**HEMANGIOL 3.75 mg/ml, oral solution**  
B/1 bottle of 120 ml (CIP: 34009 278 836 3 7)

Applicant: PIERRE FABRE DERMATOLOGIE

<table>
<thead>
<tr>
<th>INN</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (2012)</td>
<td>C07AA05 (non-selective beta blocking agent)</td>
</tr>
</tbody>
</table>

**Reason for the review:**

- Inclusion

**Lists concerned:**

- National Health Insurance (French Social Security Code L.162-17)
- Hospital use (French Public Health Code L.5123-2)

**Indications concerned**

“HEMANGIOL is indicated in the 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,
- Haemangioma with a risk of permanent scars or disfigurement. It is to be initiated in infants aged 5 weeks to 5 months.”
<table>
<thead>
<tr>
<th>Actual Benefit</th>
<th>Substantial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in Actual Benefit</td>
<td>HEMANGIOL® 3.75 mg/ml oral solution provides a moderate improvement in actual benefit (IAB III) in the treatment of proliferating infantile haemangioma requiring systemic therapy.</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>First-line treatment</td>
</tr>
<tr>
<td>Recommendations</td>
<td>Taking into account the restricted indication for HEMANGIOL and, in the interests of good use, the Committee would like to be provided with prescription data that give a picture, based on a representative sample of patients, of the characteristics of the patients treated and of the indication, doses and duration of treatment with this proprietary medicinal product.</td>
</tr>
</tbody>
</table>
01 ADMINISTRATIVE AND REGULATORY INFORMATION

| Marketing Authorisation (centralised) | Initial date: 23 April 2014  
Paediatric use marketing authorisations (PUMA)  
This product is the subject of a risk management plan associated with a request for a follow-up study of the use of HEMANGIOL (see section 8.4). |
| Prescribing and dispensing conditions /special status | List I  
Medicine for initial six-monthly hospital prescription  
Covered by a temporary authorisation for use by a named patient [ATU nominative in French] since 13 April 2010 and by a group TAU since 31 May 2012. |
| ATC Classification | 2012  
C Cardiovascular system  
C07 Beta-blocking agents  
C07A Beta-blocking agents  
C07AA Beta blocking agents, non-selective  
C07AA05 Propranolol |

02 BACKGROUND

This is an application for inclusion on the list of medicines refundable by National Health Insurance and list approved for hospital use of the proprietary medicinal product HEMANGIOL 3.75 mg/ml, oral solution (propranolol), which was approved by the CHMP on 20 February 2014 and granted Marketing Authorisation on 23 April 2014 in conjunction with a risk management plan and measures for the minimisation of risk based primarily on:

- the monitoring of identified risks: hypotension, bradycardia, bronchospasm, hypoglycaemia,
- the establishment of a framework for prescription and monitoring in children: advice on the preparation of the solution, information on the monitoring and management of hypoglycaemia and other identified risks, etc.,
- a prescription data study.

HEMANGIOL 3.75 mg/ml is a proprietary medicinal product containing propranolol formulated in a new pharmaceutical form, an oral solution suitable for use in babies and children.

03 THERAPEUTIC INDICATION

“HEMANGIOL is indicated in the 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,
- Haemangioma with a risk of permanent scars or disfigurement.

It is to be initiated in infants aged 5 weeks to 5 months.”

04 DOSAGE

See the SPC.
Infantile haemangioma is a benign tumour belonging to the group of vascular tumours according to the ISSVA (International Society for the Study of Vascular Anomalies) classification. It is diagnosed clinically and radiologically (Doppler ultrasonography).

The haemangioma appears during the first few weeks of life (70% classically in the first two weeks after birth), but can appear up to the age of two to three months in cases where it develops in the subcutaneous tissue. It most commonly presents as a spot or premonitory vascular mark, a bluish spot and sometimes as an anaemic halo.

Its course is characteristic and can be divided into three phases:
- the proliferative phase, characterised by a rapid increase in tumour size up to 6-12 months.
- the stabilisation phase from 12 to 36 months, in which the haemangioma stops growing and starts decreasing in size.
- the involution phase, in which the lesion disappears, but may leave behind residual fibroadipose tissue, cutaneous telangiectasia, scarring, etc.

The usual complications of haemangiomas occur during the proliferative phase. These are necrosis, ulceration, which may be complicated by bleeding or infection, and permanent scarring. Other complications occurring at the site of development of the haemangioma may be encountered and are mainly confined to periorificial haemangiomas (amblyopia, astigmatism, upper airways obstruction, nasal obstruction, sphincter disorders, difficulty eating) and haemangiomas encroaching on vital structures (mammary hypodevelopment, alopecia). The aesthetic prognosis may be seriously compromised in the case of facial localisations.

Only haemangiomas that are aesthetically or functionally problematic or potentially life-threatening are treated, as the majority of small haemangiomas do not require any special treatment.

When drug therapy is necessary, treatment of patients is based on:
- systemic (at doses of 3-5 mg/kg/day) or local corticosteroid therapy (off-label use) as first-line treatment (betamethasone, prednisone, dexamethasone, prednisolone, methylprednisolone), which arrests the growth of the haemangioma,
- vincristine and interferon alfa-2a (off-label use), considered as second-line treatment when corticosteroid therapy is unsuccessful or the patient’s life is at risk.

Surgical treatment (excision) can be considered in restricted indications. Photodynamic therapy and/or pulsed-dye laser treatment can also be used.

The therapeutic need is therefore partially covered.

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1 www.chirurgie-plastique-pediatrique.fr
06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

HEMANGIOL 3.75 mg/ml, oral solution is the sole proprietary medicinal product containing propranolol with Marketing Authorisation.

NB: Propranolol has previously been used in the treatment of infantile haemangiomas in the form of magistral preparations.

The other comparators are represented by certain corticosteroids indicated in “serious forms of angioma in babies”.

<table>
<thead>
<tr>
<th>Name (INN) Company</th>
<th>Indication</th>
<th>Date of Opinion</th>
<th>AB/IAB (wording)</th>
<th>Reimbursed</th>
</tr>
</thead>
<tbody>
<tr>
<td>BETNESOL (betamethasone) SIGMA- TAU FRANCE</td>
<td>Serious forms of angioma in babies</td>
<td>09/01/2013 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>CORTANCYL (prednisone) SANOFI-AVENTIS</td>
<td></td>
<td>20/11/2013 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>DECTANCYL (dexamethasone) SANOFI-AVENTIS</td>
<td></td>
<td>26/11/2008 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>HYDROCORTANCYL SOLUPRED (prednisolone) SANOFI-AVENTIS</td>
<td></td>
<td>26/11/2008 21/07/2010 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>MEDROL (methylprednisolone) PFIZER</td>
<td></td>
<td>20/11/2013 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
</tbody>
</table>

06.2 Other health technologies

Surgery may be considered, depending on the course of the infantile haemangioma, its localisation, its response to drug therapies and the long-term sequelae.

Photodynamic therapy with pulsed-dye laser (PDL) treatment is also used in the elimination of some superficial vascular tumours that are refractory to drug therapy.

> Conclusion
The relevant clinical comparators are the corticosteroids listed above.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

No applications for reimbursement have been made to date in other European countries or anywhere else in the world.
08 ANALYSIS OF AVAILABLE DATA

The clinical data in support of the efficacy and safety of HEMANGIOL in proliferating infantile haemangiomas are based on:

- a phase II/III study (V00400 SB 201) that investigated the efficacy of HEMANGIOL versus placebo in terms of complete or near-complete resolution of the haemangioma after 24 weeks, with long-term follow-up planned up to 96 weeks, i.e. 72 weeks after stopping treatment,
- data from TAUs,
- data from a literature search carried out by the applicant.

The applicant has also submitted quality of life data:
- “general” health-related data for children with haemangiomas (Hoornweg 2008, Dutch-language publication),
- in patients treated with magistral preparations containing propranolol (Hermans 2013),
  which, owing to their methodological inadequacies (small patient populations, unvalidated questionnaires, lack of randomisation, etc.), are not discussed.

08.1 Efficacy

8.1.1 Study V00400 SB 201

Method: Adaptive randomised double-blind phase II/III study comparing HEMANGIOL (propranolol) 1 or 3 mg/kg/day in two doses per day with placebo in babies with proliferating haemangioma requiring systemic treatment followed up for 24 weeks. Follow-up for up to 96 weeks (i.e. 72 weeks after stopping treatment) was also planned.

The adaptive element of this phase II/III study was organised in two stages:
- Stage 1 (phase II), comparing the four propranolol regimens (see treatments below) with placebo. At the end of this stage 1, an interim analysis was planned to select the propranolol dosage for stage 2.
- Stage 2 (phase III), comparing just the propranolol regimen selected (in stage 1) with placebo.
- Stage: Follow-up until the 96th week after inclusion.

Inclusion criteria: babies aged 35 to 150 days with a proliferating infantile haemangioma that:
- may be situated on any part of the body except for the gluteal region,
- is at least 1.5 cm in diameter,
- requires systemic treatment.

Non-inclusion criteria, in particular:
- severe cases of haemangioma, such as congenital haemangiomas, Kasabach-Merritt syndrome and PHACE syndrome,
- patients with one or more of the following haemangiomas:
  - haemangiomas that are life-threatening,
  - haemangiomas that are function-threatening (particularly respiratory or visual),

ulcerated haemangiomas irrespective of localisation,
- patients with a history of cardiovascular events: hypotension (< 50/30 mmHg), second- or third-degree heart block, cardiogenic shock, bradycardia (< 80 bpm), serious disorders of the peripheral arterial circulation, Raynaud’s syndrome, sick sinus syndrome, uncontrolled heart failure or Prinzmetal’s angina.

Treatment:
In stage 1, 190 babies were included in the ITT analysis:
Propranolol 1 mg/kg/day for 3 months + 3 months of placebo: n = 41
Propranolol 1 mg/kg/day for 6 months: n = 41
Propranolol 3 mg/kg/day for 3 months + 3 months of placebo: n = 40
Propranolol 3 mg/kg/day for 6 months: n = 43
Placebo for 6 months: n = 25.

In stage 2, after selection of the dose:
Propranolol 3 mg/kg/day for 6 months: n = 102
Placebo for 6 months: n = 55.
A total of 460 babies underwent randomisation and stage 2 was carried out on 156 patients (33.9%) after selection of the dose.
Premature discontinuation of treatment occurred in a total of 117 patients (25.4%), including 27 in the placebo group (47%) and 22 patients in the group treated with propranolol 3 mg/kg/day for 6 months (21.6%).

Primary efficacy endpoint: Change in the haemangioma at 24 weeks versus baseline. This was determined on the basis of qualitative, independent, centralised, blinded evaluations of photographs.
A successful outcome was defined as the complete or near-complete resolution of the haemangioma, near-complete resolution being defined as a minimal degree of telangiectasia, erythema, thickening of the skin, swelling of soft tissue and/or distortion of anatomical features.

Resolution was determined on the basis of the investigators’ observations, without use of a reference scale.

RESULTS: ITT analysis
Patient characteristics were globally comparable on inclusion except for a higher proportion of premature babies and lower body weight in the placebo group.

In accordance with the study methodology, only one dosage was retained at the end of stage 1 and only the results for this dosage (3 mg/kg/day for 6 months, n = 102) were analysed at week 24.

After 24 weeks of treatment, complete or near-complete resolution was observed more frequently in the propranolol 3 mg/kg/day group than in the placebo group: 61/102 (60.4%) versus 2/55 (3.6%) patients, p < 0.0001.

Follow-up at 96 weeks:
The principal objective of this long-term follow-up until week 96 was to evaluate the efficacy and safety after discontinuation of treatment in patients who completed the first part of the study up to week 24, i.e. 391/460 patients (85%), all dosages taken together.

The evaluation at 96 weeks is based on analysis of a binary success/failure criterion (see definition given in the endpoints shown above). Only the results for the propranolol 3 mg/kg/day for 6 months dosage are shown in the table below.
Persistence of efficacy at week 96 (number and percentage of patients)

<table>
<thead>
<tr>
<th></th>
<th>Inclusion</th>
<th>Successful outcome at 24 weeks</th>
<th>Successful outcome at 24 and 96 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEMANGIOL</strong></td>
<td>N = 102</td>
<td>N = 61 (60.4%)</td>
<td>P &lt; 0.001 vs. placebo</td>
</tr>
<tr>
<td>3 mg/kg/day for 6 months</td>
<td></td>
<td></td>
<td>N = 35/61 (57.4%)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>N = 55</td>
<td>N = 2 (3.6%)</td>
<td>Descriptive analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N = 2/2 (100%)</td>
</tr>
</tbody>
</table>

In the patients with a successful outcome at 24 weeks, complete or near-complete resolution of the haemangioma was maintained in 2/2 patients in the placebo group and in 35/61 patients in the propranolol 3 mg/kg/day for 6 months group (descriptive analysis).

8.1.2 Data from TAU

Temporary authorisations for use by a named patient [ATU nominative in French] have been granted since 13 April 2010, and a group TAU since 30 May 2012, in the indication “treatment of life- or function-threatening proliferating infantile haemangiomas and ulcerated haemangiomas not responding to simple wound care measures, in babies who cannot be included in a clinical study”.

Treatment had to be initiated and monitored by a doctor experienced in the treatment of infantile haemangiomas. Given the need for preassessment before commencing treatment, the first dose and any increase in dosage had to take place in a hospital setting with appropriate monitoring for at least 4 h. No tapering of the dosage was necessary when stopping treatment.

The recommended dosage was 2 mg/kg/day. A dose of 3 mg/kg/day could be given, depending on tolerability and the response to treatment.

Analysis of the cumulative data from the seven twice-yearly reports submitted to the ANSM [French National Agency for Medicines and Health Products Safety] between 13 April 2010 and 12 October 2013 allows us to determine the exposure of 1162 infants presenting different forms of high-risk proliferating infantile haemangioma requiring systemic treatment.

Characteristics of the population
The mean age at the start of treatment was 176.9 days [1; 2354]. The sex ratio was three girls to one boy.
The haemangioma had a facial localisation in 63.3% of cases and in 85.9% of cases was over 1.5 cm in diameter at its widest. The haemangiomas were life-threatening in 15.6% of cases, were causing functional impairment in 73% and in 40.4% of cases were accompanied by severe ulcerations. In 81.8% of cases the patients had not undergone any prior treatment.

Dose and duration of treatment
The mean propranolol dose was 2 mg/kg/day [0.4-4.0 mg/kg/day] and the mean duration of treatment was 256 days (8.4 months).

Efficacy data: Post-hoc analysis
Temporary authorisations for use (TAUs) have been granted to 1162 infants with high-risk infantile haemangiomas not included in study 201. The most recent TAU report (report No. 7) contains the available data for 1146 patients up to 12 October 2013 (no data for 16 patients).

The TAU protocol does not include a prospective evaluation of efficacy, consequently this was estimated indirectly by post-hoc analysis of treatment discontinuations. These data are available only for 419/1162 patients (36%). This analysis shows that 352/419 patients (84%) stopped treatment owing to “good efficacy” and that complete or near-complete resolution was observed in 154/265 patients (58.1%).
The results of this descriptive analysis must be interpreted with caution given the methodology used (post-hoc analysis based on an indirect criterion, treatment discontinuations, which could have been for reasons other than a successful outcome and is available only for 36% of patients treated).

### 8.1.3 Data from the literature review

This review is based on:
- a 2011 meta-analysis by Peridis,\(^5\) who compared propranolol with other treatments (steroids, CO\(_2\) laser and vincristine) in the treatment of infantile airway haemangiomas. This meta-analysis covering 13 studies included a total of 36 patients treated for infantile airway haemangiomas. Propranolol was effective in resolving these infantile haemangiomas (OR = 0.03; 95% CI [0.01-0.12]; \(p < 0.00001\)).

Seven studies including a total of 15 patients compared the efficacy of propranolol with that of corticosteroids. The efficacy of propranolol was found to be superior to that of corticosteroids (OR = 0.05; 95% CI [0.01-0.24]; \(p = 0.0002\)).

- a “meta-analysis” by Izadpanah 2013,\(^6\) who did not employ a comparative approach, but calculated the mean percentage success rate of the treatment arms of the studies included, is not discussed in this Opinion.

- two retrospective studies (Price 2011\(^7\) and Bertrand 2011\(^8\)), which are not discussed in this Opinion on account of their methodology.

The methodological limitations of these studies mean that their results must be interpreted with caution.

### 8.2 Safety

#### 8.2.1 Data from clinical studies

In study 201, adverse effects were observed during the two stages in 89/98 (90.8%) of patients in the propranolol 1 mg/kg/day for 3 months group, 90/102 (88.2%) of patients in the propranolol 1 mg/kg/day for 6 months group, 91/100 (91%) of patients in the propranolol 3 mg/kg/day for 3 months group, 96/106 (95%) of patients in the propranolol 3 mg/kg/day for 6 months group and in 40/55 (72.7%) of patients in the placebo group. The most commonly observed adverse effects (> 15%) were:

- Diarrhoea: 16.3% vs. 13.7% vs. 16% vs. 27.7% vs. 7.3%,
- Nasopharyngitis: 29.6% vs. 16.7% vs. 32% vs. 33.7% vs. 18.2%,
- Fever: 20.4% vs. 19.6% vs. 22% vs. 26.7% vs. 9.1%,
- Bronchitis: 5.1% vs. 7.8% vs. 11% vs. 16.8% vs. 1.8%,
- Cough: 14.3% vs. 14.7% vs. 16% vs. 11.9% vs. 7.3%
- Upper respiratory tract infections: 6.1% vs. 12.7% vs. 19% vs. 13.9% vs. 7.3%.

During the follow-up period up to 96 weeks, the observed adverse effects were similar to those observed in the initial stages of study 201.

#### 8.2.2 Data from TAUs

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Since the start of the TAU in April 2010, 113 cases (of which 25 were serious) involving 180 adverse effects have been reported in the 1162 infants treated.

The most commonly observed adverse effects have been respiratory infections (in some cases associated with respiratory failure) and hypoglycaemia (in some cases associated with hypoglycaemic seizures).

The serious cases observed included hypoglycaemia, sinus arrest with bradycardia, bronchospasm/exacerbation of bronchiolitis, malaise, hypotension, purpura of the lower limbs, malaise and aggravation of haemangiomas.

One serious case with a fatal outcome was also observed: third-degree atrioventricular block.

Prescribers and parents of patients were given a leaflet informing them of the possible occurrence of bronchospasm even in patients with no history of asthma, warnings and guidelines on bronchial manifestations that can occur during treatment with propranolol.

All in all, out of the 419 patients for whom information is available, discontinuation of treatment was reported in 352 cases, of which 30 were definitively on account of adverse effects: 3 cases of bronchospasm, 12 of severe or recurrent bronchiolitis, 5 of sleep disturbances (nocturnal awakening/nightmares), 2 of hypoglycaemia, 2 of low weight gain and loss of appetite with respiratory difficulties, 1 of bradycardia associated with sinus arrest, 1 of behavioural disorders, 1 of malaise alongside hypotension with vomiting and anorexia, 1 of complete atrioventricular block and fatal heart failure following surgery for sclerosis of oesophageal varices associated with biliary atresia, 1 of diarrhoea, 1 of purpura, and 1 discontinuation on account of contraindication.

8.2.3 SPC data

According to the SPC, the most common adverse effects (> 10%) are: “sleep disorders, aggravated respiratory tract infections such as bronchitis and bronchiolitis associated with cough and fever, diarrhoea, and vomiting”.

08.3 Summary and discussion

The clinical data in support of the efficacy of HEMANGIOL in proliferating infantile haemangiomas are based on a phase II/III study (V00400 SB 201) that sought to compare the efficacy of HEMANGIOL with placebo in terms of complete or near-complete resolution of the haemangioma in babies with proliferating haemangiomas requiring systemic treatment and TAU data.

Principal efficacy data:

In study 201, after 24 weeks of treatment, complete or near-complete resolution was observed more frequently in the propranolol 3 mg/kg/day group than in the placebo group: 61/101 (60.4%) versus 2/55 (3.6%) patients, p < 0.0001.

At follow-up 96 weeks after discontinuation of treatment, in patients with complete or near complete resolution of the haemangioma after 24 weeks, maintenance of the response was observed in 35/61 patients in the propranolol 3 mg/kg/day for 6 months group and in 2/2 patients in the placebo group (descriptive analysis).

A total of 1162 infants not included in study 201 were granted a temporary authorisation for use of propranolol for a high-risk infantile haemangiomia. An analysis of discontinuations of treatment, the criterion chosen for the post-hoc evaluation of the efficacy of treatment, was carried out. These data are available only for 419/1162 patients (36%). This analysis shows that 352/419 patients (84%) stopped treatment owing to “good efficacy” and that complete or near-complete resolution was observed in 154/265 patients (58.1%).
The results of this descriptive analysis must be interpreted with caution given the methodology used (post-hoc analysis based on an indirect criterion, treatment discontinuations, that is likely to reflect the efficacy of propranolol and for which data are available only for 36% of patients treated).

**Principal safety data:**

The adverse effects in study 201 were diarrhoea, nasopharyngitis, fever, bronchitis, cough and upper respiratory tract infections.

The TAU data show that the most commonly observed adverse effects include respiratory infections (in some cases associated with respiratory failure) and hypoglycaemia (in some cases associated with hypoglycaemic seizures). The serious cases observed include cases of hypoglycaemia, sinus arrest with bradycardia, bronchospasm/exacerbation of bronchiolitis, third-degree atrioventricular block with fatal outcome, malaise, hypotension, purpura of the lower limbs, etc.

According to the SPC, the most common adverse effects (> 10%) are: “sleep disorders, aggravated respiratory tract infections such as bronchitis and bronchiolitis associated with cough and fever, diarrhoea, and vomiting”.

**Discussion:**

Although the data from study 201 demonstrate the efficacy of propranolol 3 mg/kg/day versus placebo in terms of complete or near-complete resolution of the haemangioma (success), this demonstration is based on an endpoint determined by non-standardised photographic evaluation of the surface, thickness and colour of the haemangioma, whereas it is the subcutaneous part of the haemangioma that influences its absorption there. No local haemodynamic evaluation (vascular flow and resistance, etc.) was carried out, which would have permitted quantification of the changes to the subcutaneous part of the haemangioma as a function of treatment.

The choice of a placebo as the comparator meant that the more severe forms of infantile haemangioma were not included in this study, consequently it is not possible to transpose the results of study 201 to the population of the Marketing Authorisation, which is the population that will be treated in practice.

The only available data in patients with severe haemangioma are those from descriptive analyses of data from the group TAU.

The persistence of the treatment effect was evaluated at week 96. In this evaluation, maintenance of the effect was observed in 35/61 patients in the propranolol 3 mg/kg/day for 6 months group and in 2/2 patients in the placebo group (descriptive analysis).

There are no comparative data versus corticosteroids, which is regrettable, as these are the drugs indicated in severe forms of infantile haemangioma and it would have been useful to show that propranolol allows the long-term administration (≥ 6 months) of high doses of corticosteroids in babies to be avoided.

**08.4 Study programme and ongoing development**

As part of the RMP, the EMA has requested the performance of a follow-up study of off-label use documenting, in particular, the age of patients on initiation of treatment, the doses, the duration of treatment, the prematurity of the babies and administration errors. This study should include approximately 300 patients and be carried out in France and Germany.

The applicant has also stated that a topical propranolol dosage form for superficial infantile haemangiomas less than 5 cm in diameter is currently in development.
THERAPEUTIC USE

Only infantile haemangiomas that are aesthetically or functionally problematic or potentially life-threatening are treated; the majority of small haemangiomas do not require any special treatment.

When drug therapy is necessary, treatment of patients is based on:
- systemic or local corticosteroid therapy (off-label use) as first-line treatment (betamethasone, prednisone, dexamethasone, prednisolone, methylprednisolone), which arrests the growth of the haemangioma,
- vincristine and interferon alfa-2a (off-label use), considered as second-line treatment when corticosteroid therapy is unsuccessful or the patient’s life is at risk.

Surgical treatment (excision) can be considered in the restricted indications in the early, intermediate and late stages (sequelae). This needs to be discussed in relation to the progression, localisation, response to drug therapies and long-term sequelae.

Photodynamic therapy and/or pulsed-dye laser treatment can also be used in the elimination of some superficial vascular tumours that are refractory to treatment.

Therapeutic use of HEMANGIOL:

HEMANGIOL (propranolol) is an alternative here to corticosteroids that can be offered as a first-line treatment in the management of proliferating infantile haemangiomas requiring systemic treatment.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual benefit

Infantile haemangiroma is a benign tumour in children which, in the event of complications, may be aesthetically or functionally problematic or potentially life-threatening.

HEMANGIOL 3.75 mg/ml is a curative therapy for the treatment of proliferating infantile haemangioma requiring systemic treatment.

Its efficacy/adverse effects ratio is high.

There are available alternatives for the treatment of proliferating infantile haemangiomas requiring systemic treatment: corticosteroids.

HEMANGIOL is a first-line treatment.

Public health benefit:
Infantile haemangioma is a common benign pathology in infants that very often regresses spontaneously, but may sometimes – depending on its size or localisation – be aesthetically or functionally problematic or even life-threatening. Its typically benign character and tendency to regress spontaneously mean that the public health burden of this pathology is low. The burden of haemangiomas requiring treatment on account of complications (10-15% of cases) is likewise low, because of the limited number of infants concerned.

The availability of orphan medicinal products and paediatric forms is a public health priority.

On the basis of the available data, HEMANGIOL is expected to have a short-term impact on the morbidity of infants treated. However, because of the lack of comparative data versus the standard treatment (corticosteroids) and recurrence observed after discontinuation of treatment, it is not possible to quantify the impact of HEMANGIOL on the morbidity of infants treated, particularly in the medium and long term.

The quality of life data presented, which relate to haemangiomas requiring treatment, are based on very small numbers of patients and their quality is not guaranteed (retrospective data obtained largely through the use of unvalidated questionnaires). It is therefore not possible to quantify the impact of HEMANGIOL on the quality of life of infants and their parents.

The impact of HEMANGIOL on the organisation of healthcare is not documented.

HEMANGIOL provides an additional, but partial, response to the identified public health need. Overall, HEMANGIOL is not expected to have an impact on public health.

Consequently, the Committee considers that the actual benefit of HEMANGIOL 3.75 mg/ml oral solution is substantial in the indication in the Marketing Authorisation.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the indication “HEMANGIOL is indicated in the 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,
• Haemangioma with a risk of permanent scars or disfigurement.
It is to be initiated in infants aged 5 weeks to 5 months” and at the dosages in the Marketing Authorisation.

Proposed reimbursement rate: 65%

010.2 Improvement in actual benefit (IAB)

HEMANGIOL 3.75 mg/ml oral solution provides a moderate improvement in actual benefit (IAB III) in the treatment of proliferating infantile haemangioma requiring systemic therapy.

010.3 Target population¹

The target population of HEMANGIOL is infants with proliferating infantile haemangiomas requiring systemic treatment. It can be estimated on the basis of the following information:
- Haemangioma is the most common form of benign tumour in infants, with an approximate incidence of 10%, i.e. 81,000 infants based on the current birth rate in France (810,000 in 2013 according to the INSEE).
- Only 12% of such cases require treatment on account of complications (patient’s life at risk, risk of functional impairment, local complication or excessive long-term aesthetic risk), i.e. approximately 10,000 infants.

Estimate
The target population of HEMANGIOL can therefore be estimated at between 10,000 infants/year.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

Packaging
Appropriate for the prescribing conditions according to the indication, dosage and duration of treatment.

Request for data
Taking into account the restricted indication for HEMANGIOL and, in the interests of good use, the Committee would like to be provided with prescription data that give a picture, based on a representative sample of patients, of the characteristics of the patients treated and of the indication, doses and duration of treatment with this proprietary medicinal product.