Part VI: Summary of the risk management plan

Summary of risk management plan for Hemangiol®

This is a summary of the risk management plan (RMP) for HEMANGIOL®. The RMP details important risks of HEMANGIOL®, how these risks can be minimised, and how more information will be obtained about HEMANGIOL® risks and uncertainties (missing information).

HEMANGIOL® summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how HEMANGIOL® should be used.

This summary of the RMP for HEMANGIOL® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of HEMANGIOL® RMP.

I. The medicine and what it is used for

HEMANGIOL® is authorised for the treatment of proliferating infantile haemangioma requiring systemic therapy, i.e. 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 (see SmPC for the full indication). It contains Propranolol hydrochloride as the active substance, and it is given by oral route of administration.

Further information about the evaluation of HEMANGIOL® benefits can be found in HEMANGIOL® EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/medicines/human/EPAR/Hemangiol

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of HEMANGIOL®, together with measures to minimise such risks and the proposed studies for learning more about HEMANGIOL® risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of HEMANGIOL®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

Important information that may affect the safe use of HEMANGIOL® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of HEMANGIOL® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of HEMANGIOL®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Hypoglycemia and related seizure Bronchospasm and bronchial hyperreactivity reaction
Important potential risks	Potential risk of administration error
Missing information	Long-term effects (including on growth)

II.B Summary of important risks

Hypoglycemia including related seizure	
Evidence for linking the risk to the medicine	<u>Evidence source(s) and strength of evidence:</u> Non-selective betablockers, such as propranolol may block catecholamine-induced glycogenolysis, gluconeogenesis and lipolysis predisposing to hypoglycemia. Propranolol prevents the response of endogenous catecholamines to correct hypoglycaemia. It masks the adrenergic warning signs of hypoglycaemia,

	particularly tachycardia, shakiness, anxiety and hunger. It can aggravate hypoglycaemia in children, especially in case of fasting, vomiting or overdose. These hypoglycaemic episodes associated with the taking of propranolol may present exceptionally in the form of seizures. In case of serious hypoglycemia and/or hypoglycemic seizures, there is a risk of neurological sequelae. However, in nearly all cases, hypoglycemia that is severe enough to cause seizures or unconsciousness can be reversed without obvious harm to the brain. Cases of death or permanent neurological damage occurring with a single episode have usually involved prolonged, untreated unconsciousness, interference with breathing, severe concurrent disease, or some other type of vulnerability. Nevertheless, brain damage or death has occasionally resulted from severe hypoglycemia. Severe or prolonged hypoglycemia may result in long-term neurologic damage. <u>Characterisation of the risk:</u> Hypoglycemia was reported in 2 patients out of 480 treated with V0400SB oral formulation in the clinical studies, involving thus <0.5% of patients, no SAE was reported. In CUP, hypoglycemia was observed in 9 out of 1,661 patients, including 2 serious cases of hypoglycemic seizures.
Risk factors and risk groups	At normal doses, Hemangiol can aggravate hypoglycemia and /or mask some warning signs related to hypoglycaemia, particularly if the child is fasting or vomiting. The same can occur if overdosing Hemangiol. The infant is susceptible to hypoglycemia: - When glucose demands are increased (cold, stress, infections, increased work of breathing) - During fasting period (poor oral food intake, concomitant infection, teething, preparation for surgery) - In case of previous or concomitant treatment with corticosteroids because of adrenal suppression that may result in loss of the counterregulatory cortisol response and increases the risk of hypoglycemia.
Risk minimisation measures	Routine RMMs : *SmPC sections 4.2, 4.3, 4.4, 4.8.* *PL sections 2, 3, 4* Additional RMMs: *Educational material to care giver*

Bronchospasm and bronchial hyperactivity reactions	
Evidence for linking the risk to the medicine	<u>Evidence source(s) and strength of evidence:</u> Bronchial hyperreactivity is a direct effect of non-beta selective propranolol, resulting in a bronchospasm due to pulmonary beta 2-blockade. Propranolol, by its bronchoconstrictive properties, may aggravate the respiratory condition of the patient, in a context of viral bronchiolitis. Bronchiolitis is a potentially life-threatening respiratory condition that affects young babies. <u>Characterisation of the risk:</u> In the clinical studies, bronchospasm, bronchiolitis and bronchitis were respectively reported in 2.9%, 7.9% and 13.1% of 480 patients treated with V0400SB oral formulation. Two cases were serious: one patient was hospitalized for obstructive bronchitis positive to RSV and rhinovirus, the other experienced bronchospasm related to bronchitis one month after the discontinuation of V0400. In the CUP, out of the 1,661 patients, 47 cases of respiratory disorders were reported, including 19 serious cases, including one circulatory shock and respiratory arrest. Most of these cases of respiratory disorders occurred during wintertime (29/47) and were of infectious origin, mostly several months after treatment introduction.
Risk factors and risk groups	Risk groups or risk factors included prematurity, cardiopathy, congenital defects of the airways, history of asthma and bronchoconstriction, history of eczema, history of familial atopy, history of parental smoking, pets at home, and nursery attendance (Breast-feeding is considered protective).
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.3, 4.4,4.8.* *PL sections 2, 3, 4* Additional risk minimisation measures: *Educational material to care giver*

Potential risk of administration error	
Evidence for linking the risk to the medicine	<u>Evidence source(s) and strength of evidence:</u> The potential risks of administration error to be considered are those linked to an error in the administered dose per intake that needs to be adjusted during the treatment course: firstly during treatment titration, then with the evolution of patient's weight and those linked to an accidental double administration by 2 different persons.

	Wrong medication: The treatment is to be administered to the infant with an oral syringe graduated in mg, specifically dedicated to Hemangiol® packaged together with the bottle containing the propranolol solution. The risk of error in case of concomitant administration of several drugs in infants with different syringes is very low since the device provided is marked under the trade name "HEMANGIOL" of the drug product. *Wrong dose*: The physician will prescribe a dose in mg/kg/day in 2 separate doses. For example, a patient who weighs 6 kg with a prescription of 3 mg/kg/day will be prescribed 18 mg/day in 2 separate doses of 9 mg. However, in 2 situations, there is a risk for potential medication errors by parents or caregivers: • At the beginning of treatment, when the starting dose must be up titrated to the therapeutic dose during the first three weeks. • During the treatment period, when the dose must be regularly readjusted by the physician according to the changes in the child's weight. There is a risk of under or overdose, if the syringe is not well used and/or posology not understood. *Wrong route of administration*: There is no possibility to administer Hemangiol® by another route than the oral route with the device provided. *Wrong patient*: In the same family or in day care centre, several children can be treated with a medication administered using a syringe. However, the device is marked with the trade name of the drug product, limiting this type of error. <u>Characterisation of the risk:</u> In the clinical studies, no case of administration error was reported. In the CUP, 12 cases of administration error were reported: - 1 serious case of patients who experienced hypoglycemic seizure/bradycardia and hypoglycemia in the other case, while propranolol was not discontinued during a fasting period. - 1 serious case of a drug dispensing error; the pharmacist delivered Risperdal® (risperidone) instead of propranolol PFD. The patient recovered with important neurological sequelae. - 2 cases of errors due to the use of the syringe without occurrence of adverse reaction (one case of administration with a syringe of another product and one case with confusion between mg and mL when using the syringe). - 2 cases of drug dose omissions, - 1 case of an accidental double administration (by 2 different persons) without adverse reaction;

	- 1 case concerned a patient who received 1mg/kg/day, 3 times daily and experienced cold extremities.
Risk factors and risk groups	All patients are at risk of drug administration error.
Risk minimisation measures	Routine RMMs: *SmPC sections 4.2, 4.9* *PL sections 2, 3, 4* Additional RMMs: *Educational material to care giver*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of HEMANGIOL®.

II.C.2 Other studies in post-authorisation development plan

None