EMA/87140/2016

Summary of the risk management plan (RMP) for Kolbam (cholic acid)

This is a summary of the risk management plan (RMP) for Kolbam, which details the measures to be taken in order to ensure that Kolbam 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 Kolbam, which can be found on Kolbam's EPAR page.

Overview of disease epidemiology

Kolbam (cholic acid) is used for the treatment of inborn errors in primary bile acid synthesis due to the lack of one of the following liver enzymes: sterol 27-hydroxylase; 2-methylacyl-CoA racemase; or cholesterol 7α-hydroxylase.

Inborn errors in primary bile acid synthesis are a group of genetic diseases in which the body lacks enzymes that are needed to produce primary bile acids, which are the main component of the bile, a fluid produced by the liver that helps digestion. Instead, the body produces abnormal bile acids, which can damage the liver and potentially lead to liver failure.

Individuals with inborn errors of primary bile acid synthesis may also experience disruption to the normal flow of bile in newborn children (neonatal cholestasis), progressing to liver failure in early childhood, and damage to the nervous system (neuropathy) in adults. Various fat and fat-soluble vitamin malabsorption syndromes may also arise.

Inborn errors of primary bile acid synthesis are very rare disorders and affect about 3,000 people in the European Union. There are no known regional differences in the prevalence of the conditions.

Summary of treatment benefits

Kolbam was investigated in one main study involving 52 patients with inborn errors in primary bile acid synthesis, including 7 patients who lack either sterol 27-hydroxylase, 2-methylacyl-CoA racemase or cholesterol 7α-hydroxylase. The main measures of effectiveness were changes in bile acid levels and liver function before and after treatment with Kolbam. The efficacy of Kolbam for the authorised indications was established based on the results of this study. This is consistent with clinical expectations and literature data.

Unknowns relating to treatment benefits

The benefits of Kolbam in the treatment of certain inborn errors of primary bile acid synthesis have been demonstrated through clinical studies. There are no or limited data in:

- children aged less than one month;
- the elderly;

- patients with liver impairment unrelated to their condition;
- pregnant women;
- ethnicities other than Caucasian.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Heartburn due to stomach acid going upwards into the oesophagus (gastroesophageal reflux)	Kolbam can cause gastroesophageal reflux. This is a common condition (which may affect up to 1 in 10 people treated with Kolbam) where stomach acid goes from the stomach into the oesophagus (gullet, the long tube that runs from the mouth to the stomach).	Not preventable. Doctors should manage symptoms as appropriate.
Diarrhoea	Treatment with Kolbam can cause diarrhoea. Diarrhoea may affect up to 1 in 10 people.	Not preventable. Doctors should manage symptoms as appropriate.
Itching (pruritus)	Treatment with Kolbam can cause itching. Its frequency is unknown.	Not preventable. Doctors should manage symptoms as appropriate.
Increased levels of liver enzymes which could be indicative of liver damage (increased transaminases)	Treatment with Kolbam can cause an increase in liver enzymes which may be indicative of liver damage. Its frequency is unknown.	Not preventable. Patient should be monitored for liver function. Treatment with Kolbam should be stopped if liver function does not improve within 3 months of starting treatment. Treatment should be stopped earlier if there are clear indications of severe liver failure.

Important potential risks

Risk	What is known
Effects in pregnancy (reproductive toxicity)	There are limited safety data for the use of Kolbam in pregnant women. Animal studies do not indicate reproductive toxicity. However, one study showed that when injected into pregnant ewes in late stages of pregnancy, cholic acid appeared to induce premature labour. Any similar risk in pregnant women receiving the recommended oral (by mouth) dose of Kolbam is unlikely. Kolbam may be used during pregnancy if the doctor considers that the benefits to the patient outweigh the possible risk.

Risk	What is known
Elevated blood pressure when the heart is contracting (systolic blood pressure)	Systolic blood pressure was increased following oral administration of 80 mg/kg cholic acid in rats for 30 days. However, it is unclear whether this effect is dose-related and the clinical relevance of these observations is uncertain since increases in blood pressure following administration of lower doses of cholic acid have not been reported in humans, including infants and children.
Risk of Kolbam causing cancer (carcinogenicity)	There are no data in humans suggestive of a carcinogenic (cancer-causing) effect of cholic acid. In rats, giving cholic acid together with known carcinogens (substances which can cause cancer) has been shown to increase tumour formation compared with the known carcinogen alone. This has led to the identification of cholic acid as a tumour promoter. The potential risk is serious, particularly if patients are exposed to known carcinogens at the same time as cholic acid.
Medication error	There is a possibility that Kolbam could be administered incorrectly, particularly at the wrong dose.
Formation of gallstones	There were no reports of gallstone formation in patients treated with Kolbam during clinical trials. Formation of gallstones has been reported in the scientific literature for a few patients treated with cholic acid.

Missing information

Risk	What is known
Newborns less than 1 month of age.	Two newborns less than 28 days of age were treated during the course of the clinical trials with Kolbam. There were no cholic-acid-related adverse events reported for either of these patients.
Elderly patients	There is no experience with elderly patients in the clinical trials with Kolbam.
Pregnant or breastfeeding women	There are no reports from the clinical trials with Kolbam that any pregnant or breastfeeding women have been treated with cholic acid. A published article where two female patients with inborn errors of primary bile acid synthesis were treated with cholic acid describes four normal pregnancies in these two patients which resulted in the birth of four healthy infants (Gonzales et al., 2009).
Patients with ethnic background other than Caucasian	In the main clinical study, 35% of patients were white, 34% were of unknown race, and the remaining patients were principally of Hispanic or Middle-Eastern origin together with a few other ethnicities. None of the patients with ethnic origin other than Caucasian reported any adverse events related to Kolbam. The occurrence of inborn errors of primary bile acid synthesis is very rare, but does not appear to be limited to any particular ethnicity.

Risk	What is known
Patients with pre-existing liver disease	Liver disease as an underlying condition may vary from severe to mild depending on the defect. No case of drug-related worsening of liver disease has been reported during clinical trials with Kolbam.
Patients with brain disease caused by liver problems (hepatic encephalopathy)	If a diagnosis of inborn errors of primary bile acid synthesis is made during childhood, the infant or child may already have a range of serious liver abnormalities. Liver damage is largely irreversible, so liver transplantation may still be the only long-term option. All patients in the clinical program have responded to cholic acid, and none has developed hepatic encephalopathy.
Patients needing an urgent liver transplant	If patients diagnosed with inborn errors of primary bile acid synthesis are not treated, it is expected that their clinical condition will worsen and this may lead to liver damage and the requirement for a liver transplant. If patients are not diagnosed early, they may develop irreversible liver damage which may lead to the need for a transplant. There is evidence from one clinical trial of four patients who needed a liver transplant while being treated with Kolbam, due to a worsening of their clinical condition. No other cases of urgent liver transplant have been reported during clinical trials.
Off-label use (use outside the approved use)	As for any medicine, there is a possibility that Kolbam could be used to treat disorders for which it is not approved.

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 Kolbam can be found on Kolbam'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 in Kolbam's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Risk of the medicine being given at the wrong dose or in the wrong way (medication errors)

Risk minimisation measure: **Physician education programme**
Objective and rationale: To provide information on the correct and safe use of the medicine.
Description: Educational material will be provided to all physicians expected to prescribe Kolbam, with information on how to calculate the correct dose and to administer the product correctly, as well as

Risk minimisation measure: **Physician education programme**
information on the signs and symptoms of an overdose and how to manage it.

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**
An open-label, single-center, non-randomized continuation study of cholic acid capsules in subjects with inborn errors of bile acid synthesis (CAC-002-01)	To evaluate the therapeutic efficacy and safety of cholic acid in subjects with identified inborn errors of bile acid synthesis.	The study will assess the safety and tolerability of cholic acid capsules, in particular the incidence and severity of adverse events compared with baseline, clinical laboratory test results, vital signs, physical examination findings and malabsorption (height, weight gain, normalization of steatorrhoea (abnormal fatty stools), vitamins A, E, D and prothrombin time).	Ongoing	Progress and results from the study to be submitted with the PSURs and annual re-assessments of the medicine; final study report planned for Q3 2016
Patient registry	To collect efficacy and safety information in “real life” clinical use.	This will provide additional safety information (e.g. adverse events and routine test results) including in those patient groups not included in clinical studies. Furthermore, the proposed registry would enable assessment of any off-label use and its extent.	Planned	Progress and results from the registry to be submitted with the PSURs and annual re-assessments of the medicine.

Studies which are a condition of the marketing authorisation

The patient registry is a specific obligation of the marketing authorisation under exceptional circumstances.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 02-2016.