CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

MIGALASTAT (GALAFOLD — Amicus Therapeutics)
Indication: Fabry Disease

RECOMMENDATION

The CADTH Canadian Drug Expert Committee (CDEC) recommends that migalastat be reimbursed for the long-term treatment of adults with a confirmed diagnosis of Fabry Disease (FD) (alpha-galactosidase [alpha-Gal A]) and who have an alpha-Gal A mutation determined to be amenable by an in vitro assay, if the following criteria and conditions are met:

Criteria:

- For use in patients with an amenable mutation and who are otherwise eligible for enzyme replacement therapy (ERT) for the treatment of FD.
- Migalastat not to be used concomitantly with ERT.

Conditions:

- Migalastat should be reimbursed according to the same criteria used to reimburse ERT for the treatment of FD in patients who have an amenable mutation.
- Patients must be under the care of a clinician experienced in the diagnosis and management of FD.
- Drug plan costs of migalastat should be lower than the drug plan costs of treatment with the least-costly ERT.

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Criteria

- For use in patients with an amenable mutation and who are otherwise eligible for enzyme replacement therapy (ERT) for the treatment of FD.
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Conditions

- Migalastat should be reimbursed according to the same criteria used to reimburse ERT for the treatment of FD in patients who have an amenable mutation.
- Patients must be under the care of a clinician experienced in the diagnosis and management of FD.
- Drug plan costs of migalastat should be lower than the drug plan costs of treatment with the least-costly ERT.

Reasons for the Recommendation

1. CDEC recognized an oral treatment such as migalastat would provide an alternative to intravenous administration of ERT, and that oral alternatives are valued by patients. Although the design of the active comparator trial (ATTRACT) does not allow for inferences regarding the equivalence, superiority, or non-inferiority of migalastat relative to ERT, CDEC considered the results of this comparability trial in the context of the unmet need for an oral therapy for FD.
2. One phase III, open-label study (ATTRACT; N = 60) demonstrated that migalastat was comparable to ERT (either agalsidase alfa or agalsidase beta) with respect to effects on renal function (annualized changes in glomerular filtration rate [GFR] from baseline through month 18) in patients who were receiving ERT and had migalastat-amenable mutations. The FACETS trial (N = 67) was a phase III, double-blind trial comparing migalastat with placebo in patients with migalastat-amenable mutations who were naive to treatment with ERT for at least six months prior to study entry. Although FACETS did not meet its primary end point (proportion of patients with a ≥ 50% reduction in the average number of globotriaosylceramide [GL-3] inclusions per interstitial capillary [IC] in the intention-to-treat [ITT] population from baseline to month 6), there was a statistically significant difference in GL-3 inclusions per IC in favour of migalastat when the analysis included only patients with amenable mutations.
3. Based on the submitted price of migalastat and publicly available prices of ERTs, in a patient weighing 75 kg, migalastat has a higher annual cost ($310,250) than agalsidase alfa ($299,821) and a lower annual cost than agalsidase beta ($312,186). In a patient weighing less than 75 kg, migalastat is more costly than both ERTs. However, due to the uncertainty in the comparative clinical effectiveness of migalastat and ERTs, there is corresponding uncertainty in the cost-effectiveness of migalastat relative to ERT; this uncertainty related to the cost-effectiveness of migalastat would be mitigated if the price of migalastat per patient is clearly lower than that of ERT.

Of Note

CDEC noted that all Canadian patients with FD are followed through the Canadian Fabry Disease Initiative, which determines eligibility (patients have to be approved by a panel of five physicians for publicly funded treatment), collects registry data, and distributes funding for ERT. CDEC recommended that migalastat also be managed through this initiative.

Discussion Points

- CDEC noted several limitations in both the ATTRACT and FACETS trials, leading to uncertainty in the comparative efficacy of migalastat relative to ERT. While the ATTRACT trial met the pre-specified criteria for demonstrating comparability of migalastat and ERT for the co-primary end points, wide confidence intervals were associated with the effect estimates, and several concerns related to the internal validity of the study, including imbalances in baseline demographic characteristics between groups and unbalanced attrition. CDEC also discussed the uncertainty associated with the design of the ATTRACT trial, which was a comparability trial with a pre-specified comparability criteria defined as a difference between the means for the annualized change in GFR for migalastat and ERT of less than 2.2 mL/min/1.73 m^2/year and 95% confidence intervals (CIs) for the means greater than 50% overlap. The committee noted that the results of the ATTRACT trial should not be interpreted as a demonstration of equivalence, non-inferiority, or superiority of migalastat relative to ERT. In the FACETS trial, 30% of eligible patients (10 of 33 patients) did not have biopsy results available despite the intent of the trial to look at biopsy as the primary outcome, and CDEC noted that the results of the health-related quality of life (HRQoL) outcomes should be interpreted cautiously, given that sample sizes were not reported, there was no adjustment for multiple statistical testing, and the double-blind period of the trial was relatively short (six months).
- CDEC noted that the eligibility criteria of the ATTRACT and FACETS trials allowed for the inclusion of patients with a range of disease severity. However, the patient populations included in both trials had relatively mild and early disease, making it difficult to generalize the results to patients with advanced disease.
- CDEC heard from a clinical expert with experience in treating patients with FD that there remains an unmet need for a treatment that addresses some of the disease manifestations of FD (e.g., pain and stroke), and neither trial was designed to assess the efficacy of migalastat in addressing this need. The same expert indicated that migalastat is also unlikely to fill the role of therapy in patients who cannot tolerate ERT, as the more severe infusion reactions from ERT often occur in patients with mutations that are not amenable to treatment with migalastat.
- The Health Canada–approved indication for migalastat is for adults with FD and is not indicated for patients with a GFR < 30 mL/min/1.73 m^2; therefore, children under the age of 18 will remain an unmet need, and some patients with amenable mutations but poor renal function will not be eligible for treatment with migalastat.
- CDEC discussed the changes to the human embryonic kidney assay that occurred during the conduct of the FACETS and ATTRACT trials, noting that of the 67 patients randomized in the FACETS trial, 50 (75%) were subsequently found to have amenable mutations with the migalastat amenability assay (28 [82%] patients in the migalastat group and 22 [67%] patients in the placebo group). The committee also discussed the variability in patient response to migalastat according to the specific amenable mutation considered, noting that the Health Canada–approved product monograph indicates that, among patients with amenable mutations, individual response to migalastat treatment varied considerably.

Background

Migalastat has a Health Canada–approved indication for the long-term treatment of adults with a confirmed diagnosis of FD (deficiency of alpha-galactosidase [alpha-Gal A]) and who have an alpha-Gal A mutation determined to be amenable by an in vitro assay. Migalastat acts as a pharmacological chaperone, selectively and reversibly binding, with high affinity, to the active site of wild-type alpha-Gal A and specific mutant forms of alpha-Gal A. The Health Canada–recommended dose in adults 18 years and older is 123 mg of migalastat (one capsule) once every other day at the same time of day. Migalastat is available as a hard capsule containing 123 mg of migalastat (equivalent to 150 mg of migalastat hydrochloride [HCl]).

Summary of CDEC Considerations

The committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials and pivotal studies of migalastat and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience treating patients with FD, and patient group–submitted information about outcomes and issues important to patients and caregivers who are affected by FD.

Patient Input Information

One joint patient input submission was provided by the Canadian Fabry Association (CFA) and the Canadian Organization for Rare Disorders (CORD). Patient perspectives were obtained from written individual testimonials, semi-structured interviews, and an

Internet survey developed by CORD in collaboration with the CFA. The following is a summary of key input from the perspective of the patient groups:

- FD significantly affects the physical and emotional well-being of patients along with severely affecting their ability to perform daily activities. Severe, sharp, or excruciating pain and swelling, particularly in the hands and feet, are often proclaimed to be the most bothersome symptoms.
- Gastrointestinal (GI) problems, cognitive impairment (such as lack of concentration, poor memory, and difficulty learning), cardiovascular problems, stroke, transient ischemic attacks, excessive sweating, ringing in ears, skin lesions or rash, and nervous system issues (such as numbness and tingling) are also commonly experienced. Patients also experience financial issues, depression, and mood swings.
- Symptoms such as fatigue and lack of energy significantly affect patients' ability to perform daily activities. These symptoms have a severe impact on school performance, the ability to undertake certain jobs or to perform up to certain expectations, the ability to partake in social activities, and the ability to perform the normal tasks of living.
- Patients hope new therapies will be as effective as possible in slowing disease progression, reducing symptoms, and avoiding organ damage, and will come with few to no side effects.
- Patients are hopeful that the oral formulation of migalastat will circumvent their need to attend lengthy infusions, which are time-consuming and often force families to plan their activities and lives around attending those sessions. Infusions can be difficult for patients to tolerate and can cause a range of related adverse effects.

Clinical Trials

The CDR systematic review included two phase III clinical trials (ATTRACT and FACETS). The ATTRACT trial was an active-controlled, randomized, open-label, multinational study that compared the efficacy and safety of migalastat to intravenous ERT (either agalsidase alfa or agalsidase beta) in patients with FD who were receiving ERT prior to study entry and who had migalastat-responsive mutations of the GLA gene. ATTRACT consisted of two periods, the first period was an 18-month open-label treatment period in which patients were randomized 1.5:1 to switch from ERT to migalastat HCl (150 mg once every other day; N = 36) or continue with ERT (N = 24), followed by a 12-month open-label extension period (Period 2) in which all patients received migalastat. The FACETS trial was double-blind and compared migalastat with placebo over a six-month period in patients with FD and with amenable mutations who had not previously received ERT within six months of eligibility screening. Patients were randomized in a 1:1 ratio to receive either oral migalastat HCl (150 mg; N = 34) or matching placebo (N = 36) once every other day.

The main limitations in both trials were the sample size, no adjustment for multiple statistical testing, baseline imbalances in patient characteristics between the trial groups in both trials (which is of particular concern in trials with small participant numbers), and unbalanced attrition between groups.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Measured GFR assessed by plasma clearance of iohexol ($mGFR_{iohexol}$).
- Estimated GFR assessed by the Chronic Kidney Disease Epidemiology Collaboration equation ($eGFR_{CKD\text{-}EPI}$).
- Estimated GFR assessed by the Modification of Diet in Renal Disease equation ($eGFR_{MDRD}$).
- Kidney Biopsy Assessment for Interstitial Capillary GL-3.
- The echocardiogram — used to measure cardiac parameters, including left ventricular mass index (LVMI), ejection fraction, fractional shortening at diastole, and posterior wall thickness; and the intra-ventricular septal wall thickness.
- Renal, cardiac, or cerebrovascular events, or death:
  - Renal events were defined as a decrease in $eGFR_{CKD\text{-}EPI} \geq 15$ mL/min/1.73 m^2, with the decreased eGFR < 90 mL/min/1.73 m^2 relative to baseline; and an increase in 24-hour urine protein ≥ 33%, with the increased protein ≥ 300 mg relative to baseline.

  - Cardiac events were defined as myocardial infarction, unstable cardiac angina, new symptomatic arrhythmia (requiring anti-arrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation), congestive heart failure (New York Heart Association Class III or IV).
  - Cerebrovascular events were defined as stroke or transient ischemic attack.
- Short-Form 36-Item Health Survey (SF-36) — a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. The SF-36 consists of eight dimensions: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, role limitations due to physical problems, and role limitations due to emotional problems. SF-36 also provides two component summaries: the physical component summary and the mental component summary.
- The Brief Pain Inventory (BPI) — a self-reported measure that assesses both pain and how pain affects or interferes with life. It is composed of eight questions relating to pain.
- The Gastrointestinal Symptoms Rating Scale — examines the full range of GI symptoms by including impact on daily living, intensity of symptoms, duration of attacks, and frequency of attacks. However, individual variables can be removed from the scale to ascertain changes within specific indications that may not require the full list. The 15 individual variables that examine both upper and lower GI symptoms are scored between 0 and 3, with higher scores indicating more severe symptoms. These upper GI symptom variables include abdominal pain, heartburn, acid regurgitation, sucking sensation in the epigastrium, nausea and vomiting, borborygmus (abdominal rumbling), abdominal distention, eructation (belching), increased flatus (passing gas).

The co-primary end points in the ATTRACT trial were annualized changes in renal function from baseline through month 18 assessed by measured and estimated GFR ($mGFR_{iohexol}$ and $eGFR_{CKD\text{-}EPI}$). The primary end point of the FACETS trial was to compare the percentage of patients in the two treatment groups with a > 50% reduction from baseline to month 6 in the number of GL-3 inclusions per kidney IC.

Efficacy

The pre-specified criteria for comparability of migalastat and ERT in the ATTRACT trial (the difference between the means for the annualized change in GFR for migalastat and ERT was within 2.2 mL/min/1.73 m^2/year and the 95% CIs for the means had greater than 50% overlap) were met for both co-primary $mGFR_{iohexol}$ and $eGFR_{CKD\text{-}EPI}$ outcomes in the modified ITT population.

The six-month change in mean (± SE) mGFR in the ITT analysis in the FACETS trial was −1.19 ± 3.4 mL/min/1.73m^2 in the migalastat group (N = 34) and 0.41 ± 2.0 mL/min/1.73m^2 in the placebo group (N = 33).

In the FACETS trial ITT population (i.e., patients with amenable and non-amenable mutations based on the migalastat amenability assay), a response was seen in 41% of patients receiving migalastat and 28% of patients receiving placebo (P = 0.3). Based on the responder analysis, the primary end point was not met because the difference between groups was not statistically significant. A post hoc analysis at the end of the double-blind period (six months) was conducted in patients with amenable mutations. The change from baseline analysis demonstrated that six months of treatment with migalastat was associated with a statistically significantly larger reduction in the average number of GL-3 inclusions per IC compared with placebo: –0.250 ± 0.103 versus +0.071 ± 0.126, respectively; P = 0.008.

In the ATTRACT trial, the mean baseline LVMI was 95.3 ± 22.7 g/m^2 in the migalastat group and 92.9 ± 25.7 g/m^2 in the ERT group (modified ITT). A decrease in LVMI indicates that a treatment might be beneficial in people with cardiac complications. LVMI decreased significantly from baseline to 18 months in patients who switched from ERT to migalastat (−6.6 g/m^2; 95% CI, −11.0 to −2.2); in patients who continued on ERT, the value at 18 months showed no statistically significant change from baseline (−2 g/m^2; 95% CI, −11.0 to 7.0].

In the FACETS trial, no changes from baseline in LVMI were seen during the initial six-month, double-blind, placebo-controlled period.

During the 18-month treatment period, the percentage of patients who had a renal, cardiac, or cerebrovascular event or who died was 29% (10 of 34) of the patients who switched from ERT to migalastat compared with 44% (8 of 18) of the patients who remained on ERT.

The SF-36v2 questionnaire was used to collect HRQoL data. In the ATTRACT trial, changes from baseline did not exceed the minimum important difference at any time point for either the migalastat or the ERT group. No analysis was provided to assess if clinically meaningful or statistically significant changes were demonstrated between groups after adjusting for baseline differences. In the FACETS trial, no statistically significant differences between placebo and migalastat groups were observed from baseline to month 6.

Questions based on the BPI-Pain Severity Component were used to assess pain. In the ATTRACT trial, changes from baseline did not exceed the minimal clinically important difference at any time point for either the migalastat or the ERT group. No between-group treatments comparison was reported. In the FACETS trial, no statistically significant differences between placebo and migalastat groups were observed from baseline to month 6 for the changes in the BPI Severity Component.

In the FACETS trial, at six months, a greater percentage of patients receiving migalastat had an improvement in the diarrhea domain compared with placebo (38% versus 9%), and there was a statistically significant difference in scores for this domain between the two groups (−0.3 for migalastat versus 0.2 for placebo, $P < 0.05$).

Harms (Safety and Tolerability)

In the ATTRACT trial, the majority of patients in both the migalastat and ERT groups (94% to 95% of patients) experienced a treatment-emergent adverse event (TEAE). The most frequent adverse events were nasopharyngitis and headache, and these did not differ in frequency between the migalastat and ERT groups.

In the FACETS trial, the majority of patients (91%) in both the migalastat and placebo groups experienced a TEAE. The most frequent TEAE was headache and nasopharyngitis, and these were both more frequent in the migalastat arm (35% and 18% respectively) than in the placebo arm (21% and 6%).

In the ATTRACT trial, during the 18-month randomized treatment period, no patient discontinued treatment due to a TEAE. In the FACETS trial double-blind period (six months), no patient in the migalastat group discontinued due to a TEAE, and one patient (3%) in the placebo group discontinued due to a TEAE.

Serious adverse events (SAEs) in ATTRACT were less frequent in the migalastat arm than the ERT arm (19% versus 33%). The most commonly occurring SAE was chronic heart failure deterioration, which occurred four times in one patient while receiving ERT. Chest pain occurred once in each of three patients receiving migalastat. Morbid obesity was reported in two patients receiving migalastat.

In the FACETS trial, the frequency of SAEs was lower in the migalastat group (6%), compared with the placebo group (12%). Only two patients in the migalastat group experienced SAEs during the double-blind period (6 months); each patient experienced one SAE (post-procedural hematoma and hydronephrosis), both of which were assessed as unrelated to the study drug.

No deaths occurred in either of the trials or the open-label extension studies.

Cost and Cost-Effectiveness

Migalastat is available as a 123 mg capsule at a price of $1,700 per capsule. The recommended dose is 123 mg every other day, at an annual cost of $310,250 per patient.

The manufacturer submitted a cost-utility analysis comparing migalastat with a blended comparator of two ERTs (agalsidase alfa and agalsidase beta) for patients 49 years of age, aligned with the mean age from the ATTRACT. The model time horizon was 50 years with annual cycles, and undertaken from the perspective of the Canadian health care payer. The manufacturer assumed equivalence between migalastat and the blended ERTs based on the results of the ATTRACT trial. Adverse event rates were also obtained from the ATTRACT trial. Patient weight was derived from unpublished data from the Canadian Fabry Disease Initiative. The manufacturer reported that migalastat was dominant (associated with a cost savings of $350,953 and a gain of 1.01 quality-adjusted life-years [QALYs]) compared with ERTs.

CDR identified several limitations with the submitted analysis, the key issue being the uncertainty of the clinical efficacy of migalastat. The CDR Clinical Report noted that in the placebo-controlled FACETS trial, migalastat did not meet its primary end point for the ITT population; and the comparative effectiveness of migalastat and ERT based on the ATTRACT trial was associated with uncertainty due to wide CIs, concerns with imbalances in baseline demographic characteristics between groups, and unbalanced attrition. The following limitations were also noted: the use of a blended ERT comparator was not appropriate; the assumption of disutility associated with ERT infusion is highly uncertain, as is the magnitude of any utility decrement; and finally, a distribution around weight was not considered in the probabilistic analysis, which influences ERT dosing as it is based on patient weight. CDR also noted the model included errors in the calculation of the annual migalastat cost, the weighted cost of ERT, and a disutility associated with dyspnea, which favoured migalastat.

CDR undertook reanalyses for migalastat compared with each ERT individually for two scenarios (with and without a disutility benefit due to route of administration), and correcting for model errors. While migalastat was found to dominate agalsidase beta, it was associated with incremental cost-utility ratios of more than $200,000 per QALY compared with agalsidase alfa. However, the results were sensitive to assumptions around comparative clinical effects and disutility associated with infusions. Based on both the FACETS and ATTRACT trials, the CDR Clinical Report noted that the clinically meaningful effects of migalastat are associated with uncertainty. The cost of migalastat 123 mg every other day compared with ERT (dosed per product monograph recommendations) depends on the price of the comparator treatment and patient weight. Based on the submitted and publicly available prices, in a patient weighing 75 kg, migalastat has a greater annual cost ($310,250) than agalsidase alfa ($299,821) and a lower annual cost than agalsidase beta ($312,186).

CDEC Members

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

December 13, 2017 Meeting

Regrets

Two CDEC members did not attend.

Conflicts of Interest

None