Common Drug Review
Pharmacoeconomic Review Report

March 2017

Drug	Propranolol hydrochloride (Hemangiol)
Indication	For the treatment of proliferating infantile hemangioma requiring systemic therapy: • Life- or function-threatening hemangioma • Ulcerated hemangioma with pain and/or lack of response to simple wound care measures • Hemangioma with a risk of permanent scarring or disfigurement
Reimbursement request	As per indication
Dosage form(s)	Oral solution, 3.75 mg/mL
NOC date	September 23, 2016
Manufacturer	Pierre Fabre Dermo-Cosmétique Canada Inc.

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ABBREVIATIONS

CDR	CADTH Common Drug Review
CUA	cost-utility analysis
DSA	deterministic sensitivity analysis
ICUR	incremental cost-utility ratio
IH	infantile hemangioma
HAS	Haute Autorité de Santé
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Propranolol (Hemangiol) oral solution, 3.75mg/mL
Study Question	"To assess, from a provincial Ministry of Health (MoH) perspective, the cost-effectiveness of Hemangiol 3 mg/kg monotherapy (administered into 2 separate doses of 1.5 mg/kg) compared to placebo (wait and see approach) for the management of IH."
Type of Economic Evaluation	Cost-utility analysis
Target Population	The economic analysis assessed the population of patients included in the pivotal clinical trial (Study 201), in which treatment was initiated in infants with IH aged five weeks to five months who fulfilled the inclusion criteria of the trial. During this trial, treatment was continued for 6 months if improvement was seen at 2 months. Treatment was not used beyond 1 year of age.
Treatment	Propranolol 3 mg/kg monotherapy (administered into 2 separate doses of 1.5 mg/kg) daily (referred to as propranolol oral solution)
Outcome	Quality-adjusted life-years
Comparator	"Wait and see" approach (based on placebo arm of clinical trial)
Perspective	Canadian provincial Ministry of Health
Time Horizon	10 years
Results for Manufacturer's Base Case	Deterministic ICUR = $26,203 per QALY Probabilistic ICUR = $25,573 per QALY (1,000 simulations)
Key Limitations	The primary limitation identified by CDR was that compounded oral propranolol was not considered as a comparator, which represents the current Canadian standard treatment for patients with IH. For the submitted cost-utility analysis comparing propranolol oral solution to the "wait and see" approach, CDR noted the following key limitations: • The modelled patient population was based on a clinical trial (Study 201) that did not include patients with life-threatening or function-threatening disease, or patients with ulcerated hemangioma; thus, it is not representative of the full Health Canada–approved product monograph indication. This limits the relevance of the model results. • The modelled duration of initial treatment was shorter than what is expected in clinical practice, which favours propranolol oral solution. The CDR analysis extended treatment duration from 6 to 9 months. • There is uncertainty of the magnitude of effect based on the clinical trial results, which indicated substantial differences in treatment "success" (complete or nearly complete lesion resolution) based on differential assessments. The choice of clinical data by the manufacturer (central assessment by photographs) upholds the internal validity of the study results and favours propranolol oral solution, compared with the on-site investigator assessments, which may have more external validity. CDR conducted scenario analyses using the each of these assessments. • The assumption that treatment success results in a utility value of 1 is unrealistic and favours propranolol oral solution. The Canadian literature suggests 0.95, which was used by CDR.
CDR Estimates and Conclusions	When comparing the cost of propranolol oral solution with compounded oral propranolol (currently used in most jurisdictions) on a per milligram basis, the cost of compounded oral propranolol is less than 1% of the cost of propranolol oral solution ($0.0027 per mg vs $0.6082 per mg). When

[redacted]	considering the application of compounding fees for the compounded product, the cost of 450 mg compounded propranolol is 3% to 11% of the cost of propranolol oral solution ($9.71 to $30 vs. $273.70 per 450 mg). CDR did not identify any comparative analyses assessing propranolol oral solution and compounded oral propranolol, thus the comparative effectiveness is unknown. The Health Canada Reviewer's report for propranolol oral solution noted there is a need for safe, effective treatments that are of consistent and high quality for IHs requiring systemic therapy, and the submitted form of propranolol complies with ICH recommendations. CDR reanalyses comparing propranolol oral solution and the "wait and see" approach resulted in ICURs ranging from $113,000 per QALY to $399,000 per QALY. The relevance of the "wait and see" approach as an appropriate comparator renders the results of limited applicability where compounded propranolol represents current standard of care.

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IH = infantile hemangioma; QALY = quality-adjusted life-year.

EXECUTIVE SUMMARY

Background

Propranolol hydrochloride is a beta-blocker in clinical use since the 1960s that is indicated for several cardiovascular indications, such as hypertension, angina, and arrhythmia, as well as for the prophylaxis of migraines.[1,2] The submitted formulation of propranolol hydrochloride (Hemangiol) was developed specifically as an oral solution for pediatric use, and approved by Health Canada for the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy in patients who have: a life- or function-threatening hemangioma; an ulcerated hemangioma with pain and/or lack of response to simple wound care measures; or a hemangioma with a risk of disfigurement.[1,3] The product monograph states that treatment is to be initiated in infants aged five weeks to five months and the recommended treatment duration is six months, although treatment should be discontinued if no improvement is seen within the first two months.[3]

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.[1,3,4]

The manufacturer undertook a cost-utility analysis (CUA) from the perspective of a Canadian provincial Ministry of Health to determine the cost-effectiveness of propranolol oral solution compared with the "wait and see" approach (no treatment) in infants aged five weeks to five months who are eligible for the treatment of proliferating IH requiring systemic therapy, over a 10-year time horizon.

The manufacturer assessed treatments over three "phases" based on age (active treatment, spontaneous involution, and post-involution), and three Markov health states within each of the phases (success, no success, death). Patients entered the model at three months of age, from which time they received treatment for six months with propranolol oral solution or the "wait and see" approach, and were either deemed to experience "success" or "no success" (based on complete or nearly complete resolution of lesions), or discontinued from treatment, based on data from Study 201.[4,5] From age 1 through age 5 (spontaneous involution phase), patients were able to achieve resolution while not receiving active treatment.[4,6,7] From age 6 through age 10 (post-involution phase), patients could only achieve resolution through active treatment via surgical procedure or laser therapy.[4,6,7] During the first year of the model, patients transitioned between health states every three months. After the age of 1 year, patients transitioned between health states on an annual basis. An annual mortality rate (general mortality) was applied based on data from Statistics Canada.[8] As utility values for this population were not available, published data from a different patient population[9] and assumptions were used.[4]

The manufacturer reported an incremental cost-utility ratio (ICUR) of $26,203 per additional quality-adjusted life-year (QALY) gained for propranolol oral solution compared with the "wait and see" approach based on the deterministic analysis.

Summary of Identified Limitations and Key Results

The main limitation of the health economic submission is the choice of comparator, the "wait and see" approach. Feedback from Canadian clinical experts and published literature[10-12] indicated that compounded propranolol is currently the preferred first-line treatment in patients with IH in Canada, and feedback from plans participating in the CADTH Common Drug Review (CDR) process indicated that this treatment is widely available and reimbursed for this use. No evidence regarding the comparative efficacy of propranolol oral solution and compounded propranolol was provided by the manufacturer,

and CDR did not identify any published analyses comparing these treatments. Therefore, the comparative cost-effectiveness of propranolol oral solution and compounded propranolol could not be assessed. 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 propranolol of the same strength ($1.21, exclusive of the compounding fees). Feedback from the clinical experts consulted by CADTH noted that the concentration of the compounded suspension may vary between different pharmacies.

Where "wait and see" is considered an appropriate comparator, CDR identified the following key limitations with the manufacturer's submitted model. The modelled patient population from Study 201 did not include two of the three subpopulations of patients eligible to receive propranolol oral solution based on the Health Canada–approved product monograph (patients with life-threatening or function-threatening hemangiomas, or ulcerated hemangiomas with pain and/or lack of response to simple wound care measures). The duration of treatment and magnitude of effect were associated with substantial uncertainty based on the differential assessments in Study 201 and feedback from Canadian clinical experts. Finally, the utility value applied to treatment success biased the analysis in favour of propranolol oral solution. CDR reanalysis resulted in ICURs from $113,000 per QALY to $399,000 per QALY.

Conclusions

Published literature and input from Canadian clinical experts indicated that the current preferred first-line treatment for patients with IH in Canada is compounded propranolol tablets. The availability of this treatment is widespread across Canada. There is no comparative evidence assessing the comparative efficacy and safety of propranolol oral solution (Hemangiol) versus compounded propranolol. Although the Health Canada Reviewer's report indicates there is a need for a safe, effective, consistent, and high-quality treatment for IHs requiring systemic therapy, CDR notes there is a substantial incremental cost for the submitted propranolol oral solution (Hemangiol; $273.70 per 120 mL bottle, 450 mg) compared with the cost of the same strength of oral propranolol tablets alone (450 mg, $1.2084), and including excipient and compounding fees ($9.71 to ~$30 per 450 mg).

In the unlikely event that "wait and see" is determined to be an appropriate comparator, the ICUR for propranolol oral solution is high and uncertain ($113,000 per QALY to $399,000 per QALY).

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer undertook a cost-utility analysis (CUA) to determine the cost-effectiveness of propranolol oral solution compared with the "wait and see" approach (no treatment) in infants aged five weeks to five months who are eligible for the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy, based on the Health Canada–approved product monograph.[3,4] The manufacturer noted that although other treatments for IH were available, including propranolol tablets compounded to form an oral solution, and corticosteroids, these treatments are used off-label and thus were deemed not applicable to the submitted application.[4]

The manufacturer's CUA was undertaken from the perspective of a Canadian provincial Ministry of Health, and followed patients up to 10 years of age; the manufacturer indicated that interventions for the removal of residual lesions are rarely performed after 10 years of age.[4] A discount rate of 5% was applied to both costs and benefits. The characteristics for the population were based on data from Study 201, which may best reflect the subpopulation at risk of scarring or disfigurement (the study excluded patients with life- or function-threatening hemangiomas and ulcerated hemangiomas).[5,13]

The manufacturer assessed the treatments over three phases (active treatment, spontaneous involution, and post-involution) based on age, and included three Markov health states within each phase (success, no success, death). The model structure appears to have been based on a model previously published by El Hachem et al.[14] Patients enter the model at three months of age, at which time they receive treatment for six months with propranolol oral solution or the "wait and see" approach. During the six months of treatment, patients could either achieve "success" or "no success" (success being complete or nearly complete resolution of lesions, as defined in Study 201),[5] or discontinue treatment (the proportion of "dropouts" during Study 201). Approximately 11% of patients experienced regrowth of IH after initial success, according to clinical expert input and Pierre Fabre data on file.[4] These patients received an additional six months of treatment and it was assumed all patients achieved successful resolution of lesions upon this second round of treatment. Regrowth and retreatment was assumed to occur straight after the initial six months of treatment (at nine months in the model); costs associated with this retreatment were born between months 9 and 12 in the model.[4] In the model, patients did not receive treatment with propranolol oral solution after turning 1 year old.

From age 1 year through age 5 years (spontaneous involution phase), patients could achieve resolution while not receiving active treatment (proportions were taken from published literature[6,7]), or from non-drug interventions (surgery or laser therapy) as per clinical expert input.[4] From age 6 through age 10 (post-involution phase), patients could only achieve resolution through active treatment via a surgical procedure or laser therapy. Data for the proportion of use of surgery or laser therapy were sourced from published literature assumed to be representative and applied to the model.[6,7]

During the first year of the model, patients cycled in the model every three months. After the age of 1, patients cycled annually. An annual mortality rate (general mortality) was applied to the model using data from Statistics Canada.[8] No utility values for health states associated with IH have been published. The manufacturer assumed successful treatment led to a utility value of 1, and no success led to a utility of 0.92 based on a published utility value for acne.[9] The assumption was made that a utility impact could

not occur until a child had reached 5 years of age. Drug costs were provided by the manufacturer, while event and health state costs and resource use were based on a variety of published Canadian sources and clinical expert inputs.[4,15-18]

2. MANUFACTURER'S BASE CASE

In the manufacturer's base case, propranolol oral solution was associated with an additional 0.0925 quality-adjusted life-years (QALYs) at an additional cost of $2,424 compared with the "wait and see" approach, over the 10-year time horizon. This resulted in a deterministic incremental cost-utility ratio (ICUR) of $26,203 per additional QALY gained for propranolol oral solution compared with the "wait and see" approach (Table 2). The small incremental benefit was from the assumed difference in utility values based on treatment success, applied from age 5 years to 10 years, occurring approximately four years after treatment. Drug treatment cost made up 66% of the total costs for propranolol and 0% for the comparator. The costs associated with "wait and see" were associated with physician visits and lesion removal.

TABLE 2: SUMMARY RESULTS OF THE MANUFACTURER'S BASE CASE

	Total costs ($)	Incremental cost of propranolol ($)	Total QALYs	Incremental QALYs of propranolol	Incremental cost per QALY
"Wait and see"	1,425		7.947		
Propranolol	3,848	2,424	8.039	0.0925	$26,203

QALY = quality-adjusted life-year.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer tested the robustness of the model through both deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). The one-way DSAs tested inputs such as health state utility values, age at which utility loss is applied, patient weight, time horizon, resource use in each treatment group and model phase, treatment success rate, dropout rates, health state costs, IH regrowth rate and associated costs, and discount rate.

The results indicated that the health state utility values, resource use, age to apply disutility and patient weight had the largest effect on the ICUR (Figure 2).

The probabilistic analysis was run using 1,000 simulations. The mean ICUR was incorrectly calculated by the manufacturer, but when it was corrected, the mean probabilistic ICUR was similar to the deterministic ICUR ($25,573 per QALY), and indicated a 74% probability of an ICUR below $50,000 per QALY.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

CADTH Common Drug Review (CDR) identified the following limitations and sources of uncertainty with the manufacturer's submitted economic analysis.

Incorrect primary comparator

The comparator used in the manufacturer's submission is not the current preferred treatment for patients with IH in Canada. Feedback from clinical experts consulted by CADTH indicated that current standard first-line treatment for patients with IH is compounded propranolol tablets; this is in line with published literature.[10-12] In patients for whom propranolol is contraindicated, corticosteroids may be considered. The "wait and see" approach is not common practice. CDR undertook a cost comparison of propranolol oral solution versus compounded propranolol.

Modelled patient population differs from the indicated patient population

The data used in the model are not from a population representative of the full patient population that will be treated in clinical practice. As noted in the CDR Clinical Report, the manufacturer's pivotal study (Study 201) excluded patients with IH if the lesion was considered life- or function-threatening, and patients with ulcerated IH demonstrating pain and a lack of response to simple wound care measures. These are two of the three patient populations in which propranolol oral solution is indicated for in the Health Canada–approved product monograph. There is uncertainty as to whether the results of Study 201 can be generalized to the full patient population for which the treatment is indicated. CDR was unable to undertake any reanalyses assessing the impact of this limitation.

Uncertainty associated with the magnitude of treatment effect

The magnitude of effect of propranolol oral solution based on the primary end point in the trial ("success," defined as complete or nearly complete resolution of the primary lesion) is uncertain. The success rate reported as the primary end point based on central review of photographs taken has the benefit of internal validity, but is substantially higher than that reported by the on-site investigators in their assessment of resolution (60% versus 27%), which has greater external validity. Based on feedback from the clinical expert consulted by CADTH, a photographic review may also be more reflective of clinical practice. The manufacturer conducted a post hoc analysis to examine the divergent results between the centralized and on-site assessments of complete or nearly complete resolution, and indicated that the differences were due to the application of a more stringent threshold for success by on-site investigators. However, the clinical expert also noted that pediatricians and pediatric dermatologists treating patients with IH consider sustained improvement in patients' lesions to be of primary importance. The proportion of patients reporting sustained improvement was similar between central assessors and on-site investigators (72.7% vs. 70.9% at week 5, and 79.5% versus 82.5% at week 24; see CDR Clinical Report). The CDR base case included two scenarios using alternative success rates: the rate based on the investigator assessments (27%), and the rate based on central review of photographs (60%).

Rate of spontaneous involution is associated with uncertainty

Two publications identified by the manufacturer to determine the proportion of patients who experienced spontaneous involution reported the proportion of patients that still had lesions at the end of follow-up. These estimates differed notably between the two studies (13% and 31%). Additionally, CDR noted that in the identified published CUA, which used a model structure similar to that presented by the manufacturer,[14] the authors reported a probability of spontaneous involution of 50%, based on published evidence[19,20] and a clinical expert opinion. CDR tested each of these rates as one-way sensitivity analyses. However, given the uncertainty associated with all inputs identified by the manufacturer and CDR, and the generally minimal impact on the results of varying the spontaneous involution rate, CDR did not alter the 22% spontaneous involution rate used by the manufacturer in the CDR base case.

Duration of treatment appears to be underestimated

Based on available published evidence,[21,22] feedback from the clinical expert consulted by CADTH and patient group input, it appears that patients are likely to receive treatment for longer than the six months recommended in the product monograph and presented in the manufacturer's economic analysis. If the duration of treatment is longer than six months in clinical practice, the incremental costs compared with no treatment will increase, while any changes to the incremental benefit are uncertain. The CDR base case considered nine months for the original treatment instead of the six months used by the manufacturer. For retreatment, the CDR base case kept the six months of therapy assumed by the manufacturer.

Uncertainty with utility values

Utility values were applied from age 5 onwards in the model. It was assumed that patients who achieve "success" have a utility score of 1 (i.e., perfect health). This is questionable and favours propranolol oral solution versus "wait and see," considering that published literature estimated an average utility score for children aged 8 years and adolescents aged 12 to 16 years of 0.95.[23,24] These studies assessed Canadian patients and though the data collection strategies differed, the results were similar. Additionally, the use of a utility value based on acne for patients without successful treatment of IH is questionable. However, there is no utility value for IH available in the published literature. The CDR base case used the utility score of 0.95 for the success health state.

5. CADTH COMMON DRUG REVIEW REANALYSES

Based on published literature and feedback from Canadian clinical experts, the current preferred treatment for IH is compounded oral propranolol. No comparative clinical evidence was presented by the manufacturer or identified by CDR, thus CDR could not undertake a comparative cost-effectiveness analysis. In lieu of the comparison, CDR considered a cost comparison of the price of propranolol oral solution (450 mg in 120 mL) compared with the price of the same strength of propranolol tablets, both exclusive and inclusive of any other cost considerations. Based on the drug cost alone, the cost of the same strength of propranolol in compounded tablets is less than 1% of the cost of propranolol oral solution ($1.2084 per 450 mg versus $273.70). CDR also considered the comparative costs after including additional costs associated with compounding oral propranolol tablets (i.e., excipient and compounding fees). The costs associated with the compounding process appear to vary notably between jurisdictions ($9.71 to ~$30); however, even when considering compounding costs, the cost of compounded oral propranolol was between 3% and 11% of the cost of propranolol oral solution (refer to APPENDIX 1: COST COMPARISON for details).

In the unlikely event that there is a subpopulation in which "wait and see" is an appropriate comparator, CDR undertook revised analyses based on the manufacturer's submitted economic model comparing propranolol oral solution with "wait and see." The results were presented as two scenario analyses based on different assessments of treatment success:

- Scenario 1: Treatment "success" was based on central assessment from Study 201 (propranolol oral solution = 44.0% success at three months, 60.4% success at six months; "wait and see" approach = 3.6% at both three months and six months)
- Scenario 2: Treatment "success" was based on investigator assessment from Study 201 (propranolol oral solution = 8.2% success at three months and 26.7% success at six months; "wait and see" approach = 4.2% at three months and 10.5% at six months)

TABLE 3: TREATMENT SUCCESS RATES FROM STUDY 201

	Investigator Assessment		Central Assessment	
Time point	**Placebo**	**Propranolol**	**Placebo**	**Propranolol**
Week 12	4.2%	8.2%	3.6%	44.0%
Week 24	10.5%	26.7%	3.6%	60.4%

Source: Study 201, Clinical Study Review, Tables 21, 150 and 153.[5]

The following model components were varied in both scenario analyses:

- Application of success rates from three months after treatment initiation
- The "success" health state utility was set at 0.95
- The rate of spontaneous involution was set at 31%
- Patients were assumed to receive nine months of original treatment with propranolol oral solution.

The results of varying individually the features of the manufacturer base case for developing the CDR base case and additional reanalyses are presented in Table 16 of Appendix V.

TABLE 4: CDR BASE CASE

Analysis	Incremental Cost	Incremental QALY	ICUR (per QALY)
Manufacturer base case			
Deterministic	$2,424	0.0925	$26,203
Probabilistic (1,000 simulations)	$2,409	0.0903	$25,573
CDR base case, scenario 1: treatment success based on central assessment			
Deterministic	$3,934	0.0347	$113,419
Probabilistic (5,000 simulations)	$3,893	0.0352	$110,466
CDR base case, scenario 2: treatment success based on investigator assessment			
Deterministic	$3,955	0.0099	$399,131
Probabilistic (5,000 simulations)	$3,897	0.0093	$420,714

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

There were several areas of uncertainty that CDR was unable to address, given the available information and model structure, and the results remain uncertain.

CDR undertook price-reduction analyses on the CDR base case for scenarios 1 and 2 (Table 5). For scenario 1, a price reduction of at least 56% is required for propranolol oral solution to achieve an ICUR of $50,000 per QALY. For scenario 2, a price reduction of at least 90% is required for propranolol oral solution to achieve an ICUR of $50,000 per QALY.

TABLE 5: CDR PRICE-REDUCTION ANALYSES

Price Reduction	Manufacturer Base Case	CDR Scenario 1	CDR Scenario 2
Base price ($273.70)	**$23,203 / QALY**	**$113,419 / QALY**	**$399,131 / QALY**
10% reduction ($246.33)	$23,553 / QALY	$101,998 / QALY	$360,324 / QALY
20% reduction ($218.96)	$20,903 / QALY	$90,576 / QALY	$321,517 / QALY
30% reduction ($191.59)	$18,253 / QALY	$79,154 / QALY	$282,709 / QALY
40% reduction ($164.22)	$15,602 / QALY	$67,733 / QALY	$243,902 / QALY
50% reduction ($136.85)	$12,952 / QALY	$56,311 / QALY	$205,095 / QALY
60% reduction ($109.48)	$10,302 / QALY	$44,890 / QALY	$166,287 / QALY
70% reduction ($82.11)	$7,652 / QALY	$33,468 / QALY	$127,480 / QALY
80% reduction ($54.74)	$5,002 / QALY	$22,046 / QALY	$88,672 / QALY
90% reduction ($27.37)	$2,351 / QALY	$10,625 / QALY	$49,865 / QALY

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year.

6. ISSUES FOR CONSIDERATION

Oral propranolol is generally considered the preferred first-line treatment for IH requiring systemic therapy in Canada.[10-12] Prior to the approval of Hemangiol in Canada, oral propranolol solution 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. Health Canada reviewers, in their review of Hemangiol, noted that there is currently a need for treatment options that are safe, effective, and of consistent and high quality for IHs requiring systemic therapy.[25] Clinical experts consulted by CADTH indicated that the concentration of oral propranolol suspensions may vary between different pharmacies. The submitted propranolol oral solution is specifically formulated for pediatric use in compliance with the ICH recommendations (e.g., volume of administration less than 5 mL and the use of a selected sweetener).[25]

If a stopping rule is considered for treatment with propranolol oral solution, there is some uncertainty as to what measure is considered to be most relevant in clinical practice. The product monograph indicates that treatment should be stopped at six months, but in patients that continue to see sustained improvement and who have not yet achieved complete or nearly complete resolution, treatment is likely to be continued over a longer duration. Additionally, if no improvement is seen within the first two months, the product monograph recommends that treatment be discontinued.

7. PATIENT GROUP INPUT

Input was received from one patient group, AboutFace. The group indicated that patients may experience permanent sequelaes and deformity from hemangiomas. Additionally, laser treatment and invasive surgery were reported to be painful, may result in scarring, and may not work, leading to additional treatment and procedures. These issues may not be as serious in children, but in adults, they can lead to social problems, anxiety disorders, depression, and substance abuse, significantly affecting quality of life. The manufacturer's model does not assess the downstream impact of treatment and treatment outcomes in patients older than 10 years of age, which is a conservative approach not favouring Hemangiol when compared with the "wait and see" approach.

8. CONCLUSIONS

Published literature and input from Canadian clinical experts indicated that the current preferred first-line treatment for patients with IH in Canada is compounded propranolol tablets. The availability of this treatment is widespread across Canada. There is no comparative evidence assessing the comparative efficacy and safety of propranolol oral solution (Hemangiol) versus compounded propranolol. Although the Health Canada review indicates there is a need for a safe, effective, consistent, and high-quality treatment for IHs requiring systemic therapy, CDR notes there is a substantial incremental cost for the submitted propranolol oral solution (Hemangiol; $273.70 per 120 mL bottle, 450 mg) compared with the cost of the same strength of oral propranolol tablets alone (450 mg, $1.2084), and including excipient and compounding fees ($9.71 to ~$30 per 450 mg).

In the unlikely event that "wait and see" is determined to be an appropriate comparator, the ICUR for propranolol oral solution is high and uncertain ($113,000 per QALY to $399,000 per QALY).

APPENDIX 1: COST COMPARISON

The comparators presented in Table 6 are based on current Canadian practice. Existing Product Listing Agreements are not reflected in the table and as such it may not represent the actual costs to public drug plans. The cost table does not consider provincial dispensing fees or pharmacy mark-up fees.

TABLE 6: COST COMPARISON TABLE FOR THE TREATMENT OF INFANTILE HEMANGIOMA

Comparators	Strength	Dose Form	Price ($)	Recommended Dose[a]	Daily Drug Cost ($)
propranolol oral solution (Hemangiol)	**3.75 mg/mL, 120 mL (450 mg)**	**Bottle of oral solution**	**273.7000[b]**	**Week 1: 0.5 mg/kg twice daily; Week 2: 1 mg/kg twice daily; Week 3 onwards: 1.5 mg/kg twice daily.**	**Initial: $4.87 to $9.73 Maintenance: $14.60**
Off-label treatments used for the treatment of IH: first line					
Propranolol tablets (excluding compounding fees)	10 mg 20 mg 40 mg 80 mg	Tablet	0.0689 0.1107 0.1225 0.2034	Compounded as 450 mg of propranolol in 120 mL excipient; dose assumed the same as Hemangiol[c]	Initial: $0.02 to $0.04 Maintenance: $0.06
Propranolol tablets (including compounding fees)	10 mg 20 mg 40 mg 80 mg	Tablet	0.0689 0.1107 0.1225 0.2034	Compounded as 450 mg of propranolol in 120 mL excipient; dose assumed the same as Hemangiol[c]	Initial: $0.17 to $1.06[d] Maintenance: $0.52 to $1.59[d]
Off-label treatments used for the treatment of IH: second line (or where propranolol is contraindicated)					
Prednisolone (Pediapred)	5 mg/5 mL, 120 mL	Bottle	16.116	May vary from 5 mg to 60 mg, once daily	$0.67 to $8.06
Prednisolone (pharmascience brand)	5 mg/5 mL, 120 mL	Bottle	8.112	May vary from 5 mg to 60 mg, once daily	$0.34 to $4.06

Note: Costs were sourced from the Ontario Drug Benefit Formulary (November 2016) unless otherwise indicated.[26]
[a] Assumed weight was 8 kg (mean weight at 6 months based on WHO growth standards).[4]
[b] Price submitted by manufacturer.
[c] Cost of 450 mg compounded propranolol derived from 5 × 80 mg tablets, 1 × 40 mg tablet and 1 × 10 mg tablet ($1.2084). CDR notes that additional costs are relevant to be included in the process of compounded oral propranolol, including cost of excipient and compounding fees. These costs were reported to differ notably, depending on jurisdiction.
[d] Cost was determined by applying the cost of compounding the same amount of compounded propranolol tablet that is in a bottle of propranolol oral solution (450 mg). The cost of tablets and compounding (excluding mark-up and dispensing fee) was determined to range from $9.71 to $29.80, depending on jurisdiction.

CADTH Cost Calculation for Compounded Propranolol

Feedback from participating jurisdictions indicated that the following components would be considered for reimbursement for compounding propranolol tablets, but the values differed between jurisdictions:

- Cost of propranolol tablets
- Cost of excipient
- Compounding fees
- Dispensing fees
- Pharmacy mark-up

For comparison of compounded propranolol and propranolol oral solution, dispensing fees and pharmacy mark-ups were not considered. Hence, using information from Ontario, the total cost of the compounded product was calculated using the following factors:

- The cost of propranolol tablets (450 mg, reported in the CDR Cost Table as $1.2084)
- The cost of the excipient (reported to be negligible; assumed to be $1.00 per 120 mL)
- The compounding cost ($7.50, based on a 15-minute process at $0.50 per minute)

The total cost of the compounded product ($1.2084 + $1.00 + $7.50) is $9.7084.

Other jurisdictions reported that the total average cost of the same amount of compounded oral propranolol may be as high as $30 (including propranolol tablets cost, excipient cost and compounding fees).

Published literature indicates that compounded oral propranolol is stable for up to 120 days,[27] thus there should not be any issues with additional dispensing and compounding fees compared with the submitted propranolol oral solution, which indicates that product should be discarded two months after first opening.[13]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS PROPRANOLOL ORAL SOLUTION RELATIVE TO COMPOUNDED ORAL PROPRANOLOL?

Propranolol vs. "Wait and See" Approach	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical Outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	On a per mg basis, 450 mg of propranolol tablets costs less than 1% of the cost of the submitted propranolol oral solution. 450 mg of compounded oral propranolol (including excipient and compounding fee) is between 3% and 11% of the cost of the submitted propranolol oral solution.					

CE = cost-effectiveness; NA = not applicable.
Note: Based on the CDR base case. Assumes equivalent efficacy and safety of the two treatments.

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS PROPRANOLOL ORAL SOLUTION RELATIVE TO THE "WAIT AND SEE" APPROACH?

Propranolol vs. "Wait and See" Approach	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical Outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Scenario 1: $113,419 per QALY Scenario 2: $399,131 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
Note: Based on the CDR base case.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 9: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	The manufacturer's PE report did lack some details to fully understand the method of the analysis, such as the description of the involution phase, and what occurs between end of active treatment (9 months) and the start of the involution phase (1 year). Some aspects of the model lack flexibility.		
Was the material included (content) sufficient?	X		
Comments			
Was the submission well organized and was information easy to locate?		X	
Comments	The calculation of the ICUR from the PSA simulations was performed incorrectly.		

ICUR = incremental cost-utility ratio; PE = pharmacoeconomic; PSA = probabilistic sensitivity analysis.

TABLE 10. AUTHORS INFORMATION

AUTHORS OF THE PHARMACOECONOMIC EVALUATION SUBMITTED TO CDR			
☐ Adaptation of Global model/Canadian model done by the manufacturer ☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors included a statement indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: SUMMARY OF OTHER HTA REVIEWS OF DRUG

Propranolol oral solution (Hemangiol) has been reviewed twice by Australia's Pharmaceutical Benefits Advisory Committee (PBAC), and by France's Haute Autorité de Santé (HAS) for the treatment of infantile hemangiomas. The submissions to the PBAC are summarized in Table 11.

HAS recommended that propranolol oral solution be reimbursed, as it is associated with moderate improvement in actual benefit in the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy. The committee requested the manufacturer provide in the future a prescription data analysis assessing the characteristics of patients treated with propranolol oral solution as well as other treatment data. HAS recommended that the reimbursement rate for propranolol oral solution be set at 65%.[28]

TABLE 11: OTHER HTA FINDINGS

	PBAC March 2015[29]	PBAC November 2015[30]
Treatment	Propranolol oral liquid (Hemangiol) 3.75 mg/mL	
Indication/request	An "Authority Required" listing was requested for the treatment of proliferating IH requiring systemic therapy. Proposed limiting prescription to physicians with expertise in the diagnosis, treatment and management of IHs.	Request for a higher price than was recommended at the March 2015 PBAC meeting.
Comparator	Placebo was nominated as the appropriate comparator, as compounded propranolol and propranolol solution currently used by hospitals are not registered with the TGA and have not been evaluated by the PBAC.	NA
Price	Drug price was redacted	
Similarities with CDR submission	The manufacturer's clinical submission was based partially on Study 201.	None
Differences with CDR submission	The manufacturer submitted a CCA comparing Hemangiol with current options for accessing compounded propranolol and propranolol solution. The submission explored safety concerns associated with compounding propranolol. An additional study was identified (Hogeling et al. [2011])[31] that assessed another propranolol oral solution for IH.	The manufacturer presented a submission to establish a reference price for Hemangiol based on the cost of compounding propranolol in the community as determined by a survey of pharmacies.
Manufacturer's results	Manufacturer's results were redacted	
Issues noted by the review group	PBAC considered that the currently available propranolol treatments were the most appropriate comparators, and a CMA comparing Hemangiol with these propranolol treatments (solution, compounding, tablets; with accepting a slight price advantage for the liquid form) would have been more appropriate than	The department explored alternative weighting methods that resulted in different pricing to that submitted by the manufacturer.

	PBAC March 2015[29]	PBAC November 2015[30]
	the CCA. PBAC noted that when supplied in hospital, there is no cost to a patient, while the compounded product supplied in the community requires the patient to cover the cost of compounding. PBAC considered that a price advantage for the liquid form was appropriate, but that the magnitude of the submitted price advantage was not adequately justified.	
Results of reanalyses by the review group	All cost information was redacted	All cost information was redacted
Recommendation	PBAC recommended Hemangiol for listing on the PBS. PBAC was satisfied that Hemangiol provides the same benefits as the currently available propranolol alternatives. PBAC considered a supply up to 6 months was appropriate. PBAC considered that the cost of Hemangiol should be compared with the cost of the currently available propranolol oral solution, accepting a modest price premium, and that the submitted price was unacceptably high. PBAC considered there was the potential for off-label use in patients with less-severe, non-fatal hemangiomas.	PBAC rejected the proposed price of Hemangiol and reaffirmed its March 2015 recommendation. PBAC noted the premium factor proposed by the manufacturer was not substantiated, and exclusion of the currently available oral propranolol to be inappropriate.

CCA = cost-consequence analysis; CDR = CADTH Common Drug Review; CMA = cost-minimization analysis; IH = infantile hemangioma; HTA = health technology assessment; NA = not applicable; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; TGA = Therapeutic Goods Administration.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer's cost-utility analysis (CUA) assessed the cost-effectiveness of propranolol oral solution versus the "wait and see" approach for the treatment of proliferating infantile hemangioma (IH). The model compared propranolol versus the "wait and see" approach across three different phases using a Markov approach for two of the three phases, and a decision tree for the other (Figure 1).

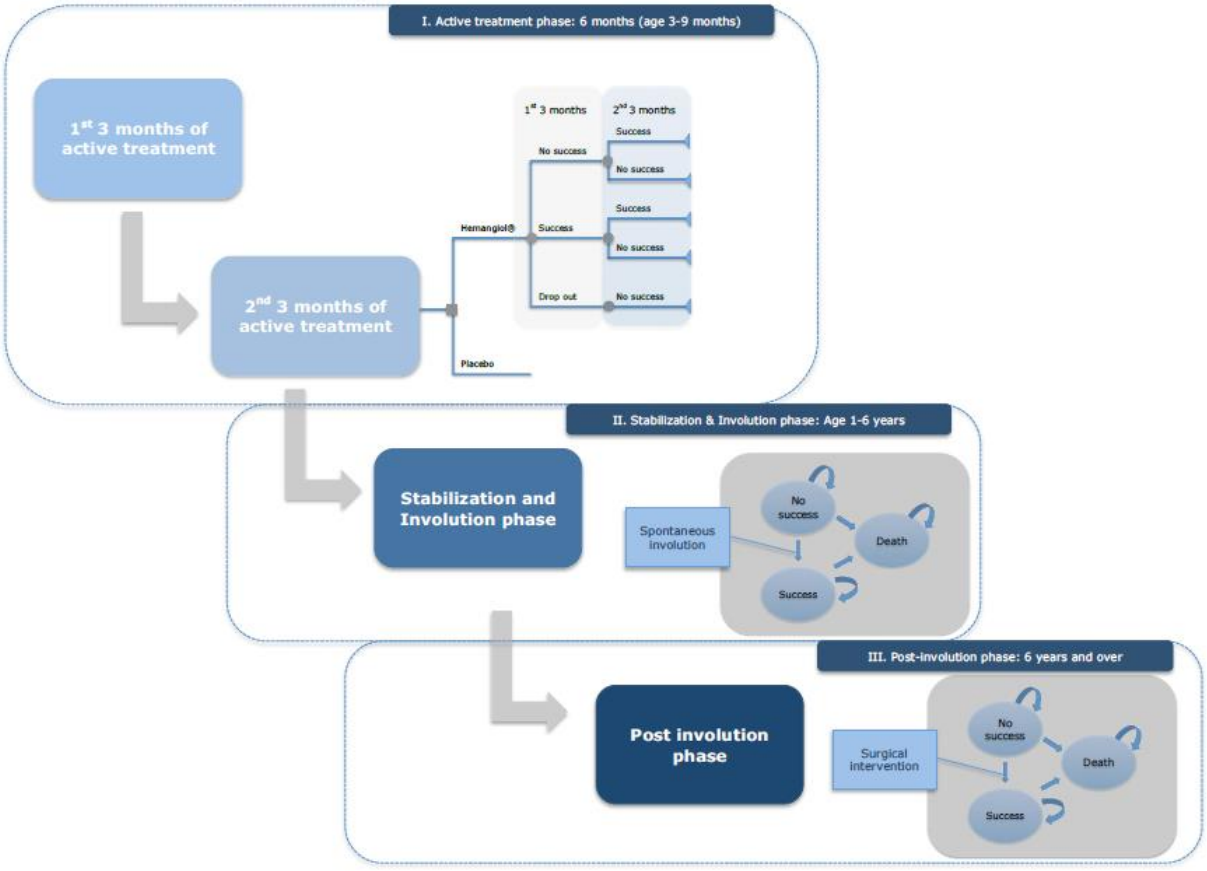
Patients did not receive active treatment with propranolol oral solution after 1 year of age. As propranolol oral solution is a weight-based treatment, the manufacturer based weight on patients in Study 201 and World Health Organization growth charts (Table 12).

TABLE 12: PATIENT WEIGHTS

Descriptor	Weight (kg)
Mean weight at 3 months[a]	6.713
Mean weight at 6 months[b]	8.054
Mean weight at treatment of regrowth[c]	9.198

[a] Calculated as mean of weight at 3 months and 6 months from Study 201.[4]
[b] Calculated as mean of weight at 6 months and 9 months from Study 201.[4]
[c] Calculated as mean of weight at 9 months from Study 201 and 15 months based on the World Health Organization Growth Chart.[4]

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



Note: to clarify, the "stabilization and involution phase" lasts from age 1 year to 5 years inclusive, while the "Post-involution phase" lasts from age 6 years to age 10 years inclusive.
Source: Manufacturer's Pharmacoeconomic Submission.[4]

The information used to populate the model is reported in Table 13, while the key assumptions of the manufacturer's economic analysis are presented in Table 14.

TABLE 13: DATA SOURCES

Data Input	Description of Data Source	Comment
Patient characteristics	Proportion of male/female based on Study 201; patient weight based on Study 201 and WHO growth charts.	Study 201 does not include the full spectrum of patients for whom treatment is indicated in the product monograph (Study 201 excluded patients with life- or function-threatening IH, and patients with severe ulceration; see CDR Clinical Report for further details), which calls into question the generalizability of the results.
Efficacy in phase I (decision tree/ active treatment phase)		
Transition probabilities (success/no success)	Head-to-head study of propranolol and placebo (Study 201).[5]	Population limitation with Study 201 noted above may limit generalizability.

Data Input	Description of Data Source	Comment
Regrowth after initial treatment success	Manufacturer data on file[4] and Canadian expert survey.[4]	Population limitation with Study 201 noted above may limit generalizability. The results of the expert survey indicated wide variance between expert responses. Feedback from a clinical expert consulted by CADTH indicated not all patients with regrowth would be retreated, so this may be a conservative estimate.
Efficacy in phase II (spontaneous involution phase)		
Probability of spontaneous resolution	Reported by age. Stated to be based on a Weibull fit from Couto et al.[6]	Weibull undertaken by manufacturer. Appears reasonable based on K-M curve in Couto. Revised probabilities do not appear to affect the results substantially.
Proportion of patients displaying spontaneous resolution	Values from Couto et al. (2012)[6] and Bauland et al. (2011)[7] were used to determine a mean value for the base case.	Values differed substantially between trials, and are associated with uncertainty as the data in the publications do not specifically represent the parameter assessed in the model.
Proportion of patients that undergo surgery or laser treatment	Based on data from a Canadian expert survey.[4]	Likely appropriate, though wide range expected across jurisdictions.
Efficacy in phase III (post-involution phase)		
Proportion of patients that undergo surgery or laser treatment	Proportion of patients with residual lesions from Couto et al. (2012)[6] and Bauland et al. (2011)[7] were used to determine a mean value for the base case. Split of treatment type based on data from a Canadian expert survey.[4]	The values reported in Couto and Bauland appeared to differ notably in terms of expected additional treatment. The median length of follow-up is not reported in the studies, therefore it is uncertain at what point these values are being determined.
Mortality	Statistics Canada (2014). Stratified by sex. Adjusted for baseline characteristics, age progression through model.[8]	Appropriate.
Utilities	Treatment success: Assumption Treatment not successful: Mittman et al. (1999)[9]	There are no published utility values in this population, thus there is substantial uncertainty regarding the appropriateness of the values used in the model.
Resource use	Head-to-head study of propranolol and placebo (Study 201).[5] Pierre Fabre Dermatologie data on file. Data from a Canadian expert survey.[4]	Feedback from the clinical expert consulted by CADTH indicated that some of the physician visit resource use assumptions may have been inaccurate. The proportion of patients requiring the various types of surgeries may also differ across provinces. Revised resource use assumptions do not have a large effect on the model results.
Costs		
Drug	Manufacturer data on file	

Data Input	Description of Data Source	Comment
Health state costs	Ontario Schedule of Benefits for Physician Services (2014)[17] and Ontario Schedule of Benefits, Laboratory Services (1999)[18] Hospital costs from CIHI PCE[15] and OCCI[16]	

CIHI = Canadian Institute for Health Information; IH = infantile hemangioma; K-M = Kaplan–Meier; OCCI = Ontario Case Costing Initiative; PCE = patient cost estimator; WHO = World Health Organization.

TABLE 14: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
The relevant comparator for propranolol oral solution is the "wait and see" approach.	The Health Canada indication states that propranolol oral solution is to be used in patients requiring systemic therapy. The "wait and see" approach, in which patients do not receive active therapy, was chosen by the manufacturer as comparator. However, it does not represent the current standard of care in Canada. Feedback from clinical experts consulted by CADTH suggested that compounded propranolol tablets are currently used as first-line treatment in IH patients, unless they are contraindicated to propranolol.
Modelled population is generalizable to the indicated population.	The population modelled is based on Study 201, which does not align with the patients eligible to receive treatment based on the indication (Study 201 excluded patients with life- or function-threatening IH, and patients with severe ulceration demonstrating pain and a lack of response to simple wound care measures), and thus leads to uncertainty in generalizing the information used in the model to the full indication population.
Age at model entry was assumed to be 3 months.	Although the product monograph indicates that patients with IH should receive initial treatment between 5 weeks and 5 months, the clinical expert consulted by CADTH indicated that patients were more likely to be treated earlier rather than later (around 5 weeks of age), thus starting the model at 3 months may be later than when patients initially receive treatment. If patients start treatment earlier, they are likely to weigh less. Assuming duration of treatment is not extended, the total cost of treatment may be lower than predicted by the model.
Patients receive 6 months of active treatment.	The clinical expert consulted by CADTH indicated that some patients would receive treatment for longer than the 6-month duration prescribed in the product monograph, but that this would be patient dependent. Patients would receive treatment until success was achieved (complete or near complete resolution) or no improvement was seen (based on Study 201 definition, see CDR Clinical Report). Feedback from the patient group indicated that regrowth was seen in some patients who stopped treatment, thus treatment may be use beyond the recommended duration.
All dropouts occur during the first 3 months of treatment, but were considered in the same manner as "no success" in the model.	The manufacturer reported this is consistent with the clinical trial data which indicated that 70% of dropouts occur in the first 12 weeks.[4] As dropouts were considered in the same manner as no success, and patients were assumed to have been dispensed 6 months of drug up front, altering the dropout rate will have minimal effect on the overall results.

Assumption	Comment
A 10-year time horizon is appropriate to capture all costs and benefits associated with IH, as there is no impact on mortality, and interventions for removal of residual lesions are rarely performed after the patient reaches 10 years of age.	Although feedback from the clinical expert consulted by CADTH considered the timelines for resolution of hemangiomas to be appropriate, the model time horizon does not allow consideration of the long-term impact of scarring, which may underestimate the benefit of treatment with propranolol.
Regrowth was assessed as a one-off cost of retreatment at the end of the original treatment period.	The clinical expert consulted by CADTH suggested that regrowth would occur in approximately 10% of patients (manufacturer data indicated 11.5%) with IH over the entire time they had the condition (manufacturer data based on 3 years). Feedback from the clinical expert consulted by CADTH indicated that patients who achieved initial success but experienced regrowth at a later point (e.g., 2 years) would be retreated as if it was the first occurrence of treatment. The increased weight of these patients underestimates costs associated with treatment. CDR accepts that later onset of regrowth is uncommon and hence this is not likely to have a large impact on the model results.
Retreatment duration was 6 months.	Feedback from the clinical expert consulted by CADTH suggested that a patient will be retreated for as long as the drug results in improvement in the patient's lesions. This is consistent with feedback from the patient group.
All patients retreated for regrowth were successful.	This assumption likely overestimates the effect of propranolol oral solution. Limited data were provided to support this assumption.
Patients could receive lesion-removal treatments (i.e., laser or surgery) during phase II (spontaneous involution).	This is likely to be appropriate based on published data; although feedback from the clinical expert consulted by CADTH suggested it was uncommon, the manufacturer's proportion appears appropriate (1.67%).
The involution phase lasts until patient turns 6 years of age.	Published data indicates the involution is completed at a median age of 3.5 to 4 years of age,[6,7] though feedback from the clinical expert consulted by CADTH suggested that spontaneous involution has been document in patients up to 10 years of age.
In phase III, patients could not spontaneously recover; recovery was only due to active treatment.	As noted above, feedback from the clinical expert consulted by CADTH suggested this may not be an accurate assumption.
In phase III, any active treatment would lead to complete success (could not move back to "no success" in a later cycle). Active treatment was surgical resection or laser treatment. Patients in complete success have the same utility and resource consumption as healthy people ("success" state).	This may not be appropriate if the surgery or laser treatment results in scarring. The model does not take this into account, which may underestimate the impact of treatment with propranolol.
Adverse events are not considered in the model.	Based on feedback from the clinical expert consulted by CADTH, there are no important AEs to include in the model given the model structure and comparators.

Assumption	Comment
Patients do not experience a change in utility (quality of life) until aged 5 years.	Feedback from the clinical expert consulted by CADTH indicated that patients would not experience a measurable quality of life impact until between 4 and 6 years of age based on the disease and treatment impact.
Patients who achieve successful resolution of the lesion are in perfect health (utility value of 1).	May overestimate the quality of life of patients, given that published literature on the general population utility value for Canadians aged 8, and 12 to 16 has reported the utility value to be 0.95.[23,24] The result of a "successful" procedural treatment may not be the same as the result of a patient with "success" due to spontaneous involution or non-procedural treatment.
Patients who do not achieve successful resolution of the lesion have a utility value equivalent to patients with acne.	The manufacturer presented other utility values for acne, port wine stains (birthmarks), and atopic dermatitis. Feedback from the clinical expert consulted by CADTH suggested that although none of these accurately capture the impact of having IH, the manufacturer's choice to use a Canadian value for acne was likely appropriate.

AE = adverse event; CDR = CADTH Common Drug Review; IH = infantile hemangioma.

Manufacturer's Results

The manufacturer's economic analysis, which aimed to assess the cost-effectiveness of propranolol compared with the "wait and see" approach, indicated that, based on the deterministic analysis, propranolol was associated with an incremental 0.0925 QALYs at an additional cost of $2,424 over the 10-year time horizon; resulting in an incremental cost-utility ratio (ICUR) of $26,203 per additional QALY gained for propranolol compared with the "wait and see" approach (Table 15). Drug costs made up 66% of the total costs for propranolol and 0% for the comparator arm.

TABLE 15: RESULTS OF THE MANUFACTURER'S BASE CASE

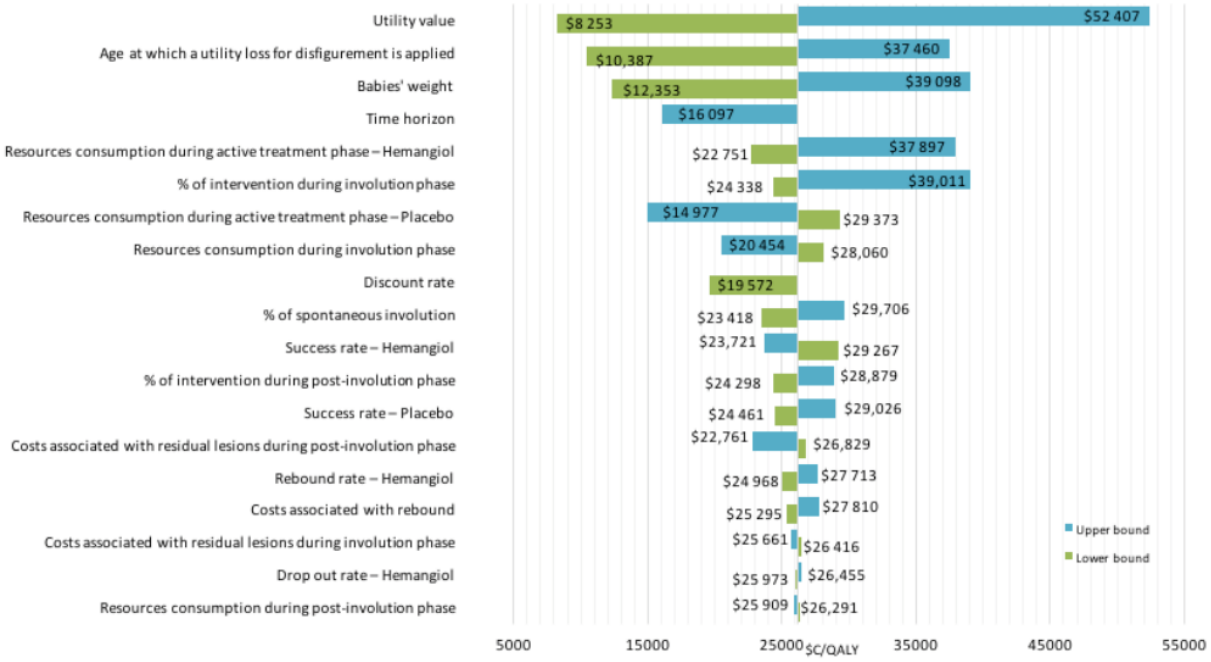
	Total costs ($)	Incremental cost of propranolol ($)	Total QALYs	Incremental QALYs of propranolol	Incremental cost per QALY
"Wait and see"	1,425		7.947		
Propranolol	3,848	2,424	8.039	0.0925	$26,203

QALY = quality-adjusted life-year.

Sensitivity analysis

The manufacturer tested the robustness of the model through both deterministic sensitivity analysis (DSA; Figure 2) and probabilistic sensitivity analysis (PSA).

FIGURE 2: MANUFACTURER'S DETERMINISTIC SENSITIVITY ANALYSIS



$c = cost; QALY = quality-adjusted life-year.
Source: Manufacturer's Pharmacoeconomic Submission.[4]

The manufacturer undertook a PSA using 1,000 simulations. The results of the analysis were presented as a cost-effectiveness acceptability curve, which reported that the likelihood of propranolol being cost-effective compared with the "wait and see" approach at a willingness-to-pay threshold of $50,000 per QALY was approximately 74%.

The manufacturer also presented the results as a cost-effectiveness plane, which reported that in no simulation was propranolol less costly than the "wait and see" approach, and propranolol was at least as effective as the "wait and see" approach in all cases.

CDR tested the stability of the model using 5,000 simulations, which reported a mean ICUR of $25,939 per QALY and a 73% probability of achieving an ICUR of $50,000 per QALY.

CADTH Common Drug Review Reanalyses

The following table shows the results of varying individually the parameters as per the CDR base case, for the comparison of propranolol oral solution versus the "wait and see" approach, using the health economic model submitted by the manufacturer.

TABLE 16: CDR ONE-WAY AND MULTI-WAY DETERMINISTIC REANALYSIS RESULTS

Analysis	Incremental cost	Incremental QALY	ICUR (per QALY)
Manufacturer's base case (deterministic)	**$2,424**	**0.0925**	**$26,203**
Manufacturer's base case (probabilistic, 1,000 simulations)	**$2,409**	**0.0903**	**$25,573**
Revised response rate			
• Response rates revised based on investigator assessment (placebo rate based on week 12 assessment)	$2,424	0.0367	$66,082
• Response rates based on investigator assessment (placebo rate based on week 24 assessment)	$2,455	0.0264	$92,916
• Response rates based on investigator assessment (combined placebo rates)	$2,445	0.0264	$92,520
Utility values			
• Age at which utility values are applied = 4 years	$2,424	0.1251	$19,377
• Age at which utility values are applied = 6 years	$2,424	0.0647	$37,460
• Base utility value = 0.95	$2,424	0.0347	$69,876
Spontaneous involution:			
• Proportion of patients with spontaneous involution (10%)	$2,405	0.1064	$22,612
• Proportion of patients with spontaneous involution (30%)	$2,436	0.0832	$29,273
• Proportion of patients with spontaneous involution (50%)	$2,468	0.0599	$41,183
Treatment duration and retreatment:			
• Additional initial 3 months of treatment	$3,727	0.0925	$40,292
Probabilistic analysis			
• 5,000 simulations	$2,420	0.0933	$25,939

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

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