5.35 PROPRANOLOL oral liquid, 3.75mg/mL; Hemangiol®; Pierre Fabre Australia Pty Ltd

1 Purpose of Application

1.1 The minor submission requested an Authority Required listing for the treatment of proliferating infantile haemangioma requiring systemic therapy.

2 Requested listing

2.1 The submission sought the following new listing. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
PROPRANOLOL 3.75mg/mL oral liquid, 120 mL	2	0	$[redacted]	Hemangiol®	Pierre Fabre

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Proliferating
Condition:	infantile haemangioma
PBS Indication:	Proliferating infantile haemangioma
Treatment phase:	Initial and continuing
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Treatment criteria:	~~Treatment should be initiated by physicians who have expertise in the diagnosis, treatment and management of infantile haemangioma.~~ *Must be treated by a physician with expertise in the diagnosis, treatment and management of infantile haemangioma.*

Clinical criteria:	*The condition must be a* life- or function-threatening haemangioma; OR *The condition must be an u*lcerated haemangioma with pain and/or lack of response to simple wound care measures; OR *The patient must be at* risk of permanent scars or disfigurement. AND *The patient must require systemic therapy*

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

3.1 Propranolol liquid was not listed on the ARTG at the time of PBAC consideration. At the June 2014 Advisory Committee on Prescription Medicines (ACPM) meeting, Hemangiol® was considered to have a negative benefit-risk profile due to the lack of robust, valid and reliable data on safety and efficacy. The Sponsor appealed this decision not to register the product. In November 2014, the Delegate revoked the initial decision and recommended the inclusion of Hemangiol on the ARTG for the following indication:

> Treatment of proliferating infantile hemangioma requiring systemic therapy:
> Life-threatening hemangioma.
> Ulcerated hemangioma with pain and/or lack of response to simple would care measures.
> Hemangiomas with a risk of permanent scars or disfigurement.

3.2 Hemangiol (propranolol liquid) has not previously been considered by the PBAC. Propranolol tablets have an unrestricted listing on the PBS.

4 Clinical place for the proposed therapy

4.1 Infantile haemangiomas are benign vascular tumours diagnosed in infants and are the most common soft-tissue tumours in this population. Most lesions are uncomplicated, however certain haemangiomas are at risk of severe, even life threatening complications.

4.2 The submission stated that there are no uniform formal guidelines for treatment of infantile haemangioma.

4.3 PBS listing of Hemangiol would not change the current treatment algorithm for infantile haemangioma as patients would otherwise continue to be treated with a compounded propranolol solution.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

5.1 The minor submission nominated placebo as the main comparator as compounded propranolol and propranolol solution (supplied by Auspman and distributed in bulk quantities to hospital pharmacies) which are currently used by hospital pharmacies for the treatment of proliferating infantile haemangioma are not TGA registered and have not been evaluated by the PBAC. The Secretariat overview noted that either of these compounded alternatives, or propranolol tablets which are an unrestricted benefit, may be suitable comparators as these are the therapies most likely to be replaced.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission presented details of two randomised controlled trials (201 study and Hogeling 2011) assessing the benefits and harms of propranolol in infantile haemangioma.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
V00400 SB 201 Léauté-Labrèze (In Press)	A randomised, controlled, multidose, multicenter, adaptive phase II/III study in infants with proliferating infantile hemangiomas requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind)	Léauté-Labrèze, C., Hoeger, P., et al. (In Press). "A Randomized Controlled Trial of Oral Propranolol in Infantile Hemangioma." New England Journal of Medicine.
Hogeling (2011a)	A randomised controlled trial of propranolol for infantile hemangiomas.	Hogeling, M., S. Adams, et al. (2011a). Pediatrics 128(2): e259-e266.
Hogeling (2011b)	A randomised controlled trial of propranolol for infantile haemangiomas.	Hogeling, M., S. Adams, et al. (2011b). Australasian Journal of Dermatology 52: 4.

Source: Table B.2.2 of the submission, p29.

6.4 In accordance with usual process for minor submissions, the clinical trial evidence, economic evaluation and financial estimates were not independently evaluated prior to consideration by the PBAC.

Comparative effectiveness

6.5 The 201 study was a two-stage randomised, controlled, multi-dose, multi-centre, adaptive phase II/III study in infants with proliferating infantile haemangiomas requiring systemic therapy. In the study, 61/101 (60.4%) of patients in the active

treatment arm compared to 2/55 (3.6%) in the placebo arm presented complete or near complete remission at week 24.

6.6 Hogeling (2011) was a small randomised placebo-controlled study conducted in 40 infants with infantile haemangioma. Patients were randomised to 2mg/kg/day of the Auspman propranolol solution (n=19) for six months or placebo (n=20) with the change in volume and colour of the haemangioma assessed at 12 and 24 weeks. A mean haemangioma volume decrease of 60% was seen in the treatment arm compared to 14.1% in the placebo arm.

Comparative harms

6.7 Frequent adverse events were reported as known side effects of propranolol or non-specific events commonly occurring in infants, with propranolol considered generally well tolerated.

Clinical claim

6.8 The submission claimed that Hemangiol had demonstrated superior efficacy over placebo, with a satisfactory safety profile.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

6.9 The minor submission presented a cost consequence analysis which compared the cost of treatment with Hemangiol to the current options for accessing propranolol oral liquid, namely, compounded from propranolol tablets in a community or hospital pharmacy, or through the oral solution supplied through Auspman to hospital pharmacies.

6.10 The requested price is shown in the table below and, according to the sponsor, was based on safety concerns in relation to compounded propranolol, drug development costs, and providing educational material to prescribers and patents for minimising risk. Each of these issues were explored in detail in the submission (pages 57-73). The Secretariat overview considered this was not an appropriate justification for price. A simple cost-minimisation to either the Auspman product, compounded product, or to propranolol tablets (with a slight price advantage for liquid formulation) may have been more appropriate.

Requested price for propranolol liquid

Max quantity (bottles per script)	Ex-man price	Wholesaler mark-up	Ex-man + wholesaler mark-up	Pharmacy mark-up	Ex-man + wholesaler mark-up + pharmacy markup	Dispensing fee	DPMQ
2	$[redacted]	7.52%	$[redacted]	4%	$[redacted]	$6.76	$[redacted]

6.11 The proposed price results in a price per milligram of $[redacted]/mg.

6.12 The submission estimated the cost of the Auspman 2mg/mL propranolol solution to be $[redacted] per 100mL bottle. This is approximately $[redacted]/mg. The Secretariat overview

noted that when supplied through a public hospital, there is usually no cost to the patient.

6.13 The submission estimated the total cost to a patient obtaining compounded propranolol liquid (5mg/mL, 100mL) through a community pharmacy to be $[redacted]. This resulted in a cost of around $[redacted]/mg. The patient is required to cover the entire cost of the privately compounded product.

6.14 Propranolol 10mg tablets (quantity 100) are an unrestricted benefit item with a DPMQ of $[redacted]. The resultant price per milligram of the tablets is $[redacted]/mg. The Secretariat overview considered that while it is reasonable for a ready-made liquid formulation which meets the needs of paediatric patients to be priced higher than a tablet, the magnitude of the price advantage was not adequately justified.

***Drug cost per patient/course*:** $[redacted] for 6 months treatment.

6.15 The submission estimated the total cost per course of treatment with Hemangiol, assuming that patients are treated for 6 months, with 11.5% requiring an additional 6 month treatment for recurrence of the disease. This is shown in the table below.

Comparative costs per course of treatment

	DPMQ	Price/mg	Price/course of treatment
Hemangiol	$[redacted]	$[redacted]	$[redacted]
Auspman	$[redacted]	$[redacted]	$[redacted]
Compounded	$[redacted]	$[redacted]	$[redacted]
Tablets	$10.53	$0.011	$52.65

Source: Tables D.2.2, D.2.4, D.2.5 pp 68-73 of the submission

6.16 The redacted table above shows the differential price between various forms of propranolol liquid.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Estimated PBS usage & financial implications

6.17 The submission used an epidemiological approach to estimate the numbers of patients treated with Hemangiol for infantile haemangioma.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prescriptions*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS^	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Average patient co-payment	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

*1 prescription provides 2 bottles

^calculated at DPMQ

Source: Tables E.2.3, E.2.6, E.2.10 pp 78-82 of the submission

6.18 The redacted table above shows the number of patients treated is likely to be less than 10,000 per year with an estimated total net cost to the PBS of less than $10 million per year.

6.19 The number of prescriptions was dependent on patient weight. The Secretariat overview noted that these estimates were uncertain, given the variation in infant weight. The estimates were based on average patient weight from clinical trial data, starting at 5.876kg and increasing approximately 400 grams per month. The number of prescriptions also assumed that 11.5% of patients would be retreated with an additional 6 month course.

6.20 The submission assumed that Hemangiol would replace compounded propranolol in 50% of patients and would replace Auspman propranolol solution in 50% of patients. This proportion of substitution was not substantiated in the submission.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

7.1 The PBAC recommended the listing of propranolol oral liquid (Hemangiol) as an Authority Required (telephone) item on the general schedule.

7.2 The PBAC was satisfied that Hemangiol provides the same benefits as seen with either of the currently available alternatives, namely, Auspman propranolol solution or compounded propranolol liquid, and that these are the therapies most likely to be replaced. Auspman propranolol solution or compounded propranolol liquid are therefore the most appropriate comparators.

7.3 The PBAC noted the clinical need for a product to treat infantile haemangiomas in high risk patients.

7.4 The PBAC noted that PBS listing is unlikely to change the current treatment algorithm for infantile haemangioma as patients would otherwise be treated with an alternative compounded product.

7.5 The PBAC considered that the PBS restriction should mirror the TGA indication: that is, for the treatment of patients requiring systemic therapy with life threatening haemangiomas, ulcerated haemangiomas with pain, or haemangiomas with risk of permanent scarring or disfigurement.

7.6 The PBAC agreed that the maximum quantity of 240mL as proposed in the submission was appropriate, but considered it appropriate for up to 2 repeats to be issued to allow patients to complete 6 months of treatment if required.

7.7 The PBAC recommended use should be limited to prescribing only by a doctor with expertise in the diagnosis, treatment and management of infantile haemangiomas, or by a General Practitioner in consultation with a doctor with expertise in the diagnosis, treatment and management of infantile haemangiomas.

7.8 The PBAC considered that Hemangiol should be cost minimised against the currently available Auspman propranolol solution with a modest price premium to be negotiated between the Sponsor and the Department in acknowledgement that Hemangiol is a commercially available product which is likely to have benefits for patients in terms of access. The PBAC noted that cost consequence method used to derive the proposed price was unsubstantiated and resulted in an unacceptably high price, noting that the proposed price of Hemangiol is [redacted] times the price of propranolol tablets (at the ex-manufacturer level). The PBAC considered a price

premium of this magnitude to be unjustified although a small price premium for oral liquids over tablets is reasonable. The price of Hemangiol was considered in the context of the table below which demonstrates that the ratio of solution price per milligram compared to the tablet price per milligram is significantly higher for Hemangiol than for other liquid dosage form products.

Drug	Form, including strength	Mg per pack	Ex-man price per pack	Price per mg	Ratio of solution price per mg to tablet price per mg
Propranolol	Oral liquid, 3.75 mg/1 mL, 120 mL	450 mg	$[redacted]	$[redacted]	[redacted]
	Tablet 10 mg, 100	1,000 mg	$3.05	$0.003	
Digoxin	Oral solution, 50 mcg/1 mL, 60 mL	3 mg	$14.04	$4.68	18:1
	Tablet 62.5 mcg, 200	12.5 mg	$3.24	$0.26	
Diazepam	Oral liquid, 1 mg/1 mL, 100 mL	100 mg	$29.63	$2.96	32:1
	Tablet 2 mg, 50	100 mg	$0.94	$0.094	
Naproxen	Oral suspension, 125 mg/5 mL, 474 mL	11,850 mg	$102.47	$0.01	50:1
	Tablet 250 mg, 50	12,500 mg	$2.80	$0.0002	

7.9 The PBAC noted that the estimated total number of prescriptions was based on patient weight. While the total patient population is likely to be small, the PBAC considered that there was a risk of Hemangiol use in patients with less severe, non-fatal haemangiomas. The Committee considered that the basis for the financial estimates should be reviewed in the context of negotiations of pricing with the Department.

7.10 The PBAC recommended that propranolol, in the form oral liquid, should not be treated as interchangeable with any other drugs.

7.11 The PBAC advised that propranolol oral liquid is not suitable for prescribing by nurse practitioners.

7.12 The PBAC recommended that the Safety Net 20 Day Rule should apply.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
PROPRANOLOL 3.75mg/mL oral liquid, 120 mL	2	2	Hemangiol® Pierre Fabre

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Proliferating
Condition:	infantile haemangioma
PBS Indication:	Proliferating infantile haemangioma
Treatment phase:	-
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by, or in consultation with, a physician with expertise in the diagnosis, treatment and management of infantile haemangioma.
Clinical criteria:	The condition must be a life- or function-threatening haemangioma; OR The condition must be an ulcerated haemangioma with pain and/or lack of response to simple wound care measures; OR The patient must be at risk of permanent scars or disfigurement. AND The patient must require systemic therapy

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Propranolol was not listed on the ARTG at the time of PBAC consideration. In June 2014, the TGA made the decision not to register Hemangiol (propranolol) oral solution in the treatment of proliferating infantile haemangioma requiring systemic therapy on the grounds that the efficacy and safety of the product had not been

satisfactorily established for the purpose for which it was to be used. The sponsor appealed this decision not to register the product under section 60 of the Therapeutic Goods Act. In November 2014, the Minister's delegate under section 60 of the Act concluded that there was satisfactory evidence of quality, safety and efficacy of Hemangiol for the purpose for which it was to be used. The Delegate revoked the initial decision and substituted the decision that Hemangiol should be included on the ARTG for the indication:

Treatment of proliferating infantile haemangioma requiring systemic therapy:

- Life- or function-threatening haemangioma
- Ulcerated haemangioma with pain and/or lack of response to simple wound care measures
- Haemangiomas with a risk of permanent scars or disfigurement.

Pierre Fabre welcomes the decision of PBAC and will work toward a rapid listing on the PBS.