CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

PROPRANOLOL ORAL SOLUTION
(Hemangiol — Pierre Fabre Dermo-Cosmétique Canada Inc.)
Indication: Infantile Hemangioma Requiring Systemic Therapy

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that propranolol oral solution be reimbursed for the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy in the following circumstances: life- or function-threatening hemangioma; ulcerated hemangioma with pain and/or lack of response to simple wound care measures; or hemangioma with a risk of permanent scarring or disfigurement, if the following condition is met:

Condition:
- Substantial reduction in price.

Reasons for the Recommendation:
1. One adaptive, phase II/III, randomized, double-blind, placebo-controlled trial demonstrated that propranolol-treated patients were statistically significantly more likely to achieve complete or near complete resolution of the target hemangioma at 24 weeks than placebo-treated patients when assessed by blinded centralized reviewers (61/101 [60.4%] versus 2/55 [3.6%]; $P < 0.0001$). Efficacy results were similar when stratified by age group (35 to 90 days or more than 90 days) and hemangioma location (facial or non-facial).
2. Compounded propranolol is the current first-line treatment option for IH requiring systemic therapy. The cost of compounded oral propranolol is less than 1% of the cost of propranolol oral solution ($0.0027 per mg versus $0.6082 per mg). When including the cost of compounding fees for the compounded product, the cost of 450 mg of compounded oral propranolol is between 3% and 11% of the cost of propranolol oral solution.

Of Note:
- CDEC noted that although the trial did not include patients with life- or function-threatening hemangioma or with ulcerated hemangioma with pain and/or lack of response to simple wound care measures, it would be unethical to randomize such patients in a placebo-controlled trial. The effectiveness of propranolol oral solution in these patients is supported by observational data and the experience of the clinical experts consulted by CADTH.

- CDEC noted that the Health Canada–approved product monograph for propranolol oral solution states that therapy should be initiated and monitored by health care professionals experienced in the use of beta-blockers in infants and in the management of IH.

Other Discussion Points:
CDEC noted the following:

- Patients with life-threatening, function-threatening, and/or severely ulcerated hemangiomas were excluded from Study 201. In the absence of controlled studies, CDEC considered the observational data regarding the use of propranolol in these patients from the manufacturer's compassionate use program (CUP). The CUP included 1,661 patients from France with proliferating IH that were considered to be life-threatening, function-threatening, or ulcerated, and not responding to simple treatment. The study was not designed to evaluate the efficacy of propranolol for the treatment of IH and the available data were incomplete (i.e., only reported for 697 of 1,661 patients), uncontrolled, unblinded, and were analyzed in a manner that was not pre-specified. The only effectiveness data reported for this study were based on whether or not treatment success (i.e., good efficacy) was cited as a reason for discontinuation in a subset of patients for whom data were available. Overall, the manufacturer reported that 88.3% of the 697 patients with data available discontinued from the CUP as a result of efficacious treatment with oral propranolol.
- Oral propranolol is generally considered to be the preferred first-line treatment for IH requiring systemic therapy in Canada. Before the approval and marketing of oral propranolol solution in Canada, oral propranolol was only available through compounding facilities. Although compounded oral propranolol is not specifically approved by Health Canada for the treatment of proliferating IH, it is currently reimbursed by the majority of CDR-participating drug plans. CDEC considered compounded propranolol to be an appropriate comparator for cost considerations and recognized that a small price premium may be warranted for a commercially available product that is formulated for pediatric use.

Background:
Hemangiol is an oral solution containing 3.75 mg/mL propranolol that is indicated for the treatment of proliferating IH requiring systemic therapy in the following circumstances: life- or function-threatening hemangioma; ulcerated hemangioma with pain and/or lack of response to simple wound care measures; or hemangioma with a risk of permanent scarring or disfigurement. The product monograph states that treatment should be initiated in infants aged five weeks to five months and the age for treatment initiation should be corrected in cases of premature birth.

The recommended therapeutic dose of propranolol for the treatment of IH is 3 mg/kg per day (administered as 1.5 mg/kg twice daily). The product monograph recommends that the first dose and each dose escalation should be administered in a clinical setting where there are adequate facilities for handling adverse events, including events that require urgent measures.

Summary of CDEC Considerations
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs, a critique of the manufacturer's pharmacoeconomic

evaluation, and patient group–submitted information about outcomes and issues important to those affected by IH.

Patient Input Information:

One patient group (AboutFace Craniofacial Family Society) responded to the CDR call for patient input. Information was obtained through social media, email, and one-on-one telephone discussions. The following is a summary of key information provided by the patient group:

- Patients with IH can experience deformity and functional impairment and may be required to undergo painful and invasive treatments (e.g., laser treatment or surgery), which may be associated with a risk of scarring.
- The psychosocial effects of IH can have a negative impact on the development and well-being of patients. Former patients and caregivers reported that hemangiomas that are located on a child's face are particularly concerning and patients may encounter bullying and discrimination. These can result in an avoidance of social situations, increased isolation, and damage to one's sense of self-worth.
- Caregivers also reported feeling anxiety and stress due to the anticipated psychosocial impacts of raising a child with IH that negatively affect their social network, self-esteem, mental health, and aspirations for both themselves and their children. They may also face challenging decisions regarding whether or not to pursue treatment for IH, which may be painful for the child and may not be successful, or whether to opt out of treatment and potentially risk long-term consequences.
- Individuals who have experienced IH and caregivers reported a need for additional therapies, especially non-surgical options, for the treatment of IH. They indicated that an orally administered treatment for IH would be beneficial, particularly if it can reduce the need for invasive procedures such as surgery or laser treatment.

Clinical Trials

The CDR systematic review included one adaptive, phase II/III, randomized, double-blind, placebo-controlled trial conducted to evaluate the efficacy and safety of propranolol oral solution in patients with IH requiring systemic therapy (N = 460). The inclusion criteria for Study 201 specified that patients were required to have proliferating IH requiring systemic therapy; however, those with the more severe forms of IH (i.e., life-threatening, function-threatening, and/or severely ulcerated) were excluded. Study 201 consisted of a 24-week active treatment phase, followed by an open-label follow-up period of up to 72 weeks. Patients were randomized 1:2:2:2:2 to receive placebo or propranolol at one of the following doses: 1 mg/kg/day for three months; 1 mg/kg/day for six months; 3 mg/kg/day for three months; or 3 mg/kg/day for six months.

Study 201 used the following adaptive trial design: stage 1 was conducted to identify the dose and duration of propranolol treatment using an interim analysis conducted on the first 190 randomized patients and stage 2 was conducted to compare the selected dosage regimen(s) of propranolol against placebo at 24 weeks. Based on the stage 1 interim analysis, an independent data monitoring committee selected one dosage regimen for the final analysis (i.e., 3 mg/kg/day for six months). This dosage is reflective of the Health Canada–approved dosage regimen for oral propranolol solution and is the focus of the CDR review report.

Outcomes

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

- Complete/nearly complete resolution at 24 weeks was evaluated by centralized reviewers (primary end point) and by the on-site study investigators (secondary end point). Complete resolution was undefined in the study protocol and nearly complete resolution was defined as a minimal degree of telangiectasia, erythema, skin thickening, soft tissue swelling, and/or distortion of anatomical landmarks. The definition of nearly complete resolution was expanded beyond the visual assessment to include a minimal palpable component for the on-site evaluations.
- Complete resolution at 48 weeks was evaluated by the on-site study investigators and was defined as complete resolution of the target hemangioma with no sequelae or with minimal sequelae (i.e., minimal telangiectasis, macular discoloration, and/or textural change).
- Target IH evolution was evaluated by the central reviewers, on-site study investigators, and caregivers. The evaluation was conducted relative to the previous study visit using the following three-point scale: improvement, stabilization, or worsening. Criteria for concluding that the target IH had shown improvement, stabilization, or worsening were not provided in the study protocol and were assigned based on the judgment of the assessor.
- Time to first sustained improvement was defined as the interval between randomization and the time point where the target IH demonstrated consistent improvement. The proportion of patients with sustained improvement at each time point was reported using Kaplan–Meier estimates.
- Changes in the size and colour of the target hemangioma were assessed by the central reviewers.
- On-site investigators documented the following complications related to the target IH: functional impairment, ulceration, or hemorrhaging.

Efficacy

- When complete or nearly complete resolution was evaluated by the centralized reviewers, a statistically significantly greater proportion of propranolol-treated patients demonstrated complete or nearly complete resolution compared with placebo-treated patients (61/101 [60.4%] versus 2/55 [3.6%]; $P < 0.0001$).
- Subgroup analyses based on age (35 to 90 days or more than 90 days) and IH location (facial or non-facial) demonstrated results that were similar to the primary analysis:
  - Age 35 to 90 days: propranolol (67.6% [25/37]) versus placebo (10.0% [2/20])
  - Age > 90 days: propranolol (56.3% [36/64]) versus placebo (0.0% [0/35])
  - Facial IH: propranolol (60.6% [43/71]) versus placebo (5.0% [2/40])
  - Non-facial IH: propranolol (60.0% [18/30]) versus placebo (0.0% [0/15]).
- When complete or nearly complete resolution was evaluated by the on-site study investigators, there was no statistically significant difference between the propranolol and placebo groups (24/90 [26.7%] versus 2/19 [10.5%]; $P = 0.4419$).
- There was no statistically significant difference between the propranolol and placebo groups with respect to the proportion of patients with investigator-determined complete resolution at week 48 (7.9% versus 1.8%; $P = 0.4876$).
- Using the centralized evaluations, 72.7% of propranolol-treated patients had demonstrated sustained improvement compared with 5.4% of the placebo group after five weeks. At the final week 24 evaluation, 79.5% of patients in the propranolol group and 9.0% of patients in

the placebo group were estimated to have had a sustained improvement. The results from the on-site assessments were similar to the centralized assessment for propranolol (i.e., 70.9% at week 5 and 82.5% at week 24), but were considerably higher than the centralized assessment for the placebo group (i.e., 20.1% at week 5 and 32.4% at week 24). The difference in the proportion of patients with sustained improvement between propranolol and placebo was statistically significant for both the centralized and on-site assessments (both $P < 0.0001$).

- Compared with the placebo-treated patients, the propranolol-treated patients demonstrated a statistically significant reduction in the surface area of the target IH at week 12 ($P = 0.0001$) and week 24 ($P = 0.0093$).
- The propranolol group also demonstrated statistically significant reductions in the colour density of the target IH compared with placebo at both 12 and 24 weeks (both $P < 0.0001$). There were no statistically significant differences between the propranolol and placebo groups for changes in the maximum diameter of the target IH.
- Functional impairment, ulceration, and invasive procedures were rare in Study 201. There were no invasive procedures conducted on any target IH in either treatment group during the 24-week study period.
- In the open-label extension phase of Study 201, 11.5% (7/61) of patients who had achieved treatment success at 24 weeks with propranolol experienced regrowth that required additional treatment (5/7 of these patients achieved complete/near complete resolution by week 96).

Harms (Safety and Tolerability)

Mean exposure to the study treatments was much greater in the propranolol group compared with the placebo group (160.97 days versus 82.60 days). Due to this marked difference in exposure, any comparisons regarding the frequency of adverse events between the active and placebo groups should be interpreted with caution.

- The overall proportion of patients who experienced at least one treatment-emergent adverse event was greater in the propranolol group compared with the placebo group at 24 weeks (96.0% versus 76.4%, respectively). Nasopharyngitis, diarrhea, pyrexia, teething, bronchitis, upper respiratory tract infection, cough, vomiting, and gastroenteritis were reported in at least 10% of propranolol-treated patients.
- The proportion of patients who experienced at least one serious adverse event was similar in the propranolol and placebo groups (5.9% versus 5.5%, respectively). “Condition aggravated” (two placebo-treated patients) and “drug ineffective” (one patient in each group) were the only serious adverse events that were reported for more than one patient.
- Withdrawals due to adverse events were more commonly reported in the placebo group (10.9%) compared with the propranolol group (3.0%). Similar to the evaluation of serious adverse events, “drug ineffective” was noted as a reason for discontinuation for one patient in both the propranolol and placebo groups; “condition aggravated” was cited as a reason for discontinuation for two placebo-treated patients. Bronchiolitis and bronchitis were cited as reasons for discontinuation for one patient in the propranolol group.
- Hypoglycemia was reported in one patient from the propranolol group (the event was not severe and did not result in discontinuation) and no patients in the placebo group.
- Hypotension was reported for one patient in the placebo group and no patients in the propranolol group.
- There were no events of bradycardia reported in either the propranolol or placebo groups.

- Three patients treated with propranolol experienced at least one event potentially linked with bronchospasm compared with one patient in the placebo group.

Cost and Cost-Effectiveness

Propranolol oral solution is available at a strength of 3.75 mg/mL, dispensed in a 120 mL bottle at a price of $273.70 per bottle.

The manufacturer submitted a cost-utility analysis comparing propranolol oral solution with the "wait and see" approach (no treatment) in infants with proliferating IH requiring systemic therapy, during a 10-year time horizon. The model assessed patient evolution over three "phases" based on age: active treatment (up to 1 year of age), spontaneous involution (from age 1 year to 5 years), and post involution (from age 6 years to 10 years). Three Markov health states were used within each of the phases (success, no success, and death). Patients entered the model at three months of age and received treatment for 6 months. Treatment success was defined as complete or near complete resolution of lesions. The model cycle length varied from every three months in the first year and then annually thereafter. The manufacturer's incremental cost-utility ratio (ICUR) for propranolol oral solution was $26,203 per additional quality-adjusted life-year (QALY) when compared with "wait and see."

The primary limitation identified by CDR was the comparator in the economic analysis. Feedback from clinical experts consulted by CADTH for this review indicated that compounded propranolol is currently the first-line treatment for patients with IH in Canada. The comparative cost-effectiveness of propranolol oral solution and compounded propranolol could not be assessed due to a lack of evidence. The relative cost of propranolol oral solution ($273.70 per 120 mL bottle, 450 mg) is substantively greater than the cost of 450 mg of compounded oral propranolol of the same strength ($1.21, exclusive of the cost for the compounding act at the pharmacy, estimated between $9.71 and $30).

Where "wait and see" is considered an appropriate comparator, CDR identified several limitations and sources of uncertainty with the manufacturer's analysis: the modelled patient population did not consider the full range of patients eligible for treatment; the magnitude of treatment effect differed markedly based on the two different assessments (review of photographs or investigator visual assessment) in Study 201; the duration of treatment may have been underestimated; and, the utility value associated with success was overestimated. The CDR re-analysis resulted in ICURs ranging from $113,000 per QALY to $399,000 per QALY depending on the determination of treatment response (review of photographs or investigator visual assessment). Based on this, a price reduction of between 56% and 90% is required for the ICUR to decrease to $50,000 per QALY.

Research Gaps:

CDEC noted that there is limited evidence regarding the following:

- The pharmacoeconomic evaluation submitted by the manufacturer did not include two of the three subpopulations of patients eligible to receive propranolol oral solution based on the Health Canada–approved product monograph (i.e., patients with life-threatening or function-threatening hemangiomas; or ulcerated hemangiomas with pain and/or lack of response to simple wound care measures), and CDR could not perform this evaluation due to a lack of data. Therefore, the cost-effectiveness of propranolol oral solution in these patients is unknown.

- The optimal duration of therapy with propranolol oral solution in routine clinical practice requires further evaluation.

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

January 18, 2017 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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