

## CADTH Reimbursement Recommendation

# Pitolisant Hydrochloride (Wakix)

**Indication:** For the treatment of excessive daytime sleepiness or cataplexy in adult patients with narcolepsy

**Sponsor:** Paladin Labs Inc.

**Final recommendation:** Do not reimburse

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## What Is the CADTH Reimbursement Recommendation for Wakix?

CADTH recommends that Wakix not be reimbursed by public drug plans for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy.

### Why Did CADTH Make This Recommendation?

- It is still not known whether Wakix offers any therapeutic benefit over other treatments used for EDS or cataplexy. Two double-blind, randomized, controlled, comparative studies failed to show that Wakix was at least as good as modafinil for treating EDS and did not show any clinical benefit of Wakix over modafinil. One study focused on cataplexy, but this study was versus placebo and results were inconsistent for cataplexy outcomes across the studies.
- Based on the evidence, the expert committee could not conclude that Wakix met any of the needs that were identified as important to patients, including being more effective and reliable for controlling narcolepsy symptoms and to which patients would be less likely to develop tolerance.

## Additional Information

### What Is Narcolepsy?

Narcolepsy is a chronic sleep disorder. It is characterized by excessive drowsiness during the day, also known as EDS, and may also be characterized by sudden muscle weakness (cataplexy). Approximately 1 in 2,000 people in Canada are affected by narcolepsy and of these, approximately 60% to 70% experience cataplexy on top of EDS. However, the number of people with narcolepsy is likely underestimated as this condition is hard to diagnose.

### Unmet Needs for Controlling Symptoms of Narcolepsy

There is a need for better medicines that are more reliable for controlling narcolepsy symptoms. There is also a need for treatments that are easier to take, need to be taken less often, and less likely for patients to develop tolerance.

### How Much Does Wakix Cost?

Treatment with Wakix is expected to cost approximately \$6,074 to \$12,147 per patient per year.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that pitolisant hydrochloride not be reimbursed for the treatment of 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). Pitolisant hydrochloride did not meet the criteria for noninferiority to modafinil in the HARMONY I and HARMONY Ibis trials in terms of EDS; therefore, the direct comparative data available for review did not demonstrate a benefit compared with modafinil for excessive sleepiness. Furthermore, there was no comparison to available drugs in the HARMONY CTP trial, which focused on outcomes reflecting symptoms of cataplexy. Although the studies suggest that treatment with pitolisant may have some benefit for cataplexy outcomes, results were inconsistent across the trials. In addition, the secondary outcomes in which cataplexy was measured varied, and there were differences in the overall proportion of patients who experienced some benefit. No other relevant direct or indirect evidence was identified; therefore, the comparative efficacy of pitolisant hydrochloride for the treatment of EDS or cataplexy remains unknown.

Patients identified a need for medications that are more reliable and effective in controlling narcolepsy symptoms. Furthermore, patients expressed a need for treatments that 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 when compared to standard treatment.

## Discussion Points

- Although other drugs such as psychostimulants and anticataplectics are available for the treatment of EDS and cataplexy, CDEC recognized that these treatments are associated with various risks and acknowledged the need for a new treatment that is safe and effective for patients with EDS or cataplexy. However, no robust evidence to support a superior safety profile for pitolisant was available.
- The clinical experts indicated that patients who experience both EDS and cataplexy would benefit from a single drug that is able to provide an 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. During the initial meeting, CDEC concluded that it is 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. This same issue was discussed during the reconsideration meeting, and CDEC upheld the initial conclusion.

- During the initial meeting, CDEC noted the lack of other direct and indirect comparative evidence available for this review given that other treatments for narcolepsy are currently available; no indirect evidence was submitted to CADTH in the sponsor's submission. During the reconsideration meeting, CDEC discussed that the network meta-analyses identified in the sponsor's request for reconsideration were characterized by substantial limitations that may bias the findings, namely significant heterogeneity across studies for most end points. Therefore, CDEC was unable to determine whether pitolisant hydrochloride provided any additional clinical benefit over other currently available treatment options.
- During the reconsideration meeting, CDEC discussed the need for another treatment option with decreased potential for abuse and 1 where patients would be less likely to develop tolerance and require increasing doses to maintain the treatment effect. CDEC could not conclude that pitolisant would meet this need due to the lack of robust comparative evidence.
- 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 that 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. As there was uncertainty with the clinical evidence, CDEC considered the criteria for significant unmet need that are described in section 9.3.1 of the [Procedures for CADTH Reimbursement Reviews](#). The committee concluded that the evidence for pitolisant did not meet the criteria for allowing for additional uncertainty with the evidence.

## 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 episodes of drowsiness during the day, also known as 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 health care providers with experience in narcolepsy.

Narcolepsy can affect all aspect of life in work and social settings, and affect a patient's day-to-day functioning and their health-related quality of life and productivity. Patients can experience EDS during common daily situations 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 overall mortality. In Canada, the current treatment standard for EDS in narcolepsy is modafinil, which is thought to improve wakefulness by reducing dopamine reuptake.

Pitolisant hydrochloride is an inverse agonist-antagonist of the histamine 3 (H3) receptor. The human H3 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 EDS or cataplexy in adult patients with narcolepsy. It received a Health Canada Notice of Compliance on May 25, 2021. The reimbursement request is per the indication.

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 3 randomized controlled trials (RCTs) in patients with narcolepsy with or without cataplexy
- patients perspectives gathered by 1 patient group, Wake Up Narcolepsy, Inc.
- input from the 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
- information submitted as part of the request for reconsideration (described in the following).

## Stakeholder Perspectives

### Patient Input

One patient group, Wake Up Narcolepsy, Inc., submitted patient input for this review. Wake Up Narcolepsy, Inc. 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 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 the Clinical Experts Consulted by CADTH

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 more than 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 abovementioned treatment options address the fundamental underlying neurochemical abnormality of loss of hypocretin cells and secondary absence or reduction of available central nervous system hypocretin associated with narcolepsy.

Several problems persist with existing treatment options. For selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants, not all patients respond to treatment and/or become tolerant to treatment. Tolerance to the rapid eye movement (REM)-suppressing effects of selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, and tricyclic antidepressant medications frequently occurs, leading to persistent cataplexy. Side effects can be problematic and include stomach upset, night sweats, sexual side effects, headaches, and others. Some can be excessive sedating in the day, which can be a problem despite anticataplectic effects. For stimulants, daytime sleepiness may not be fully resolved and/or drugs may or may not wear off at inopportune times, leading to excess daytime sleepiness in the evenings and/or insomnia difficulties at night. Side effects can be problematic and include 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 and/or 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 the 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 an H3 antagonist-inverse agonist, and its relatively favourable 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 in its most recent (2021) guidelines for the treatment of hypersomnolence disorders.<sup>12</sup> It will be an early drug to consider for treatment of narcolepsy. It may also find a niche as an adjunct treatment to be combined with other therapies to boost their efficacy. It may also become a drug 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 those who cannot tolerate stimulant therapies, those who are concerned about getting pregnant, and those with a history of drug abuse. Jurisdictions should continue to provide coverage to prior therapies that are currently considered standard of care in combination with pitolisant hydrochloride, because the mechanism of action of pitolisant hydrochloride is quite different than any current available drug, 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 EDS 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 people's ability to do basic daily activities such as driving, working, and interacting with people. Cataplexy (which occurs in 60% to 70% of patients with narcolepsy) is equally if not more debilitating when left uncontrolled. Patients cannot drive or walk outside safely as surprises could trigger a cataplectic attack. Basic daily activities such as showering and bathing, dressing, and eating can be dangerous and/or challenging when the patient is 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 EDS 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 frequently delayed, often occurring 10 years or longer after symptom onset, potentially leading to significant suffering, but if appropriate, once treatment is initiated, tolerated, and maintained, a patients can retain up to 80% of functional capacity.

The primary outcomes(s) in clinical practice will likely be the degree to which EDS is reduced, as well as the frequency, intensity, duration, and predictability of cataplexy episodes. Clinically meaningful responses to treatment include the reduction in frequency, severity, and 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 that no longer trigger episodes like they had experienced before. Other parameters that may be used probably would include a 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 the degree of reduction of EDS and possibly a reduction in frequency of cataplexy spells. The use of Epworth Sleepiness Scale (ESS) scores in clinical practice for coverage of pitolisant may not be ideal. ESS is very subjective and patients 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 or 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 out of 24 or higher on the ESS (severe sleepiness), 15 to 17 is considered moderate sleepiness, and 11 to 14 is mild sleepiness.

There is very little data on defining “what is effective reduction of cataplexy.” Trials on sodium oxybate demonstrated a more than 90% reduction in cataplexy episodes. 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 those who are breastfeeding may not be suitable. There should be more caution and/or concern for use in children or the elderly due to a lack of data. Patients who are on multiple medications (more potential for drug interactions, particularly those affecting the corrected QT interval or drugs that are significant 2D6 inhibitors) and patients who have a history of significant kidney and/or liver failure may also not be ideal (difficult to predict metabolism) candidates for pitolisant hydrochloride. 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 and/or 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 drug 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 drugs for narcolepsy, there should be close follow-up in the first month and subsequent months of therapy. The first follow-up should be 1 month after starting the drug, then every 1 to 2 months for the next several months, and then intermittent after that, with probably, at a minimum, at least yearly follow-up long-term. Medical supervision in an outpatient sleep medicine setting with a 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 and/or symptoms outside of narcolepsy. At this time, as the approved indication for pitolisant hydrochloride is only for narcolepsy, with a conditional recommendation from the American Academy of Sleep Medicine for idiopathic hypersomnia, prescribing should probably be limited to those with specialty training in sleep medicine.

## 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, phase III, placebo-controlled RCTs met the inclusion criteria for the systematic review.<sup>13-15 13,14</sup> In all 3 trials, patients were included if they had narcolepsy with cataplexy. The HARMONY I and HARMONY Ibis trials also included patients without cataplexy (narcolepsy type 2). The HARMONY I and HARMONY Ibis trials required patients to have an ESS score of 14 out of 24 or greater during the baseline period, whereas the HARMONY CTP trial required an ESS score of 12 out of 24 or greater. The HARMONY CTP study 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, which were administered for at least 1 month before the trial.

The HARMONY I and HARMONY Ibis trials were 8-week trials that assessed the superiority of pitolisant hydrochloride compared to placebo with regard to EDS in patients with narcolepsy. An additional efficacy objective was a noninferiority comparison of pitolisant hydrochloride with modafinil. The HARMONY CTP study 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 the frequency of cataplexy attacks in patients who had narcolepsy with cataplexy. The maximum dosages for pitolisant hydrochloride were 20 mg daily in the HARMONY Ibis trial, while the HARMONY I and HARMONY CTP trials had a maximum daily dosage of 40 mg. Titration of the 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 the HARMONY I trial, █ of all patients in the HARMONY Ibis trial, and 10% of all patients in the HARMONY CTP trial.

#### Efficacy Results

##### *Excessive Daytime Sleepiness*

In the HARMONY I trial, the adjusted mean difference in the final ESS score for pitolisant hydrochloride compared with placebo was -3.10 (95% confidence interval [CI], -5.73 to -0.46;  $P = 0.022$ ). Sensitivity analyses on the per-protocol (PP) population and without accounting for the centre effect showed similar results. As the superiority of pitolisant hydrochloride over placebo for EDS was demonstrated at the a priori  $\alpha = 0.025$ , the noninferiority 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 noninferior to modafinil at the prespecified noninferiority margin of 2. A patient was considered a responder when final ESS was below 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 odds ratio (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 the HARMONY Ibis trial, the mean ESS score reductions from baseline (standard deviation [SD]) were █ in the placebo group, █ in the pitolisant hydrochloride group, and █ 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. As the superiority of pitolisant hydrochloride over placebo for EDS was demonstrated at the a priori alpha = 0.05, the noninferiority of pitolisant hydrochloride to modafinil was tested. The adjusted mean difference in the final ESS score between pitolisant hydrochloride and modafinil was 2.75 (95% CI, 1.02 to 4.48); thus, pitolisant hydrochloride was judged to not be noninferior to modafinil at the prespecified noninferiority margin of 2. A patient was considered a responder when the final ESS was 10 or lower, or the change from baseline was 3 or greater. The response proportions were [redacted] and [redacted] for the placebo, pitolisant hydrochloride, and modafinil groups, respectively. The adjusted relative risk (RR) for the difference between pitolisant hydrochloride and placebo was [redacted]. The adjusted RR for the difference between pitolisant hydrochloride and placebo was [redacted].

In the HARMONY CTP trial, 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 last observation carried forward (LOCF), baseline observation carried forward (BOCF), and the PP population were consistent with the main analysis. A patient was considered a responder when the final ESS was 10 lower, or the change from baseline was 3 or greater. The response proportions were 34.0% and 68.6% for placebo and 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 the HARMONY I trial, 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 the HARMONY Ibis trial, where the adjusted mean difference between placebo and pitolisant hydrochloride was 1.46 (95% CI, 1.06 to 2.01). The adjusted mean difference in final score between pitolisant hydrochloride and modafinil was [redacted]. In the HARMONY CTP trial, the geometric mean of ratios (final and 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 the HARMONY I trial, the adjusted mean difference between the pitolisant hydrochloride and placebo treatment arms was 0.82 (95% CI, 0.67 to 0.99) for "no-go", 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 "no-go", 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 the HARMONY Ibis trial, the ratio of mean change between pitolisant hydrochloride and placebo was significant (0.83; 95% CI, 0.69 to 0.99), whereas the difference between pitolisant hydrochloride and modafinil was [redacted] [redacted].

### ***Clinical Global Impression of Severity and of Change on EDS***

In the HARMONY I and HARMONY Ibis trials, a higher proportion of patients in the pitolisant hydrochloride and modafinil groups improved Clinical Global Impression of Severity and of Change (CGI-C) for EDS compared to placebo. However, the change in CGI-C scores

was similar for pitolisant hydrochloride and modafinil arms. In the HARMONY I study, 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 the HARMONY CTP trial, the mean reduction of the CGI-C score of pitolisant hydrochloride compared with placebo was  $-0.95$  (95% CI,  $-1.36$  to  $-0.54$ ). Mean CGI-C score was  $3.5$  (SD =  $1.1$ ) with placebo versus  $2.6$  (SD =  $1.1$ ) with pitolisant hydrochloride. Similar results were observed for the PP population, with a mean reduction of  $-0.86$  (95%CI,  $-1.29$  to  $-0.43$ ).

### ***Frequency and Severity of Cataplexy Attacks***

In HARMONY I, the final mean of complete and partial cataplexy episodes (episodes per day) was  $0.68$  (SD =  $1.66$ ),  $0.28$  (SD =  $1.11$ ), and  $0.65$  (SD =  $1.62$ ) in the placebo, pitolisant hydrochloride, and modafinil groups, respectively. In the exposed population, the RR of daily rates of complete and partial cataplexy episodes at the end of treatment for pitolisant hydrochloride compared to placebo was  $0.38$  (95% CI,  $0.15$  to  $0.93$ ). The RR of daily rates of complete and partial cataplexy episodes at the end of treatment for pitolisant hydrochloride compared to modafinil was  $0.54$  (95% CI,  $0.24$  to  $1.23$ ). In the HARMONY Ibis trial, 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 end point of the HARMONY CTP trial was the measure of anticataplectic 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 the placebo arm and  $2.27$  (95% CI,  $1.51$  to  $3.41$ ) in the pitolisant hydrochloride arm 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 the pitolisant hydrochloride arm compared to the placebo arm. 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 the HARMONY I trial, the mean final CGI-C score was  $3.4$  (SD =  $1.4$ ),  $2.9$  (SD =  $1.5$ ),  $3.0$  (SD =  $1.6$ ) in the placebo, pitolisant hydrochloride, and modafinil arms, respectively. The number of patients who improved compared to baseline was  $6$  ( $24.0\%$ ) in the placebo arm,  $9$  ( $34.6\%$ ) in the pitolisant hydrochloride arm, and  $8$  ( $28.6$ ) in the modafinil arm. The number of patients who reported no change compared to baseline was  $15$  ( $57.7$ ) in the placebo arm,  $15$  ( $57.7$ ) in the pitolisant hydrochloride arm, and  $16$  ( $57.1$ ) in the modafinil arm. There were  $2$  ( $8.0$ ) patients who reported worsened CGI-C scores in the placebo arm and  $1$  ( $3.6$ ) in the modafinil arm.

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

In the HARMONY CTP trial, the mean reduction of the CGI-C score with pitolisant hydrochloride compared to placebo was  $-0.95$  (95% CI,  $-1.36$  to  $-0.54$ ). 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,  $-1.29$  to  $-0.43$ ).

## Harms

In the HARMONY I trial, adverse events (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 the HARMONY Ibis trial, approximately █ of the patients in the pitolisant hydrochloride and modafinil groups reported AEs, while █ of patients receiving placebo reported AEs. In the HARMONY CTP trial, approximately 35% of patients experienced an AE. For the HARMONY I trial █, there was a greater percentage of nervous system disorders in the pitolisant hydrochloride arm, but the placebo arm had greater nervous system disorders in the HARMONY CTP trial.

In the pitolisant hydrochloride arm in the HARMONY I study, pyelonephritis and hemorrhoids were reported as serious AEs (SAEs) █. The HARMONY CTP trial reported 1 SAE in the pitolisant hydrochloride arm only.

In the HARMONY I trial, 1 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.) █ In the HARMONY CTP trial, 1 patient receiving pitolisant hydrochloride discontinued due to severe nausea as a treatment-emergent AE (TEAEs). 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 and 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. The HARMONY I trial █ had between-group study differences for previous medication usage and proportion with cataplexy, which could suggest differences in disease severity. In the HARMONY Ibis trial █ of patients had a history of cataplexy in the pitolisant hydrochloride group compared to █ in the placebo group. In the HARMONY I trial, patients with at least 1 chronic medication within 3 months before inclusion ranged from 70% (the modafinil arm) to 85.2% (the placebo and pitolisant hydrochloride arms). The maximum dosages for pitolisant hydrochloride were 20 mg daily for the HARMONY Ibis trial, while the HARMONY I and HARMONY CTP trials had a maximum daily dosage of 40 mg. Titration of the 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 antiepileptic medications. Patients on antiepileptic medications represented 35% of all patients in the HARMONY I trial, █ of all patients in the HARMONY Ibis trial, and 10% of all patients in the HARMONY CTP trial. There were between-group study differences in the HARMONY I and HARMONY CTP trials for the proportion of patients on antiepileptic medications during the trial. In the HARMONY I trial, 33.3% of patients receiving placebo compared to 40.7% patients receiving pitolisant hydrochloride and 56.7% patients receiving modafinil remained on authorized medications during the study. In the HARMONY CTP trial, 16% of those in the placebo

group remained on antiepileptic medication, compared with 7% in the pitolisant group. Inconsistency in concomitant antiepileptic 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 had previously received modafinil may have recognized the study drug.

The primary efficacy outcome for the HARMONY I and HARMONY Ibis trials, change in EDS, was measured using the validated ESS. The ESS is a subjective, self-administered questionnaire, but is widely used in narcolepsy trials. The primary outcome for the HARMONY CTP trial was weekly rate of cataplexy captured by patient diaries. All primary outcomes were assessed using unvalidated tools. Other secondary end points assessing EDS were not validated, such as the CGI-C and patient global opinion tools. The Maintenance of Wakefulness Test and the Sustained Attention to Response Task 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 the HARMONY CTP trial 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 I 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 minimal important difference as 3. To remain less than the minimal important difference 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 the HARMONY I trial included the change from assessing the superiority of pitolisant compared with modafinil to a noninferiority analysis. The change in type of analysis would not bias the results since the noninferiority analysis was reported appropriately for both the intention-to-treat and PP populations.

According to the clinical experts consulted for this review, the baseline characteristics of study patients are reflective of patients in Canada with narcolepsy seeking further treatment options. The drug titration would be reflective of clinical practice. The primary outcome measures used 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 antiepileptic drugs, according to the clinical experts. This may decrease

the generalizability of the trial population. Adherence to treatment remained high at higher than 80% in all trials.

## Other Relevant Evidence

The open-label extension study HARMONY III<sup>16,17</sup> provides long-term safety and efficacy data that supplements the evidence from the RCTs in the systematic review.

### Description of Studies

The HARMONY III trial is a long-term, open-label, uncontrolled extension study conducted to evaluate the efficacy and safety of pitolisant at 5 mg, 10 mg, 20 mg, or 40 mg per day for the treatment of EDS in patients with narcolepsy with or without cataplexy for up to 5 years of treatment. Of the 102 patients enrolled in the HARMONY III trial, 86 were patients who were treatment naive and 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. Treatment-naive 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<sup>13</sup>, HARMONY II<sup>18</sup>, or HARMONY Ibis.<sup>14</sup>

At study inclusion, patients from the CUP could continue at their established pitolisant dose (20 mg or 40 mg per day) without up-titration. Treatment-naive patients began pitolisant treatment with a 1-month individual up-titration scheme starting at 5 mg per day and increasing up to 40 mg per day. Patients recruited from France who had at least 1 dose of pitolisant and completed the initial 1-year period of the HARMONY III trial, 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 or greater to enrol into the extension study. The overall mean age for all participants was 38.0 (SD = 14.9) years and slightly more than half were female (55.9%). About 75% of each treatment-naive patients and those from the CUP 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 patients from the CUP (56.3%) were taking concomitant medications than treatment-naive patients (31.4%). Overall, the baseline characteristics of patients enrolled in the HARMONY III trial were generally consistent with the baseline characteristics of the patients randomized in the pivotal trials. Characteristics of the patients from the CUP who continued into the 5-year extension period were similar to 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 change from baseline for the ESS score was -3.99 (SD = 4.56). Fifty-seven (58.2%) patients were considered responders, defined as an ESS score of 10 or less or a change from baseline of 3 or greater. Among treatment-naive patients, the mean change from baseline was -4.30 (SD = 4.47). Forty-nine (59.8%) patients were considered responders. For patients from the CUP, who were already

receiving pitolisant treatment at inclusion and had a lower mean ESS score at baseline, the mean change from baseline for the ESS score was  $-2.38$  (SD = 4.79). Eight (50.0%) patients were considered responders.

Regarding patients taking concomitant narcolepsy treatments, the mean change from baseline was  $-3.15$  (SD = 4.01),  $-3.64$  (SD = 4.55), and  $-4.00$  (SD = 2.35) for patients taking psychostimulants (n = 26), antiepileptics (n = 14), and both psychostimulants and antiepileptics (n = 13), respectively. For patients taking pitolisant only (i.e., no concomitant treatments) (n = 45) the mean change from baseline was  $-4.67$  (SD = 5.27). Thirteen (50.0%), 8 (57.1%), and 10 (76.9%) patients taking psychostimulants, antiepileptics, and psychostimulants and antiepileptics 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 patients from the CUP who continued the long-term follow-up, the ESS mean change from baseline was  $-4.41$  (SD = 5.38) at year 2 (n = 45),  $-4.45$  (SD = 6.16) at year 3 (n = 38),  $-4.76$  (SD = 5.73) at year 4 (n = 34), and  $-6.07$  (SD = 7.19) at year 5 (n = 14), respectively. At 5 years, the mean change from baseline was  $-8.17$  (SD = 8.93) and  $-4.50$  (SD = 5.71) for treatment-naive patients (n = 6) and patients from the CUP (n = 8), respectively. Of the 14 patients remaining at 5 years, 10 (71.4%) were considered responders, including 5 (83.3%) treatment-naive patients and 5 (62.5%) patients from the CUP.

Regarding patients taking concomitant narcolepsy treatments, the mean change from baseline in ESS after 5 years was  $-5.67$  (SD = 6.11),  $-6.33$  (SD = 7.77), and  $-5.50$  (SD = 3.87) for patients taking psychostimulants (n = 3), antiepileptics (n = 3), and both psychostimulants and antiepileptics (n = 4), respectively. For patients taking pitolisant only (i.e., no concomitant treatments) (n = 4) the mean change from baseline was  $-6.75$  (SD = 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 treatment-naive patients and 66.7% of patients from the CUP 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 patients from the CUP 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 of treatment, 83.4% of treatment-naive patients (n = 5) and 50.0% of patients from the CUP (n = 4) were at least much improved; 16.7% of treatment-naive patients (n = 1) and 37.5% of patients from the CUP (n = 3) were minimally improved; and 12.5% of patients from the CUP (n = 1) reported no change.

A total of 75.0% of patients (75.0% treatment-naive and 75.1% from the CUP) evaluated the effect of pitolisant as "moderate" to "marked" on the 6-item patient's global opinion test after 1-year of treatment. Among patients from the CUP who continued the long-term follow-up, the proportion of patients who reported a "moderate" to "marked" effect of pitolisant on the 6-item patient's global opinion 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% of treatment-naive patients and 50.0% of patients from the CUP 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 change in total cataplexy from baseline was -0.25 (SD = 1.37) among all patients, -0.25 (SD = 1.38) among treatment-naive patients, and 0.00 (SD = not available [NA]) among patients from the CUP. The mean change in partial cataplexy from baseline was -0.49 (SD = 1.94) among all patients, -0.49 (SD = 1.96) among treatment-naive patients, and 0.53 (SD = NA) among patients from the CUP.

### ***HRQoL***

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

Among patients from the CUP who continued the long-term follow-up, the mean of the EQ VAS was 70.5 (SD = 15.9) at 2 years (n = 44), 69.5 (SD = 13.2) at 3 years (n = 38), 72.2 (SD = 13.3) at 4 years (n = 33), and 75.0 (SD = 12.2) at 5 years (n = 14) of treatment, respectively. At 5 years, the EQ VAS was 80.5 (SD = 12.5) among treatment-naive patients and 70.9 (SD = 10.9) for patients from the CUP, with a change of 13.8 (SD = 15.5) and 2.4 (SD = 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 change in the daily number of sleep attacks from baseline was -0.37 (SD = 1.41) for all patients, -0.39 (SD = 1.42) for treatment-naive patients, and 0.47 (NA) for patients from the CUP. The mean change in the duration of diurnal involuntary sleep attacks (minutes) from baseline was -0.37 (SD = 1.41) for all patients, -0.39 (SD = 1.42) for treatment-naive patients, and 0.47 (SD = NA) for patients from the CUP.

### ***Nocturnal Sleep Properties***

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

### ***Number of Hallucinations***

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

### **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 treatment-naïve patients and 56.3% of patients from the CUP were taking concomitant treatment at baseline and over the course of the 1 year after inclusion, 51.2% of treatment-naïve patients and 62.5% of patients from the CUP 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 subset from the CUP, 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 treatment-naïve patients and 68.8% of patients from the CUP 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 subset of patients from the CUP.

During the initial 1-year period treatment period, 58 patients (56.9%) reported 168 TEAEs, the most common being headache (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depression (4.9%), and nausea (4.9%). In the subset of patients from the CUP, over the 5-year period, 72.7% 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 subset of patients from the CUP, 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 Beck Depression Inventory-Short Form 13 questions (BDI-SF-13) score was 4.1 (SD = 3.5) at baseline and 3.8 (SD = 4.1) at the 1-year visit. The mean BDI-SF-13 score among the subset of patients from the CUP at the year 5 visit was 2.4 (SD = 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 end points. 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 end points in the HARMONY III trial 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. More than one-third of patients discontinued the extension study within the first year, mainly due to AEs or a lack of perceived efficacy. This attrition could have resulted in a population of patients who 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 AEs, potentially resulting in greater efficacy and fewer AEs 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 time point, LOCF was used for those without final values for the primary efficacy outcome of ESS, 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 patients in Canada were enrolled in the extension study, the characteristics of the patients enrolled in the trials were representative of patients with narcolepsy 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

**Table 1: Cost and Cost-Effectiveness**

Component	Description
<b>Type of economic evaluation</b>	Cost-utility analysis Decision tree during the trial period followed by a Markov model
<b>Target population</b>	Adult patients with narcolepsy, assessed within 2 subgroups: <ul style="list-style-type: none"> <li>• EDS without cataplexy</li> <li>• EDS with cataplexy</li> </ul>
<b>Treatment</b>	Pitolisant hydrochloride
<b>Submitted price</b>	Pitolisant hydrochloride: 5 mg, \$16.63 per tablet; 20 mg, \$16.63 per tablet
<b>Treatment cost</b>	Annual cost of pitolisant ranges from \$6,074 to \$12,147
<b>Comparators</b>	EDS without cataplexy: <ul style="list-style-type: none"> <li>• SOC (consisting of a weighted basket comparator including modafinil, methylphenidate HCl, d-amphetamine sulphate, and lisdexamfetamine dimesylate)</li> <li>• no treatment</li> </ul> EDS with cataplexy: <ul style="list-style-type: none"> <li>• cataplexy SOC (consisting of a weighted basket comparator including off-label anti-cataplectic drugs [i.e., imipramine, desipramine, clomipramine, fluoxetine, and venlafaxine] combined with modafinil, methylphenidate HCl, d-amphetamine sulphate, and lisdexamfetamine dimesylate individually)</li> <li>• no treatment</li> </ul>

Component	Description
<b>Perspective</b>	Canadian publicly funded health care payer
<b>Outcomes</b>	QALYs and LYs
<b>Time horizon</b>	Lifetime (70 years)
<b>Key data source</b>	Clinical efficacy was modelled using evidence from HARMONY I, HARMONY CTP, HARMONY Ibis, and HARMONY III trials.
<b>Key limitations</b>	<ul style="list-style-type: none"> <li>• The clinical efficacy of pitolisant in comparison to SOC in treating patients experiencing EDS with and without cataplexy is highly uncertain. Clinical evidence that compares pitolisant 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 noninferior to modafinil for improvement in EDS, and due to methodological limitations, the evidence for the cataplexy subgroup is uncertain.</li> <li>• 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 drug, 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.</li> <li>• The submitted model based on response and nonresponse 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.</li> </ul>
<b>CADTH reanalysis results</b>	<ul style="list-style-type: none"> <li>• 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 therapies for the treatment of EDS with and without cataplexy.</li> <li>• The annual cost of pitolisant (\$12,147 for the most common doses of 10 mg or 40 mg per day from the trials, requiring 2 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.</li> <li>• 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 the upper and lower recommended doses, respectively.</li> <li>• 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 anticataplectic drug combination (methylphenidate HCl plus venlafaxine) at the upper and lower recommended doses, respectively.</li> </ul>

CGI-C = Clinical Global Impression of Severity and of Change; EDS = excessive daytime sleepiness; HCl = hydrochloride; 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 patients with narcolepsy 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 the proportion of patients with narcolepsy who receive treatment. In the CADTH base case, the anticipated budget impact of reimbursing pitolisant for the treatment of 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 3-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.

## Request for Reconsideration

The sponsor filed a request for reconsideration for the draft recommendation for pitolisant hydrochloride for the treatment of EDS or cataplexy in adult patients with narcolepsy. In their request, the sponsor identified the following issues:

- CDEC's assessment of unmet need
- CDEC's conclusion that the comparative efficacy of pitolisant hydrochloride for the treatment of EDS or cataplexy remains unknown and that the drug may not offer additional benefits over standard treatments
- the conclusion that there was insufficient evidence to conclude whether pitolisant hydrochloride met the needs identified by patients
- that CDEC was unable to determine with certainty that patients with both EDS and cataplexy can derive a full range of symptomatic relief from monotherapy with pitolisant hydrochloride
- that the limitations of the study design noted by CDEC (the small sample sizes and short trial durations) reduced the certainty in results
- the conclusions within the CADTH Clinical Review report that primary outcomes in the HARMONY trials were assessed using unvalidated tools and CADTH's conclusions that the interactions between concomitant medications and pitolisant hydrochloride are unknown and that the evidence for cataplexy subgroup is uncertain
- that, in the view of the sponsor, the recommendation does not align with the input from the clinical experts consulted by CADTH.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- feedback from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in the diagnosis and management of narcolepsy
- feedback from the public drug plans
- feedback from 2 clinician groups: The Ottawa Hospital Sleep Clinicians and the Sleep Disorders Clinic of Hamilton and McMaster Sleep Medicine Training Programme
- feedback from 1 patient group: Wake Up Narcolepsy, Inc.

All stakeholder feedback received in response to the draft recommendation from patient and clinician groups and the public drug programs is available on the CADTH website.

## CDEC Information

### Initial Meeting Date: June 23, 2022

#### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, 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.

**Regrets:** One expert committee member did not attend.

**Conflicts of interest:** None.

### Reconsideration Meeting Date: November 23, 2022

#### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, 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.

**Regrets:** One expert committee member did not attend.

**Conflicts of interest:** None.