VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Gallstones (cholelithiasis)

Gallstones are abnormal masses of a solid mixture of cholesterol crystals, mucin calcium bilirubinate,. occuring when mechanism for the solubilisation of cholesterol or bilirubin fails (1).

In the United States, about 20 million people (10-20 % of adults) have gallstones. Every year 1-3% of people develop gallstones and about 1-3% of people become symptomatic. The prevalence of cholelithiasis in other Western cultures is similar to that in the United States, but it appears to be somewhat lower in Asia and Africa. A Swedish study found that the incidence of gallstones was 1.39 per 100 person-years. In an Italian study, 20% of women had stones, and 14% of men had stones. In a Danish study, gallstone prevalence in persons aged 30 years was 1.8% for men and 4.8% for women; gallstone prevalence in persons aged 60 years was 12.9% for men and 22.4% for women (2).

Treatment of asymptomatic gallstone patients is not routinely recommended. Symptomatic gallstone patients do need treatment, which includes analgesic therapy of biliary colic and medical or surgical therapy or both together. Oral litholysis (the dissolution of urinary calculi) with UDCA is appropriate for subset of patients who do not want or are unfit for surgery with small (≤5 mm in size) radiolucent cholesterol gallstones in a functional gallbladder (1).

Gall reflux gastritis

Bile reflux gastritis is due to an excessive reflux of bile, pancreatic and intestinal secretions into the stomach. Data on prevalence of bile reflux gastritis is limited. Study by Vere (2005) concluded that the incidence of alkaline reflux gastritis was higher between 51 and 80 years (3).

Primary biliary cirrhosis (PBC)

PBC is a rare disease with prevalence ranging from 28 to 402 per million, which is highly variable based on geographical location. PBC primarily affects middle aged women. Several reports indicate that the incidence and prevalence of PBC is increasing in the UK, US, Finland and Australia (4).

Cystic fibrosis

Cystic fibrosis is a chronic progressive disease, it exists in every ethnic group and it is equally common in both sexes. The prevalence of cystic fibrosis varies according to ethnicity, from 1/1800 to 1/5000 in Caucasians born alive in Europe, in the US and in Canada, 1/14000 in Afro-Americans, and 1/40000 in Finland. It is considered a rare disease among Asians and Africans. Cirrhosis, ascites, portal hypertension, esophageal varices and bleeding are complications of hepatobiliary disease associated with cystic fibrosis, and frequently affect teenagers and adults (5).

VI.2.2 Summary of treatment benefits

Ursodeoxycholic acid has capability to suppress the synthesis and secretion of cholesterol by the liver and inhibits intestinal absorption of cholesterol. Because of this property ursodeoxycholic acid is used to treat cholesterol-rich gallstones in patients with functioning gallbladder.

In cholestasis, liver disease and duodenogastric reflux, the efficacy of ursodeoxycholic acid is presumably due to reduced metabolism of lipophilic toxic endogenous bile acids in favour of hydrophilic cytoprotective, non-toxic ursodeoxycholic acid, and improvement in the hepatocytes' capacity for excretion and immune-regulatory process.

VI.2.3 Unknowns relating to treatment benefits

None.

VI.2.4 Summary of safety concerns

Table 15. Important identified risks

Important Identified Risk	**What is known**	**Preventability**
Diarrhoea might be caused by using the drug (Drug-induced gastro-intestinal disorders (diarrhoea)	In clinical trials, reports of pasty tools or diarrhoea during ursodeoxycholic acid therapy were common.	The patient should inform his/her doctor if he/she has diarrhoea. Dose reduction or discontinuation of treatment is recommended.
Frequent cramp-like pain in the upper abdomen. (Biliary colic)	Ursodeoxycholic acid can be used for dissolution gallstones only if the gall bladder is working.	The product must not be used in patients who have frequent cramp-like pain in the upper abdomen (biliary colic).
Severe worsening during the treatment in patients with advanced chronic inflammatory disease of the biliary ducts. (Decompensation of hepatic cirrhosis in patients with advanced stage of primary biliary cholangitis)	In patient with advanced biliary ducts damage, liver function may deteriorate. In very rare cases it can lead to worsening of state with poor liver function and worsening of liver scaring.	If decompensation of hepatic cirrhosis occurs, the treatment must be stopped.
Allergy to bile acids (like ursodeoxycholic acid) and skin	All drugs may cause allergy. Urticaria can occurvery rarely	The cases of urticaria are not predictable.

Important Identified Risk	What is known	Preventability
problems (Hypersensitivity and skin reactions)	(may affect up to 1 in 10 000 patients treated with ursodeoxycholic acid).	If such cases occur treatment is symptomatic.

Table 16. Important potential risks

Important Potential Risk	What is known (including reason why it is considered a potential risk)
Teratogenicity	In studies in rats, tail malformations occurred after a dose of 2,000 mg of ursodeoxycholic acid per kg of body weight. In rabbits, no teratogenic effects were found, although there were embryotoxic effects (from a dose of 100 mg per kg of body weight).

Table 17. Missing information

Missing Information	What is known
Off-label use in patients with radio-opaque calcified gallstones, occlusion of the biliary tract, frequent episodes of biliary colic and impaired contractility of the gall bladder and biliary tract.	Ursodeoxycholic acid is approved for dissolution of cholesterol gallstones only when the gallstones do not produce any shadows on the radiograph and are not of greater diameter than 15 mm, and only when the gall bladder is functioning. Using ursodeoxycholic acid in patients who have calcified gallstones, occlusion of the biliary tract, frequent episodes of biliary colic and impaired contractility of the gall bladder and biliary tract is
Off-label use in patients with acute inflammation of the gall bladder or biliary tract.	Ursodeoxycholic acid is approved for dissolution of cholesterol gallstones only when the gallstones do not produce any shadows on the radiograph and are not of greater diameter than 15 mm, and only when the gall bladder is functioning. Using ursodeoxycholic acid in patients with acute inflammation of the gall bladder or biliary tract is contraindicated.
Off-label use in children with biliary atresia.	Ursodeoxycholic acid is approved for treatment of hepatobiliary disorders associated with cystic fibrosis in children aged 6 to 18 years. Using ursodeoxycholic acid in children with biliary atresia who have poor bile flow even after surgery is contraindicated.
Use in brestfeeding women.	There are no sufficient data regarding use of ursodeoxycholic acid in breastfeeding women. According to few documented cases of breastfeeding women milk levels of ursodeoxycholic acid are very low and probably no adverse reactions are to be expected in breastfed infants.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for UDCA Kappler 250 mg hard capsules can be found on the National Health Authority website

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post-authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

As this is the first version of RMP, summary of changes to the risk management plan is not presented.