## VI.2 Elements for a public summary

### *VI.2.1 Overview of disease epidemiology*

*Dissolution of cholesterol gallstones*

This product is used for dissolution of gallstones that are composed of cholesterol in patients:

- having one or more radio-opaque (radio-negative) gallstones, preferably with a diameter of no more than 2 cm, in a properly functioning gallbladder;
- refusing surgical intervention or for whom surgical procedures are not indicated;
- in whom cholesterol supersaturation has been demonstrated by chemical testing on bile obtained via duodenal drainage.

Gallstones are hardened deposits of digestive fluid that can form in your gallbladder.

Cholesterol gallstones are the most common type of gallstones. These gallstones are composed mainly of undissolved cholesterol, but may contain other components. If a gallstone lodges in a duct and causes a blockage, it may cause sudden and rapidly intensifying pain. Gallstone pain may last several minutes to a few hours. Chronically, gallstones in the gallbladder may cause progressive fibrosis and loss of function of the gallbladder, a condition known as chronic cholecystitis.

Burden of gallstones is highest in people of northern European descent, and in Hispanic populations and Native American populations. Burden of gallstones is lower in Asians and African Americans. Women are more likely to develop cholesterol gallstones than men, especially during their reproductive years, when the incidence of gallstones in women is 2-3 times that in men. The difference appears to be attributable mainly to estrogen, which increases biliary cholesterol secretion. Risk of developing gallstones increases with age. Gallstones are uncommon in children in the absence of congenital anomalies or hemolytic disorders.

Beginning at puberty, the concentration of cholesterol in bile increases. A Swedish epidemiologic study found that the occurence 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 burden in persons aged 30 years was 1.8% for men and 4.8% for women; gallstone burden in persons aged 60 years was 12.9% for men and 22.4% for women.[1]

*Gallstone shockwave dissolution (lithotripsy)*

This product is used as adjuvant medication before and after gallstone shockwave dissolution (lithotripsy). This procedure uses ultrasound waves to break up gallstones. It may be used alone or along with bile acids (like ursodeoxycholic acid) to break up stones.

*Primary biliary cholangitis (PBC, previously known as primary biliary cirrhosis)*

This product is used for the treatment of primary biliary cholangitis (PBC – chronic disease of the bile ducts ending with cirrhosis) in patients without decompensated cirrhosis (diffused chronic liver disease in which the disease-related reduced output of the liver cannot longer be balanced). PBC is considered an autoimmune disease, in which the body turns against its own cells.

PBC is more common in Northern Europeans and is less common in populations of African descent. Women account for 75-90% of patients with PBC. PBC mostly affects middle-aged women, with a mean age of 39 years. Onset usually occurs in persons aged 30-65 years. However, patients as young as 22 years and as old as 93 years at the time of diagnosis have been reported.[2]

*Hepatobiliary disorders as a result of cystic fibrosis in children aged 6 to 18 years.*

This product is used for the treatment of liver disease associated with cystic fibrosis (mucoviscidosis) in children aged 6-18 years. The worldwide occurence varies from 1 per 377 live births in parts of England to 1 per 90,000 Asian live births in Hawaii. Cystic fibrosis is an inherited disorder that causes severe damage to the lungs and digestive system. Patients with cystic fibrosis have increased risk for developement of gallstones, as many as 15% of young adults with cystic fibrosis have gallstones.[3]

### *VI.2.2 Summary of treatment benefits*

Ursodeoxycholic acid is a well-known active substance with established efficacy and tolerability used in the dissolution of cholesterol gallstones and also in the treatment of primary biliary cholangitis of the liver.

### *VI.2.3 Unknowns relating to treatment benefits*

Unknowns relating to treatment benefits are not identified.

### *VI.2.4 Summary of safety concerns*

Table 15 Important identified risks

| Important Identified Risk | What is known | Preventability |
|---|---|---|
| Drug-induced gastrointestinal disorders (diarrhoea) | Soft, loose stools or diarrhoea are common side effects of ursodeoxycholic acid.<br>Diarrhoea is passing looser or more frequent stools than is normal for you (at least three loose or liquid bowel movements each day). It can result in dehydration due to fluid loss. Signs of dehydration often begin with loss of the normal stretchiness of the skin and changes in personality. This can progress to decreased urination, loss of skin color, a fast heart rate, and a decrease in responsiveness as it becomes more severe. | Yes, inform your doctor if you suffer from diarrhoea. Reduction of the dose or discontinuation of the treatment with ursodeoxycholic acid may be required.<br>This medicine should be used under medical supervision. |
| Allergic and skin reactions (Hypersensitivity and skin reaction) | Very rarely ursodeoxycholic acid may cause urticaria (hives). Some individuals may be allergic (hypersensitive) to to ursodeoxycholic acid or bile acids, or any of the other ingredients of this medicine. Hypersensitivity symptoms may be non-severe (e.g. skin rash) and severe, like anaphylaxis. Anaphylaxis is characterized by a rapid onset of symptoms that include slurred speech, difficulty breathing or swallowing, anxiety and confusion, palpitations and fainting or light-headedness. Anaphylaxis is a serious, life-threatening condition and anyone who is suspected of having an anaphylactic reaction should receive immediate medical care. | Yes, use of product in patients with hypersensitivity to the active substance, bile acids or to any of the excipients is contraindicated.<br>This medicine should be used under medical supervision. |
| Worsening of liver cirrhosis during therapy of the advanced stages of primary biliary cholangitis(Decompensation of hepatic cirrhosis during therapy of the advanced stages of primary biliary cholangitis) | In very rare cases decompensation of liver cirrhosis has been observed, which partially regressed upon discontinuation of treatment.<br>In patients with PBC, the clinical symptoms may worsen in rare cases at the start of treatment, e.g. pruritus may increase. In this case, the dosage of UDCA capsules can be reduced to one 250 mg capsule per day and subsequently should be gradually increased to the recommended dose as described in section 4.2. | Yes, in the first 3 months of treatment your doctor should monitor your liver function regularly every 4 weeks. Thereafter, the controls should be carried out every 3 months.<br>This medicine should be used under medical supervision. |
| Biliary colic | If the gallbladder cannot be visualised on X-ray images, or in cases of calcified gallstones, impaired contractility of the gallbladder or frequent episodes of cramp-like pains in the upper abdomen, treatment with UDCA must be discontinued. | Do not take this product if you suffer from frequent cramp-like pains in the upper abdomen. |

Table 16 Important potential risks

| Important Potential Risk | What is known (including reason why it is considered a potential risk) |
|---|---|
| Structural body defects of fetus and effects on the development of the baby during pregnancy and after birth<br>(Foetal malformations and pre-/post-natal developmental effects) | Studies in animals have demonstrated that very high doses of ursodeoxycholic acid may cause certain defects and also toxic effects in their offsprings.<br>You should not take this product during pregnancy unless your doctor considers it absolutely necessary.<br>Even if you are not pregnant, you should still discuss this matter with your doctor. Women of childbearing potential should be only treated with concomitant use of reliable contraceptive measures. Non-hormonal contraceptive measures or oral contraceptive containing low dose of oestrogen (the "pill") are recommended. If you are taking this product to dissolve gallstones you should use effective non-hormonal contraceptive measures because hormonal contraceptives can promote the formation of gallstones.<br>Before starting treatment your doctor will exclude the possible existence of pregnancy. |

Table 17 Missing information

| Missing information | What is known |
|---|---|
| Use for an unapproved indications in the following cases: if you have a gallstone calcification; if your bile ducts are closed; if you suffer from frequent cramp-like pains in the upper abdomen; if your gall bladder ability to contract is impaired<br>(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 gallbladder or the biliary tract) | Product is not indicated for these patients, because its safety and efficacy in the treatment of such conditions is not established.<br>Do not take this product if you have a gallstone calcification; if your bile ducts are closed; if you suffer from frequent cramp-like pains in the upper abdomen or if your gall bladder ability to contract is impaired. |
| Use in children for an unapproved indication in case of closure of bile ducts<br>(Off-label use in children with biliary atresia) | Product is not indicated for these patients, because its safety and efficacy in the treatment of such condition is not established. |
| Use in breastfeeding women | There are only a few documented cases of taking of ursodeoxycholic acid during lactation. The levels of ursodeoxycholic acid in breast milk are very low. Therefore adverse reactions in nursing infants are unlikely. |
| Use for an unapproved indication if you have an inflammation of the gall bladder or bile ducts<br>(Off-label use in patients with acute inflammation of the gall bladder or biliary tract) | Product is not indicated for these patients, because its safety and efficacy in the treatment of such conditions is not established. |

### *VI.2.5 Summary of additional minimisation measures by safety concern*

All medicines have a Summary of Product Characteristics (SPC) 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 (PIL). The measures in these documents are known as routine risk minimisation measures.

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*

Not applicable for the initial RMP.