 1.03 (95% CI: 0.83 to 1.28) for NOGO, 1.03 (95% CI: 0.56 to 1.15) for GO, and 0.90 (95% CI: 0.70 to 1.14) for TOTAL scores. Sensitivity analyses using the PP population was consistent with the main analysis. In HARMONY I bis, the ratio of mean change between pitolisant hydrochloride and placebo was significant: 0.83; 95% CI [0.69, 0.99], whereas the difference between pitolisant hydrochloride and modafinil was [redacted]

Clinical Global Impression of Severity and of Change on EDS

In HARMONY I and HARMONY I bis, a higher proportion of patients in the pitolisant hydrochloride and modafinil groups improved CGI-C for EDS compared to placebo. However, the change in CGI-C scores was similar for pitolisant hydrochloride and modafinil arms. In HARMONY I, the subgroup of patients with a history of cataplexy improved the CGI-C scores for EDS, but a greater proportion reported an improvement in the modafinil arm. In HARMONY CTP, the mean reduction of the CGI-score of pitolisant hydrochloride compared with placebo was -0.95 (95%CI [-1.36, -0.54]). Mean CGI-C score was 3.5 (1.1) with placebo versus 2.6 (1.1) with pitolisant hydrochloride. Similar results were observed for the PP population, with a mean reduction of -0.86 (95%CI [-1.29; -0.43]).

Frequency and severity of cataplexy attacks

In HARMONY I, the final mean of complete and partial cataplexy episodes (episodes per day) was 0.68 (1.66), 0.28 (1.11), 0.65 (1.62) in the placebo, pitolisant hydrochloride, and modafinil groups, respectively. In the exposed population, the relative risk of daily rates of complete and partial cataplexy episodes at end of treatment for pitolisant hydrochloride compared to placebo was 0.38 (95% CI: 0.15 to 0.93). The relative risk of daily rates of complete and partial cataplexy episodes at end of treatment for pitolisant hydrochloride compared to modafinil was 0.54 (95% CI:0.24 to 1.23). In HARMONY I bis, the mean least square of daily cataplexy rate for those with cataplexy between the final 7 days of treatment and baseline was [redacted] for pitolisant hydrochloride compared to placebo.

The primary endpoint of HARMONY CTP was the measure of anti-cataplectic efficacy. The geometric means of the weekly rate of cataplexy at the end of treatment decreased respectively to 4.51 (95% CI: 2.90 to 7.02) in placebo and 2.27 (95% CI: 1.51 to 3.41) in pitolisant hydrochloride during the stable dose period. The ratio of geometric means during the stable dose period was 0.51 (95% CI: 0.43 to 0.60), $p < 0.0001$ for pitolisant hydrochloride compared to placebo. Similar results were observed for the PP population, with a ratio of 0.50 (95% CI: 0.34 to 0.74), $p < 0.0001$ for pitolisant hydrochloride compared to placebo. The effect of pitolisant hydrochloride on weekly cataplexy rate remained consistent at 20 mg and 40 mg doses. The proportion of patients with a high frequency of weekly cataplexy episodes (>15) during the stable-dose period was 5.6% of patients in the pitolisant hydrochloride group and 17.6% in the placebo group (OR 0.035 [95% CI: 0.0035 to 0.352]). The effect remained consistent regardless of whether patients were taking permitted anticataplectic medications during the trial.

Clinical Global Impression of Severity and of Change on Cataplexy

In HARMONY I, the mean final CGI-C score was 3.4 (1.4), 2.9 (1.5), 3.0 (1.6) in the placebo, pitolisant hydrochloride, and modafinil arms, respectively. The number of patients who improved compared to baseline was 6 (24.0%) placebo, 9 (34.6%) pitolisant hydrochloride, and 8 (28.6) modafinil. The number of patients who reported no change compared to baseline was 15 (57.7) placebo, 15 (57.7) pitolisant hydrochloride, and 16 (57.1) modafinil. There were 2 (8.0) patients reporting worsened CGI-C scores in placebo and 1 (3.6) in the modafinil arm.

In HARMONY I bis, the number of patients who improved compared to baseline was [redacted] placebo, [redacted] pitolisant hydrochloride, and [redacted] modafinil. The number of patients who reported no change compared to baseline was [redacted] placebo, [redacted] pitolisant hydrochloride, and [redacted] modafinil. There were [redacted] patients reporting worsened CGI-C scores in placebo, [redacted] in pitolisant hydrochloride, and [redacted] in the modafinil arm.

In HARMONY CTP, the mean reduction of the CGI-score of pitolisant hydrochloride compared with placebo was -0.95 (95%CI [-1.36, -0.54]). Mean CGI-C score was 3.5 (1.1) with placebo versus 2.6 (1.1) with pitolisant hydrochloride. Similar results were observed for the PP population, with a mean reduction of -0.86 (95%CI [-1.29; -0.43]).

Harms

In HARMONY I, AEs after initiation of treatment were reported by 66.7% of patients in the placebo group, 64.5% in the pitolisant hydrochloride group and 69.7% of patients in the modafinil arm. In HARMONY I bis, approximately [redacted] of the patients in the pitolisant hydrochloride and modafinil groups reported adverse events, while [redacted] of placebo patients reported adverse events. In HARMONY

CTP, approximately 35% of patients experienced an adverse event. For HARMONY I [redacted], there was a greater percentage of nervous system disorders in the pitolisant hydrochloride arm, but placebo had greater nervous system disorders in HARMONY CTP.

In HARMONY I, in the pitolisant hydrochloride arm, pyelonephritis and hemorrhoids were reported as serious adverse events. [redacted] HARMONY CTP reported 1 serious adverse event in the pitolisant hydrochloride arm only.

In HARMONY I, one patient in the pitolisant hydrochloride arm discontinued due to pregnancy. An additional patient in the pitolisant hydrochloride arm temporarily discontinued the study, but the study code was not broken and treatment was resumed so the study resumed. [redacted]. In HARMONY CTP, one patient receiving pitolisant hydrochloride discontinued due to severe nausea as a treatment emergent adverse event. No deaths were reported in any of the trials.

Critical Appraisal

All included trials were double-blinded, placebo-controlled studies with a short duration (7- or 8-week treatment phase). All trials had a small sample size between 96 to 164 patients, which can limit the power to detect significant changes in the efficacy outcomes. The allocation sequence was random and balanced for all trials, and remained concealed for the duration of the trial. HARMONY I and [redacted] had between-group study differences for previous medication usage and proportion with cataplexy, which could suggest differences in disease severity. In HARMONY I bis [redacted] of patients had a history of cataplexy in the pitolisant hydrochloride group compared to [redacted] in the placebo group. In HARMONY I, patients with at least one chronic medication within 3 months before inclusion ranged from 70% (modafinil) to 85.2% (placebo and pitolisant hydrochloride). The maximum dosages for pitolisant hydrochloride were 20 mg daily for HARMONY I bis, while HARMONY I and HARMONY CTP had a maximum daily dosage of 40 mg. Titration of study drug was at the discretion of the study investigators, which could affect efficacy and potentially threatened blinding to treatment arms.

All studies authorized patients to remain on stable doses of anticataplectic medications. Patients on anticataplectic medications represented 35% of all patients in HARMONY I, [redacted] of all patients in HARMONY I bis, and 10% of all patients in HARMONY CTP. There were between-group study differences in HARMONY I and HARMONY CTP for proportion of patients on anticataplectic medications during the trial. In HARMONY I, 33.3% of placebo patients compared to 40.7% pitolisant hydrochloride patients and 56.7% modafinil patients remained on authorized medications during the study. In HARMONY CTP, 16% of those in the placebo group remained on anticataplectic medication, compared with 7% in the pitolisant group. Inconsistency in concomitant anticataplectic medications between trials cannot be clearly explained. The interactions between pitolisant hydrochloride and the concomitant treatments are unknown. Although the trials were double-blinded, some patients who received modafinil previously may have recognized the study drug.

The primary efficacy outcome for HARMONY I and HARMONY I bis, change in excessive daytime sleepiness, was measured using the validated Epworth Sleepiness Scale. ESS is a subjective, self-administered questionnaire, but it is widely used in narcolepsy trials. The primary outcome for HARMONY CTP was weekly rate of cataplexy captured by patient diaries. All primary outcomes were assessed using unvalidated tools. Other secondary endpoints assessed EDS were not validated, such as the CGI-C and patient global opinion tools. The MWT and SART outcomes were validated, however, the statistical analyses did not adjust for multiplicity. Patient diaries were completed daily and reviewed by the investigators for completion, which may have biased future outcome assessments. The primary outcome of HARMONY-CTP was the change in weekly cataplexy rate, which was recorded using daily patient diaries. The placebo group also reported a reduction in cataplexy episodes. This could be caused by the use of concomitant treatments or placebo effect.

Missing values for all trials were imputed for ESS and cataplexy outcomes. Any missing values at the end of treatment were imputed using LOCF or BOCF. It is unclear whether these would be reflective of the true trajectory of the outcomes. Sensitivity analyses using the PP population were provided, which can minimize potential bias. In addition, for all outcomes other than the primary outcome in all trials, there was no adjustment for multiplicity which increases the risk of type 1 error and limits the ability to draw conclusions. Subgroups were outlined a priori. Conclusions could not be drawn for the subgroups due to the lack of adjustment for multiplicity and were therefore considered exploratory analyses.

The NIM was calculated based on historical trials of ESS, which were not specified, that set the MID as 3. To remain less than the MID and the proportion of difference between placebo and pitolisant hydrochloride, the NMI of 2 was chosen. In addition, sample size calculations assumed that the effects of pitolisant hydrochloride and modafinil were similar.

All trials noted protocol amendments. A major amendment in HARMONY I included the change from assessing the superiority of pitolisant compared with modafinil to a non-inferiority analysis. The change in type of analysis would not bias the results since the non-inferiority analysis was reported appropriately for both ITT and PP populations.

According to the clinical experts consulted for this review, the baseline characteristics of study patients are reflective of Canadian patients with narcolepsy seeking further treatment options. The drug titration would be reflective of clinical practice. The primary outcome measures utilized in the trials are used by physicians in clinical practice and measured outcomes important to patients (EDS and cataplexy). Patients were allowed to combine conventional narcolepsy medication with the drug under study. The clinical experts noted that it is common for combination therapy to be used in clinical practice; however, the interactions between concomitant medications and pitolisant hydrochloride are unknown. On that note, tricyclic antidepressants were not allowed as concurrent medications, despite them being common anticataplectic drugs according to the clinical experts. This may decrease the generalizability of the trial population. Adherence to treatment remained high at >80% in all trials.

Other Relevant Evidence

The open-label extension study Harmony III[16,17] provides long-term safety and efficacy data that supplements the evidence from the RCTs in the systematic review.

Description of studies

HARMONY III is a long-term, open-label, uncontrolled extension study conducted to evaluate the efficacy and safety of pitolisant at 5, 10, 20 or 40 mg/d for the treatment of EDS in narcoleptic patients with or without cataplexy for up to 5 years of treatment. Of the 102 patients enrolled HARMONY III, 86 were naïve patients who were not receiving pitolisant at the time of study inclusion enrolment and 16 were patients from the French Compassionate Use Program (CUP) who were already being treated with pitolisant within the 2 weeks preceding the study. Naïve patients were comprised of 73 patients who had never been treated with pitolisant as well as 13 patients who were previously treated with pitolisant during single- or double-blind trials including HARMONY I[13], HARMONY II[18], or HARMONY Ibis[14].

At study inclusion, CUP patients could continue at their established pitolisant dose (20 or 40 mg/d) without up-titration. Naïve patients began pitolisant treatment with a 1-month individual up-titration scheme starting at 5 mg/d and increasing up to 40 mg/d. Patients recruited from France who had at least 1 dose of pitolisant and completed the initial 1 year-period of HARMONY III, were eligible to continue treatment in a follow-up extension up to 5 years.

A total of 102 patients with narcolepsy from France (n = 77) and Hungary (n = 25) (8 centres) were enrolled into the extension study, HARMONY III, with the first patient enrolled in June 2011. After the initial 12-month treatment period, 48 patients from France continued with the 5-year extension follow-up. Patients were required to have had an ESS score of ≥ 12 to enroll into the extension study. The overall mean (SD) age for all participants was 38.0 (14.9) years and slightly more than half were female (55.9%). About 75% of each of naïve and CUP patients reported a history of cataplexy. Patients in the extension study could take concomitant medications for narcolepsy including anticataplectics and/or psychostimulants. At inclusion, 35.3% of all patients were taking concomitant medications and more CUP patients (56.3%) were taking concomitant medications than naïve patients (31.4%). Overall, the baseline characteristics of patients enrolled in HARMONY III were generally consistent with the baseline characteristics of the patients randomized in the pivotal trials. Characteristics of the French patients who continued into the 5-year extension period were similar compared with those of the total study population.

Efficacy Results

Sleepiness/Alertness/Severity of Daytime Sleepiness

In the Harmony III extension study, at year 1, the mean (SD) change from baseline for the ESS score was -3.99 (4.56). Fifty-seven (58.2%) of patients were considered responders, defined as an ESS score ≤ 10 or change from baseline ≥ 3. Among naïve patients,

the mean (SD) change from baseline was -4.30 (4.47). Forty-nine (59.8%) patients were considered responders. For CUP patients, who were already receiving pitolisant treatment at inclusion and had a lower mean ESS score at baseline, the mean (SD) change from baseline for the ESS score was -2.38 (4.79). Eight (50.0%) patients were considered responders.

Regarding patients taking concomitant narcolepsy treatments, the mean (SD) change from baseline was -3.15 (4.01); -3.64 (4.55); -4.00 (2.35) for patients taking psychostimulants (n = 26), anticataplectics (n = 14), and both psychostimulants and anticataplectics (n = 13), respectively. For patients taking pitolisant only (i.e., no concomitant treatments) (n = 45) the mean (SD) change from baseline was -4.67 (5.27). Thirteen (50.0%), 8 (57.1%), and 10 (76.9%) of patients taking psychostimulants, anticataplectics, and psychostimulants and anticataplectics were considered responders, respectively. Twenty-six (57.8%) patients taking pitolisant only (i.e., no concomitant treatments) were considered responders.

The changes from baseline in ESS scores remained similar during the long-term follow up among the French cohort. Among French patients who continued the long-term follow-up, the ESS mean (SD) change from baseline was -4.41 (5.38) at year 2 (n = 45), -4.45 (6.16) at year 3 (n = 38), -4.76 (5.73) at year 4 (n = 34), and -6.07 (7.19) at year 5 (n = 14), respectively. At 5 years, the mean (SD) change from baseline was -8.17 (8.93) and -4.50 (5.71) for naïve (n = 6) and CUP patients (n = 8), respectively. Of the 14 patients remaining at 5 years, 10 (71.4%) were considered responders, including 5 (83.3%) naïve patients and 5 (62.5%) CUP patients.

Regarding patients taking concomitant narcolepsy treatments, the mean (SD) change from baseline in ESS after 5 years was -5.67 (6.11), -6.33 (7.77), and -5.50 (3.87) for patients taking psychostimulants (n = 3), anticataplectics (n = 3), and both psychostimulants and anticataplectics (n = 4), respectively. For patients taking pitolisant only (i.e., no concomitant treatments, (n = 4) the mean (SD) change from baseline was -6.75 (11.95). All patients remaining at 5 years, regardless of concomitant treatment, were considered responders.

A total of 71.7% of the 67 patients who completed the initial 1-year treatment period reported a CGI-C score of 1 (very much improved) or 2 (much improved), 22.4% reported a score of 3 (minimally improved), and 6% reported a score of 4 (no change). Three-quarters (73.1%) of naïve patients and 66.7% of CUP patients were at least much improved, while 21.2% and 26.7% respectively were minimally improved and 5.8% and 6.7% respectively reported no change. Among French patients who continued the long-term follow-up, the proportion of patients who reported a “much improved” or “very much improved” CGI-C score compared to baseline was 77.3% at 2 years (n = 44), 84.2% at 3 years (n = 38), 73.5% at 4 years (n = 34), and 64.3% at 5 years (n = 14) of treatment, respectively. At 5 years 83.4% naïve patients (n = 5) and 50.0% of CUP patients (n = 4) were at least much improved; 16.7% of naïve patients (n = 1) and 37.5% of CUP patients (n = 3) were minimally improved; 12.5% of CUP patients (n = 1) reported no change.

A total of 75.0% of patients (75.0% naïve and 75.1% CUP) evaluated the effect of pitolisant as “moderate” to “marked” on the PGO test after 1-year of treatment. Among French patients who continued the long-term follow-up, the proportion of patients who reported a “moderate” to “marked” effect of pitolisant on the PGO test was 72.8% at 2 years (n = 44), 84.2% at 3 years (n = 38), 84.4% at 4 years (n = 32), and 64.3% at 5 years (n = 14) of treatment, respectively. At 5 years 83.4% naïve and 50.0% CUP patients evaluated the effect of pitolisant as “moderate” to “marked”.

Frequency and Severity of Cataplexy Attacks

At the end of the initial 1-year study period, among patients who completed the sleep diary (n = 44), the mean (SD) of change in total cataplexy from baseline was a -0.25 (1.37) among all patients, -0.25 (1.38) among naïve patients, and 0.00 (NA) among CUP patients. The mean (SD) change in partial cataplexy from baseline was -0.49 (1.94) among all patients, -0.49 (1.96) among naïve patients, and 0.53 (NA) among CUP patients.

HRQoL

The mean (SD) of the EQ-5D VAS for all patients was 65.5 (16.1) at baseline and 72.4 (16.2) at 1-year, with a mean (SD) change of 6.8 (15.4) from baseline. For naïve patients the mean (SD) of the EQ-5D VAS was 64.3 (15.9) at baseline and 73.5 (17.5) at 1-year; with a mean (SD) change of 9.2 (15.4) from baseline. For CUP patients the EQ-5D VAS was 69.6 (16.7) at baseline and 68.8 (11.4) at 1-year; with a mean (SD) change of -0.8 (12.7) from baseline.

Among French patients who continued the long-term follow-up, the mean (SD) of the EQ-5D VAS was 70.5 (15.9) at 2 years (n = 44), 69.5 (13.2) at 3 years (n = 38), 72.2 (13.3) at 4 years (n = 33), and 75.0 (12.2) at 5 years (n =14) of treatment, respectively. At 5 years, the EQ-5D VAS was 80.5 (12.5) among naïve patients and 70.9 (10.9) for CUP patients, with a change of 13.8 (15.5) and 2.4 (12.5) from baseline, for each, respectively.

Sleep Attacks

At the end of the initial 1-year study period, among patients who completed the sleep diary (n = 44), the mean (SD) change in the daily number of sleep attacks from baseline was -0.37 (1.41) for all patients, -0.39 (1.42) for naive patients, and 0.47 (NA) for CUP patients. The mean (SD) change in the duration of diurnal involuntary sleep attacks (mins) from baseline was -0.37 (1.41) for all patients, -0.39 (1.42) for naive patients, and 0.47 (NA) for CUP patients.

Nocturnal Sleep Properties

Among patients who completed the sleep diary (n = 44), the mean (SD) change in daily number of nocturnal awakenings from baseline to the 1-year visit was -0.42 (1.18) for all patients, -0.42 (1.19) for naive patients, and -0.14 (NA) for CUP patients. The mean (SD) change in the duration of nocturnal awakening (hours) from baseline to the 1-year visit was -0.09 (0.73) for all patients, -0.10 (0.73) for naive patients, and 0.18 (NA) for CUP patients. The mean (SD) change in the duration of nocturnal sleep (hours) from baseline to the 1-year visit was -0.10 (1.19) for all patients, -0.09 (1.21) for naive patients, and -0.37 (NA) for CUP patients.

Number of Hallucinations

At the end of the initial 1-year study period, among patients who completed the sleep diary (n = 44), the mean (SD) change in the frequency of hallucinations from baseline was -0.06 (0.25) for all patients, -0.06 (0.20) for naive patients, and 0.0 (NA) for CUP patients.

Concomitant Medication Use

The proportion of patients taking a concomitant treatment for narcolepsy or cataplexy changed from 35.3% at baseline to 52.9% over the course of the 1-year after inclusion. A total of 31.4% of naïve and 56.3% of CUP patients were taking concomitant treatment at baseline and over the course of the 1-year after inclusion, 51.2% of naïve and 62.5% of CUP patients were taking concomitant medications. The most frequent treatments over the course of the study were methylphenidate (22.5%), modafinil (17.6%), and venlafaxine (13.7%). Eleven patients (10.8%) took sodium oxybate. In the French subset, the proportion of patients taking allowed concomitant treatment for narcolepsy or cataplexy in addition to pitolisant changed from 44.2% at baseline to 70.1% over the 5-year period. A total of 70.5% of naïve and 68.8% of CUP patients were taking concomitant treatments over the 5-year period, respectively. The most frequent treatments were methylphenidate (31.2%), modafinil (29.9%), venlafaxine (19.5%), and sodium oxybate (16.9 %).

Harms Results

All combinations of concomitant medications for narcolepsy or cataplexy were well tolerated, except for a greater frequency of insomnia in the subgroup of patients taking concomitant modafinil (55%, n = 5) in the follow-up extension study among the French subset of patients.

During the initial 1-year period treatment period, 58 patients (56.9%) reported 168 TEAEs, the most common being headache (11.8% of patients), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depression (4.9%) and nausea (4.9%). In the French subset of patients, over the 5-year period, 72.7% of patients reported 296 TEAEs, the most common being headache (19.5%), weight increase (18.2%), nausea (11.7%), anxiety (11.7%), insomnia (11.7%), and depression (11.7%).

A total of 16 patients reported SAEs in the 5-year period among the French subset of patients, with the most common being depression (3.9%) and pregnancy (3.9%). All SAEs were considered unrelated to the study drug, except for 1 spontaneous abortion in a patient who discontinued the study drug and permanently withdrew from the trial. One death was reported in follow-up extension study after the initial 1-year study period. The clinical study report indicated that the death was determined to be not related to the study medication.

Among all patients, the mean (SD) BDI-SF-13 score was 4.1 (3.5) at baseline and 3.8 (4.1) at the 1-year visit. The mean (SD) BDI-SF-13 score among the French subset of patients at the year-5 visit was 2.4 (2.8) (n = 12). At each time point, no more than 1 patient had a severe depression.

Critical Appraisal

The long-term extension study allowed for the investigation of long-term efficacy and harms of pitolisant for up to 5 years. Limitations of the extension study include the absence of an active comparator which limits causal conclusions. An additional limitation is the open-label study design and unblinding of the study drug in the extension phase can bias the reporting of endpoints. There was no sample size calculation or statistical testing for changes from baseline making it difficult to detect a clinically relevant treatment effect. All the endpoints in HARMONY III were subjective, therefore it is possible that efficacy outcomes and known harms could have been overestimated. Findings are at a high risk of confounding due to use of concomitant treatments and a lack of control for confounding variables. None of the p-values were adjusted for multiplicity and should be considered hypothesis-generating.

Subgroup analyses were descriptive and often limited to few patients reducing the chance of detecting a true effect. Interpretation of these patient-reported outcomes are also limited by the large amount of missing data due to attrition. Over one-third of patients discontinued the extension study within the first year, mainly due to adverse events or a lack of perceived efficacy. This attrition could have resulted in a population of patients that were more tolerant of pitolisant, as those not responding to treatment may be less likely to continue participation in the extension study. Having patients more tolerant of pitolisant can also lead to biased estimates of efficacy and adverse events, potentially resulting in greater efficacy and fewer adverse events being reported. The use of concomitant psychostimulant and/or anticataplectic drugs among patients throughout the extension study may have increased the risk of observing additional side effects not attributable to pitolisant alone. Furthermore, for the 1-year timepoint, for the primary efficacy outcome of ESS, LOCF was used for those without final values, which may bias the efficacy results as these values may not be reflective of the true trajectory of this outcomes.

External Validity With respect to external validity, although no Canadian patients were enrolled in the extension study, the characteristics of the patients enrolled in the trials were representative of narcoleptic patients in Canada, according to the clinical experts consulted. Doses of pitolisant administered were in line with what would be expected in clinical practice.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree during the trial period followed by a Markov model
Target population	Adult patients with narcolepsy, assessed within two subgroups: • EDS without cataplexy • EDS with cataplexy
Treatment	Pitolisant hydrochloride
Submitted price	Pitolisant hydrochloride:5 mg, $16.63 per tablet; 20 mg, $16.63 per tablet
Treatment cost	Annual cost of pitolisant ranges from $6,074 to $12,147.
Comparators	EDS without cataplexy: • standard of care (SOC; consisting of a weighted basket comparator including modafinil, methylphenidate HCl, d-amphetamine sulfate, and lisdexamfetamine dimesylate) • no treatment EDS with cataplexy: • cataplexy SOC (consisting of a weighted basket comparator including off-label anti-cataplectic agents (imipramine, desipramine, clomipramine, fluoxetine, and venlafaxine) combined with modafinil, methylphenidate HCl, d-amphetamine sulfate, and lisdexamfetamine dimesylate individually) • no treatment
Perspective	Canadian publicly funded health care payer

Component	Description
Outcomes	QALYs and LYs
Time horizon	Lifetime (70 years)
Key data source	Clinical efficacy was modelled using evidence from HARMONY I, HARMONY CTP, and HARMONY III trials.
Key limitations	• The clinical efficacy of pitolisant in comparison to SOC in treating patients experiencing EDS with and without cataplexy is highly uncertain. Clinical evidence in comparison with all relevant SOC comparators was unavailable, with only information available for pitolisant in comparison with modafinil and no treatment. Based on the CADTH clinical review, the pivotal trials demonstrated that pitolisant was not non-inferior to modafinil for improvement in EDS, and due to methodological limitations, the evidence for the cataplexy subgroup is uncertain. • SOC was inappropriately modelled as a weighted basket comparator instead of as individual interventions. Adverse events and discontinuation rates specific to each treatment were also excluded from the model. The cost-effectiveness of pitolisant compared to each SOC agent, or combination, for EDS with and without cataplexy is unknown. Given the availability of various treatment options for EDS with and without cataplexy, the relevance of no treatment as a comparator is limited and its inclusion in the sponsor's base case may affect the interpretability of the results. • The submitted model based on response and non-response assessed by EDS or CGI-C score thresholds omits key aspects of the treatment paradigm (e.g., partial response and likely treatment sequencing) and aspects of disease expected to affect patient health-related quality of life and costs.
CADTH reanalysis results	• Given the key limitations with the available clinical evidence, the comparative clinical effects of pitolisant compared to SOC for EDS with and without cataplexy are highly uncertain. The CADTH reanalysis assumed that there would be no difference in treatment effects (i.e., no difference in total QALYs) and a cost comparison between pitolisant and its comparators was conducted to highlight the differences in drug costs. CADTH notes that this assumption may be conservative as there is no evidence to support that pitolisant is not worse than SOC agents for the treatment of EDS with and without cataplexy. • The annual cost of pitolisant ($12,147 for the most common doses of 10 or 40 mg per day from the trials, requiring two tablets) is more expensive than all SOC treatments, which range from $81 to $2,677 for EDS without cataplexy and $114 to $3,421 for EDS with cataplexy. • There is no clinical evidence to justify a price premium for pitolisant in either subgroup. For EDS without cataplexy, a price reduction of at least 97% to 99% is required for the submitted price of pitolisant to be equivalent to the lowest priced generic stimulant (methylphenidate HCl) at upper and lower recommended doses, respectively. • For EDS with cataplexy, a price reduction of at least 96% to 99% is required for the submitted price of pitolisant to be equivalent to the lowest price generic stimulant plus anti-cataplectic agent combination (methylphenidate HCl plus venlafaxine) at upper and lower recommended doses, respectively.

EDS = excessive daytime sleepiness; HCl = hydrochloride; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY= quality-adjusted life-year; SOC = standard of care.

Budget Impact

CADTH identified several limitations with the sponsor's analysis: The anticipated market uptake for pitolisant was likely underestimated; the proportion of narcolepsy patients who receive treatment was likely underestimated by the sponsor; and the discontinuation criteria for pitolisant is unclear and may be a driver of budget impact estimates. A CADTH reanalysis increased the market shares for pitolisant and proportion of patients with narcolepsy who receive treatment. In the CADTH base case, the anticipated budget impact of reimbursing pitolisant for the treatment EDS in narcolepsy with and without cataplexy in adult patients is $1,790,647 in year 1, $4,297,152 in year 2, and $6,946,649 in year 3, for a three-year total of $13,034,448. This estimate was substantially different from that of the sponsor. CADTH found the budget impact of pitolisant to be sensitive to market shares and changes to the proportion of patients assumed to be treated for narcolepsy.

Canadian Drug Expert Committee (CDEC

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting Date: June 23, 2022

Regrets

1 expert committee member did not attend

Conflicts of Interest

None