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Summary of the risk management plan (RMP) for Hemangiol (propranolol)

This is a summary of the risk management plan (RMP) for Hemangiol, which details the measures to be taken in order to ensure that Hemangiol is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Hemangiol, which can be found on Hemangiol's EPAR page.

Overview of disease epidemiology

Infantile haemangiomas are benign tumours (abnormal non-cancerous growths) of blood vessels. They are the most common benign tumours of childhood, estimated to occur in 3 to 10% of the population.

Most infantile haemangiomas are not visible at birth but appear during the first 4 to 6 weeks of life. Characteristically, they exhibit an early rapid growth within weeks following birth, followed by a stabilisation phase and a slow spontaneous shrinkage over several months or years.

Known risk factors for their development are: female sex (female to male ratio of 2.4:1), Caucasian ethnicity, low birth weight, and being born to a mother who has had multiple pregnancies.

While most infantile haemangiomas are uncomplicated, about 12% of cases require referral to a specialist for consideration of systemic treatment (treatment which can have an effect on the whole body). This will be chosen based on the size and location of the infantile haemangiomas and how fast they are growing.

Summary of treatment benefits

Hemangiol is a solution to be taken by mouth that contains propranolol, a beta-blocking agent. It is used to treat children suffering from proliferating infantile haemangioma requiring systemic therapy. Treatment with Hemangiol should be started in children between five weeks to five months of age.

The effectiveness of propranolol in infants with proliferating infantile haemangiomas requiring systemic therapy has been assessed in one main study involving 460 children. Children treated with Hemangiol received either a dose of 1 or 3 mg/kg/day for 3 or 6 months, and were compared with children receiving placebo (a dummy treatment). Around 71.3% of children were female; 37% aged 35-90 days old and 63% aged 91-150 days old. The target haemangioma was located on the head for 70% of the children, and the majority (89%) of the infantile haemangiomas were localised (confined within an area).

Treatment success was defined as the complete or almost complete disappearance of the haemangioma as evaluated by independent assessments made on photographs taken 6 months after the start of treatment, provided treatment had not been stopped early.

Hemangiol at the most effective dose of 3 mg/kg/day for 6 months resulted in 60.4% (61 out of 101) of children with complete or almost complete disappearance of their target haemangioma, compared with 3.6% (2 out of 55) of the children who received placebo. Factors such as age (35-90 days / 91-150 days), gender and haemangioma location (head compared with body) did not influence the response to Hemangiol.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Bradycardia (decreased heart rate) Atrio-ventricular block (a type of heart rhythm disorder)	Propranolol is a beta-blocking agent. Its ability to reduce the heart rate and affect heart rhythm is well established.	Hemangiol must not be given to children with bradychardia below the following limits: - 100 heart beats/min (children 0-3months) -90 heart beats/min (children 3-6 months) -80 heart beats/min (children 6-12 months). Before starting treatment with propranolol, the child must be screened for heart rhythm disorders or bradycardia. This requires an analysis of the medical history and a full clinical examination of the child, including heart rate measurement and cardiac auscultation (listening to the child's heart). In case of a suspected cardiac abnormality, specialist advice must be sought before starting treatment. Treatment is started at a low dose of 1 mg/kg/day (given as two separate doses of 0.5 mg/kg) which is gradually increased to the therapeutic dose of 3 mg/kg/day. After receiving the first dose, the child must be monitored (including measuring the heart rate) at least hourly for 2 hours. If bradycardia (slow heart rate) with symptoms, or bradycardia under 80 beats per minute occur, immediate specialist advice must be sought. Each dose increase must be managed and monitored by a doctor. Monitoring of the child's condition and dose adjustment need to be performed at least monthly.
Hypotension (low blood pressure)	Propranolol reduces blood pressure through its beta-blocking activity.	Hemangiol must not be given to children with blood pressure below the following limits: -65/45 (children 0-3 months) -70/50 (children 3-6 months) -80/55 (children 6-12 months).

Risk	What is known	Preventability
		Before starting treatment with propranolol, a screening for the risks associated with the use of propranolol must be performed. An analysis of the medical history and a full clinical examination of the child must be performed including blood pressure measurement. In case of suspected cardiac abnormality, specialist advice must be sought before starting treatment to determine if there is any underlying condition for which the medicine is contraindicated. After the first dose and each time the dose is increased, the blood pressure should be monitored for the first two hours. If the blood pressure drops, treatment should be stopped and specialist advice should be sought. Monitoring of the child's condition and dose adjustment need to be performed at least monthly.
Hypoglycaemia (low blood sugar levels)	Propranolol prevents the effects of catecholamines (hormones produced in the body during periods of stress) to correct hypoglycaemia. It masks the warning signs of hypoglycaemia, particularly tachycardia (increased heart rate), shakiness, anxiety and hunger. It can aggravate hypoglycaemia in children, especially following fasting, vomiting or overdose. Hypoglycaemic episodes associated with propranolol may present exceptionally as seizures (fits) and/or coma.	Hemangiol is contraindicated in children predisposed to hypoglycaemia. The daily dose is to be administered in 2 separate doses, one in the morning and one in late afternoon, with an interval of at least 9 hours between the two doses. Hemangiol should be given during or right after a feed to avoid the risk of hypoglycaemia. It should be administered directly into the child's mouth using the syringe, labelled with the units of propranolol in mg, which is supplied with the bottle. The child must be fed regularly to avoid prolonged fasting. If the child is not eating or is vomiting, it is recommended that a dose be skipped. If the child spits out a dose or if it is not certain whether he/she took all of the medicine, parents/carers should not give another dose: they should just wait until it is time for the next scheduled dose. If a dose is forgotten, parents/carers should not give a double dose to make up for a forgotten dose. They should continue the treatment at the usual frequency: one dose in the morning and one in the late afternoon. In addition, Hemangiol and the feed must be given by the same person in order to avoid any confusion about whether the child has had both. If

Risk	What is known	Preventability
		different persons are involved, good communication is essential.
Bronchospasm (temporary narrowing of the airways)	An overreaction of the airways may result in bronchospasm due to the beta-blocking activity of propranolol in the lungs.	Hemangiol is contraindicated in asthma and if there is a history of bronchospasm. Before starting treatment with propranolol, a screening for the risks associated with its use must be performed. An analysis of the medical history and a full clinical examination of the child must be performed including pulmonary auscultation (listening to the child's lungs). In case of acute (short-lived) problems with the lungs or airways, the start of the treatment should be postponed. The starting dose of 1 mg/kg/day must be adjusted gradually to the maintenance dose of 3 mg/kg/day. Each dose increase must be managed and monitored by a doctor.

Important potential risks

Risk	What is known
In patients with PHACE syndrome (large haemangioma on the face with abnormalities of several organs) there is an increased risk of cerebrovascular complications (problems with blood flow to the brain)	In the medical literature, some cases of cerebrovascular complications have been reported in patients with PHACE syndrome and severe cerebrovascular abnormalities. Propranolol may increase the risk of stroke in PHACE syndrome patients with severe cerebrovascular abnormalities by lowering blood pressure and restricting the blood flow through narrow blood vessels in the brain.
In patients with large ulcerated haemangioma there is a risk of hyperkalaemia (high potassium levels in blood)	In the medical literature, two cases of hyperkalaemia in patients with large ulcerated infantile haemangioma have been reported in the days following the start of treatment with propranolol.
Potential risk of administration error	There is a potential risk for medication errors because: - the dose to administer will change during the dose adjustment phase and will change according to the child's weight; - the treatment may be given to the infant by different persons.
Potential risk of drug interaction with anaesthetic agents	There is a potential risk of drug interaction with general anaesthetics, due to an increased risk of hypotension (low blood pressure). When a patient is scheduled for surgery, beta-blocking therapy should be stopped at least 48 hours before the procedure.

Missing information

Risk	What is known
Off label use (use of the medicine outside of its approved indications)	Hemangiol could potentially be used off-label to treat patients with proliferating infantile haemangioma who do not require treatment with propranolol. It could also be used off-label to treat certain heart problems in children. It could be given off-label to elderly patients who have problems swallowing propranolol pills.
Long-term effects (including on growth)	In juvenile rats given doses of up to 40 mg/kg/day of propranolol, no effects were seen on the development of the reproductive system, nervous system and heart function.
Drug interaction through breast-feeding	No cases of drug interaction through breastfeeding have been reported in children treated with propranolol.
Dosing and treatment of premature infants before the corrected age of at least 35 days	In the French compassionate use programme, among 922 patients, four infants less than five weeks of age have been treated with propranolol. The safety profile of the 4 infants was similar to the other patients treated.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Hemangiol can be found on Hemangiol's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Hemangiol's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Medication errors, low blood sugar levels, low heart rate; low blood pressure, bronchospasm

Risk minimisation measure: Educational material for caregivers in order to minimise the risks associated with medication errors, hypoglycaemia, bradycardia, hypotension and bronchospasm.
Objective and rationale: considering the potential severity of the identified risks, carers should be educated on the risks of medication errors, low blood sugar levels, low heart rate, low blood pressure and bronchospasms, and informed of the need to monitor children for these side effects and about how to manage them.
Description: The educational materials for caregivers treating children with Hemangiol should include

the following key safety elements:

- Information on the conditions for which Hemangiol should not be given.
- Information on the correct procedure for product preparation and administration including:
  - instructions on how to prepare the solution with Hemangiol;
  - advice on how to feed children during treatment.
- Information on how to detect and manage any sign of hypoglycaemia during treatment with Hemangiol.
- Instructions on when to stop the administration of Hemangiol.
- The need to monitor and to contact a healthcare professional if the following signs and symptoms occur after treatment:
  - for bradycardia and hypotension: fatigue, coldness, pallor, bluish-coloured skin, and fainting;
  - for hypoglycaemia: minor symptoms like pallor, tiredness, sweating, shakiness, palpitations, anxiety, hunger and difficulty waking up; major symptoms like excessive sleeping, difficulty to get a response, poor feeding, temperature decrease, convulsions (fits), brief pauses in breathing and loss of consciousness.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Drug utilisation study	To assess the off-label use and measure effectiveness of risk minimisation measures	Off label use	Planned	Q2 2017 (final report)
V0400SB201 long term safety follow-up	To investigate long-term safety profile (including neurodevelopment assessment)	Long-term safety	Started	Final study report planned Q2 2014

Studies which are a condition of the marketing authorisation

None of the above studies is a condition of the marketing authorisation

Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in 04-2014.