IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Cholurso 250 mg film-coated tablets
Ursodeoxycholic acid
PA1913/002/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This product was initially authorised under procedure number FR/H/0551/001-002 with FR as RMS. The responsibility of RMS was transferred to Ireland on [02/07/2020 under procedure number IE/H/1136/001-002/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1913/002/001-002
Marketing Authorisation Holder: Laboratoires Mayoly Spindler

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the decentralised procedure for DOZURSO 250 and 500 mg, film-coated tablets from MAYOLY SPINDLER was approved on 3rd November 2014. The concerned member states are BE, DE, HU, IT, PT, and UK.

The product is indicated in adults for:
- Treatment of primary biliary cirrhosis (PBC) in patients without decompensated cirrhosis.

- Dissolution of radiolucent cholesterol gallstones not larger than 15 mm in diameter in patients with a functioning gallbladder and for whom surgical treatment is not indicated.

The dose is 12-16 mg/kg/day for PBC (depending on the body weight of the patient) and 8-10 mg/kg/day for the dissolution of gallstones.

Ursodeoxycholic acid (UDCA) is a naturally occurring bile acid present in small quantities in human bile. UDCA has been used for decades to treat hepatobiliary disorders. It is approved and marketed in France (since 1980) and in the EU as well as outside the EU.

Within the EU the approved solid dosage forms are supplied as capsules or tablets of 100 mg to 500 mg/unit. Some oral suspensions are also registered and marketed within the EU (250 mg/5 ml). Given that UDCA is registered and marketed for more than 10 years with a recognised efficacy and satisfactory level of safety this application for a Marketing Authorization was presented in accordance with Article 10a of the Directive 2001/83/DC "well-established use" with a detailed reference to published scientific literature.

II. QUALITY ASPECTS

2. QUALITY ASPECTS

2.1 Introduction

The medicinal product Dozurso is presented as film coated tablet containing 250mg and respectively 500mg of the active substance ursodeoxycholic acid. The excipients are maize starch, sodium lauryl sulfate, povidone, colloidal anhydrous silica, magnesium stearate, and Opadry white film coating. Dozurso film coated tablets is packaged in aluminium/ PVC/ PVDC blisters.

2.2 Drug substance

The active substance is ursodeoxycholic acid, a known molecule, described in the Ph Eur.

The active substance manufacturer has presented a certificate of suitability (CEP) issued by EDQM in support of the chemistry and control documentation.

The active substance specifications include tests performed in accordance with the Ph Eur monograph, warranting the identity, assay, and purity. The retest period is documented.

Ursodeoxycholic acid is of animal origin; the risk of transmitting agents of animal spongiform encephalopathies (TSE/BSE) has been addressed.

2.3 Medicinal product

The drug product Dozurso 250 mg film-coated tablets and 500 mg scored film-coated tablets contains the active substance ursodeoxycholic acid, a known active substance.

The pharmaceutical development is addressed; the qualitative and quantitative formula was developed to obtain similarity with the product Delursan®; the formula of the 500mg strength is proportional to the 250mg strength. The subdivision of the 500mg scored tablets has been addressed.

The manufacturing process is described and consists of wet granulation, calibration, lubrication, compression, and coating.

The excipients used are commonly used excipients, described by the Ph Eur, except for the coating agent, opadry II white, which is adequately documented by the applicant.

The control of drug product is assured via in-house specifications; the tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose. Same specifications apply at release and shelf-life with justified exceptions. The analytical methods are described and validated. Batch analysis data is within specifications and demonstrate batch-to-batch consistency.

The container closure consists of Aluminium/PVC /PVDC blisters; the conformity to the current EU requirements is confirmed.

Stability studies were performed according to ICH under long-term, intermediate, and accelerated conditions. Results are overall within specifications and support the shelf-life claimed in the SmPC (36 months).

III. NON-CLINICAL ASPECTS

3. NON-CLINICAL ASPECTS

Ursodeoxycholic acid (UDCA) is a naturally occurring bile acid present in small quantities in human bile. Unlike endogenous bile acid, UDCA is very hydrophilic and devoided of detergent properties. UDCA has been used for decades to treat hepatobiliary disorders.

UDCA is a potent intracellular signaling agent that stimulates impaired hepatocellular secretion, possesses anti-apoptotic effects and could mediate cholangiocyte protection.

After oral administration of ursodeoxycholic acid (500 mg/kg/day to 4 g/kg/day) to rats, changes such as cholangitis, bile duct hyperplasia and focal necrosis were observed at higher doses (1 to 4 g/kg/day). In a 1-year toxicity study conducted in monkeys, the NOAEL for UDCA was found to be 50 mg/kg/day. At higher doses (300 mg/kg/day and 900 mg/kg/day), gross pathological lesions and histopathological lesions in liver were observed.

Oral administration of UDCA in pregnant rats or rabbits was not teratogenic.
UDCA was not mutagenic in the Ames test, mutation assay in mouse lymphoma cells, sister chromatid exchange assay in human lymphocytes, chromosomal aberrations assay in mouse germ cells and *in vivo* micronucleus test in Chinese hamster bone marrow cells.

In 104-week and/or 126-138 week dietary carcinogenic studies conducted in mice and rats there was no evidence for carcinogenic potential of UDCA.

Concerning the environmental risk and according to the Applicant's estimation, the $PEC_{surface\ water}$ is 5700 ng/L which is significantly higher than the limit value of 10 ng/L. In the case in point, the guideline EMEA/CHMP/SWP/4447/00 corr 1* specifies that a Phase II environmental fate and effect analysis should be performed. Therefore the Applicant is committed to provide the results of phase II environmental assessment, 3 semesters after the grant of the Marketing Authorisation. To date the Applicant has not yet submitted these data.

IV. CLINICAL ASPECTS

4. CLINICAL ASPECTS

4.1 Introduction

UDCA is the 7 β-hydroxy epimer of chenodeoxycholic acid (CDCA). It is normally present in very small quantities in humans. Oral administration of UDCA increases this fraction in a dose related manner and UDCA may become the predominant bile acid. The total bile acid pool size, which is decreased in gallstone patients, may be increased with UDCA along with increased bile acid secretion rates. Faecal bile acid loss is increased with therapy and cholesterol secretion into the bile is reduced, without a reduction in phospholipids. The cholesterol saturation of bile is decreased allowing gradual solubilisation of cholesterol from gallstones to occur.

4.2 Pharmacokinetics

UDCA protein binding in plasma is 96–98%. First pass extraction of UDCA from the portal vein by the liver ranges from 50 to 70 %. UDCA is conjugated to glycine and taurine and then excreted into bile and passes to the small bowel. In the intestine, some conjugates are deconjugated and reabsorbed in the terminal ileum. Conjugates may also be dehydroxylated to lithocholic acid, part of which is absorbed, sulphated by the liver and excreted by the biliary tract.

In healthy subjects the main route of elimination is in faeces while in patients with a severe liver disease, renal excretion becomes a major route for elimination of bile acids. The biological half-life of orally administered UDCA is 3.5-5.8 days (Ursofalk® Monography, Dr. Falk Pharma GmbH).

The degree of bile saturation with UDCA correlates with the total daily dose absorbed orally by the patient. However, over a certain dose no additional enrichment occurs due to the inability of UDCA to inhibit synthesis of bile acids as well as to the epimerization of UDCA in chenodeoxycholic acid.

Conjugated UDCA is absorbed mainly in the distal ileon, where it enters into competition with endogenous bile acids for active transportation and undergoes an enterohepatic circulation. Unabsorbed conjugated UDCA reaches the colon, is deconjugated and converted to lithocholic acid by intestinal bacteria. Due to the fact that its water solubility is low, most of the lithocholic acid remains insoluble in the colon. A fraction of the lithocholic acid reaches the liver again, is sulphated and then excreted into the stool (Poupon, 2012). This is the reason why in case of overdose a diarrhea is observed and that other symptoms of overdose are unlikely because the absorption of UDCA decreases with increasing dose and therefore more is excreted with the faeces. Therefore no specific countermeasures are necessary and the consequences of diarrhoea should be treated symptomatically with restoration of fluids and electrolytes balance.

Several published clinical trials demonstrated the efficacy of UDCA when taken explicitly in fed state (administration of UDCA together with a meal) in the proposed indications PBC (Primary biliary cirrhosis) and cholesterol biliary lithiasis. The published clinical studies and conditions are presented hereafter:

Table 1 - Administration of UDCA together with a meal

Authors, Year	Indication	Doses of UDCA	Time
Angulo 1999	Primary biliary cirrhosis	5-7 $mg.kg^{-1}.day^{-1}$ 13-15 $mg.kg^{-1}.day^{-1}$ 23-25 $mg.kg^{-1}.day^{-1}$	In four divided doses, given with meals and a bedtime snack
Van de Meeberg 1996	Cholestatic liver disease	10 $mg.kg^{-1}.day^{-1}$ (Ursofalk, Germany)	In a single dose, taken with a small snack at bedtime, or in three divided doses with meals
Poupon 1997	Primary biliary cirrhosis	13-15 $mg.kg^{-1}.day^{-1}$ 14 $mg.kg^{-1}.day^{-1}$	In two doses or doses divided, with meals In one dose with the evening meal
Jorgensen 1995	Primary biliary cirrhosis	13-15 $mg.kg^{-1}.day^{-1}$	With meals and a bedtime snack three to four times per day
Roda 2002	Primary biliary cirrhosis	Dose range: 8.2 to 39 $mg.kg^{-1}.day^{-1}$ (600, 1200 and 1800 $mg.day^{-1}$ 900, 1500 and 2100 $mg.day^{-1}$)	In two or three divided doses after meals
Erlinger 1984	Dissolution of gallstones	2.1, 4.2, 8.4 and 16.2 $mg.kg^{-1}.day^{-1}$ (125, 250, 500 and 1000 mg/day) (4 tablets)	At breakfast and bedtime

Moreover, it should be noticed that the SmPC of several European UDCA does contain the mention "during a meal" (Ursofalk Belgium) or "after meals" (Ursochol Belgium, Destolit UK). This is confirmed by the current information leaflets available for UDCA marketed in Europe, where instructions to patients are: "preferably during or after meals" (UDCA Ratiopharm Italy), "Administer preferably with meals" (Ursobilane Spain), "Take the tablets in the evening at bedtime" (Ursofalk 500 tablets UK). Thus for treatment of primary biliary cirrhosis, it is recommended to take Dozurso during the meals.

The degree of biliary enrichment of UDCA does not depend on the formulation or the number of doses administered per day, but rather the total daily dose. After absorption UDCA enters into the enterohepatic circulation which preserves bile acids to a high degree with only minor faecal and urinary loss. Biliary UDCA enrichment is dependent on the total daily dose and the function of the hepatocytes and cholangiocytes in the liver.

The efficacy of UDCA is related to its concentration in bile rather than in plasma, serum levels being not indicative of bioavailability in clinical settings (Urso® Monography, Aptalis Pharma Canada Inc.).

In this dossier, one bioequivalence study versus Delursan was submitted as complementary information which was considered as not relevant.

4.3 Pharmacodynamics

Bile acids are acidic steroids that are synthesized from cholesterol within the hepatocytes. UDCA represents a hydrophilic dihydroxy (i.e. 3α, 7β-dihydroxy-5β-cholan-24-oic acid) bile acid.

In humans, UDCA accounts for up to 4% of the bile acids pool and because it is not synthesized in the liver it likely originates in the colon by bacterial 7β epimerization of the primary bile acid chenodeoxycholic. Following its formation, UDCA is passively absorbed by the colonic mucosa to enter the portal circulation and subsequently the pool of bile acids.

Ursodeoxycholic acid, a bile acid with fewer hepatotoxic properties than endogenous bile acids, competes with the endogenous bile acids for absorption in the terminal ileum.

The mechanism of action of ursodeoxycholic acid is uncertain and is probably multifactorial.

UDCA exerts its actions in liver through multiple possibly interrelated pathways as shown in an overview on Figure 1.

Experimental evidence suggests the following major mechanisms of action: protection of cholangiocytes against cytotoxicity of hydrophobic bile acids, stimulation of hepatobiliary secretion, and protection of hepatocytes against bile acid–induced apoptosis. One or all of these mechanisms may be of relevance in individual cholestatic disorders and/or different stages of the cholestatic liver disease.

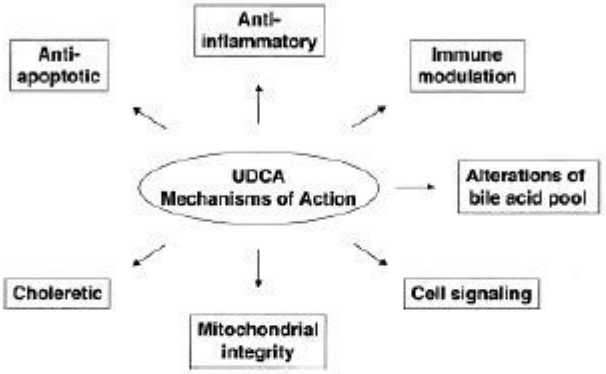

Figure 1. Overview of UDCA mechanisms of action (Lazaridis, 2001)

4.4 Clinical efficacy

4.4.1 Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) appears to be a autoimmune disease in which a variety of environmental toxins or infectious agents, including viruses, bacteria, and chemicals, may trigger an immune response that becomes self-perpetuating. It is a chronic cholestatic disease with a progressive course which may extend over many decades. The rate of progression varies greatly among individual patients.

PBC is classified into four stages of severity on the basis of histologic findings on liver biopsy (see Table 2).

Table 2 - Histologic Staging of Primary Biliary Cirrhosis

Stage	Histologic Findings
I	Inflammation in the portal space
I	Inflammation extending into the hepatic parenchyma
III	Septal or bridging fibrosis
IV	Cirrhosis with regenerative nodules

- Bibliographic data on the effect of UDCA in Primary biliary cirrhosis

Most of studies performed with UDCA have a methodological weakness (limited sample size, heterogeneous population in terms of disease stage and limited observation periods too short for a slowly

progressing disease) and did not meet current standard criteria (i.e performed prior to establishment of GCP) lacking some of the rigour of today's trial design.

To overcome the lack of power of clinical trials in assessing the long-term effectiveness of UDCA therapy, combining data sets were conducted and allowed assessment of these effects:

- A Markov model has been used to study the effect of UDCA on the natural history of PBC (Corpechot 2005). The study showed that survival was substantially better than that predicted by the model and the survival rate was better than the spontaneous survival rate as predicted by the updated Mayo risk score model (relative risk: 0.5, P<0.01). The survival rate of UDCA treated patients in stage 1 and 2 is similar to that in a control population and overall survival rates without liver transplantation were 84% and 66% at 10 years and 20 years, respectively.

- A combined analysis of three randomized-controlled trials including 548 patients with PBC showed improved survival free of liver transplantation in patients with moderate to severe disease treated with UDCA at doses of 13 to 15 mg/kg/day for up to 4 years (Poupon 1997). In this analysis, UDCA treatment was associated with a significant reduction in the likelihood of liver transplantation or death.

Moreover, long-term observational studies from France, Spain and the Netherlands (Poupon, 1999, Pares, 2006, ter Borg, 2006) have shown that UDCA therapy provides a better survival than that predicted by the Mayo model (Murtaugh, 1994).

Meta-analyses which excluded studies of short duration (less than 24 months for a disease with an estimated duration of one to two decades without intervention) and those that used an ineffective dose of UDCA concluded that long-term UDCA significantly improved transplant-free survival and delayed histologic progression in early-stage patients [Shi, 2006, Goulis, 1999].

Table 3 - Summary of efficacy for UDCA trials in PBC

Reference	Products Dose (g) frequency and duration	Endpoints	Design	Country	Endpoints Results
Main studies					
Corpechot 2005	UDCA: 13-15 mg/kg/j Mean follow-up : 8 years (range 1-22 years)	Long-term effect of UDCA Multistate modelling approach (Markov model): histologic stage progression, death, and survival without OLT	N=262	FR	**POSITIVE** Overall survival substantially better than that predicted by the model. Overall survival rates without OLT: 84% and 66% at 10 years and 20 years, respectively. ⇒Treatment with UDCA alone normalizes the survival rate of patients with PBC when given at early stages
Shi 2006	UDCA: 10-12 to 14-16 mg/kg/day Follow-up : 24 to 88 months	Long-term efficacy of mid-dose UDCA treatment for PBC	Meta-analysis : 7 long-term RCT comparing mid-dose UDCA with placebo or no treatment was performed N=1038	China	**POSITIVE** Long-term treatment with mid-dose UDCA can improve liver biochemistry and survival free of liver transplantation in patients with PBC (p=0.05). In addition, UDCA therapy can delay the histological progression in the early-stage patients (p<0.03)
Gong 2008	UDCA: 7.7 to 15.5 mg/kg/day (median : 10 mg/kg/day) Follow-up: 3 to 92 months (median :24 months)	Mortality and liver transplantation.	Meta-analysis of RCTs Cochrane : UDCA vs placebo or no treatment N=1447	DK	**NEGATIVE** ⇒This systematic review did not demonstrate any benefit of UDCA on mortality or liver transplantation.
Supportive studies					
Kuiper 2009	UDCA: 13-15 mg/kg/d Median follow-up: 9.7 years	Comparison of prognosis with biochemical response.	Prospective cohort study N=375	NL	Biochemical improvements in serum bilirubin and albumin levels associated with improved prognosis Therapeutic effect of UDCA in PBC, irrespective of the stage of the disease. Survival responders > non responders (p<0.01)
Kuiper 2011	UDCA: 13-15 mg/kg/d Median follow-up: 10.3 years	Long term evolution of liver biochemical and immmunological	Prospective multicenter cohort study N=225	NL	Biochemical response to UDCA maintained in PBC patients treated up to 17 years.
Corpechot 2011	UDCA: 13-15 mg/kg/d Median follow-up: 7 years	Best biochemical criteria of response to UDCA (Barcelona, Paris, Rotterdam, and Toronto criteria) to predict the absence of poor outcome	Combinating analysis N=165	FR	Early-stage patients who show ALP and AST~1.5x ULN, and normal bilirubin level after 1 year of treatment appear to be at very low or no risk of liver failure or progression to cirrhosis.

OLT: orthotopic liver transplantation - RCTs : Randomised clinical trials

- Bibliographic data on UDCA dose in Primary biliary cirrhosis

Dosage regimens have not been properly evaluated in clinical trials and none of the studies provided aimed at statistically comparing low vs high dosage regimen.

Angulo (1999) performed a study comparing three different doses of UDCA showed that a dose of 13-15 mg/kg/day appeared superior to either a lower dose of 5-7 mg/kg/day or a higher dose of 23-25 mg/kg/day in biochemical responses and cost :improvements in alkaline phosphatase (p=0.0001), aspartate aminotransferase (p=0.0001), Mayo risk score (p=0.002) were significantly greater in the standard and high-dose groups compared to the low-dose group (N=155).

- Guidelines supporting UDCA in the management of Primary biliary cirrhosis

1. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases (2009)

EASL guideline considers that over the past two decades, increasing evidence has accumulated indicating that UDCA (13–15 mg/kg/d) is the treatment of choice for patients with PBC based on placebo-controlled trials and more recent long-term case-control studies.

UDCA has been demonstrated to:
- exert anticholestatic effects in various cholestatic disorders,
- markedly decrease serum bilirubin, AP, cGT, cholesterol and immunoglobulin M levels;
- and ameliorate histological features in patients with PBC in comparison to placebo treatment although no significant effects on fatigue or pruritus were observed in these large trials.

Moreover, long-term treatment with UDCA delayed the histological progression of the disease in patients in whom treatment was started at an early stage.

EASL recommendations state that:

- Patients with PBC, including those with asymptomatic disease, should be treated with UDCA (13 - 15 mg/kg/d) on a long-term basis;

- Favorable long-term effects of UDCA are observed in patients with early disease and in those with good biochemical response (II-2/B1), which should be assessed after one year.
A good biochemical response after one year of UDCA treatment is currently defined by a serum bilirubin $\leq$ 1 mg/dL (17 µmol/L), Alk Ph $\leq$ 3x ULN and AST $\leq$ 2x ULN (''Paris criteria") or by a decrease of 40% or normalization of serum AP (''Barcelona criteria").

2. AASLD PRACTICE GUIDELINES Primary Biliary Cirrhosis (2007)

AASLD guideline stipulates that UDCA in a dose of 13-15 mg/kg/day is the only therapy for PBC approved by the U.S. Food and Drug Administration and a number of studies have shown the benefit of UDCA and an improvement in survival in this context.

Several clinical, biochemical, and histologic features have prognostic significance in PBC although bilirubin level is the best predictor of survival and is the most important component in all mathematical models of prognosis in PBC. Some of these models have been useful in predicting survival in UDCA-treated patients as well.

Improvement in liver tests will be seen within a matter of a few weeks and 90% of the improvement usually occurs within 6-9 months. About 20% of patients will have normalization of liver biochemistries after 2 years and a further 15% or 35% of the total will have normalization by 5 years.

The effect of treatment can be based on response of serum alkaline phosphatase activity or Mayo risk score, which is dependent on age, albumin, bilirubin, prothrombin time, and presence or absence of fluid retention.

4.4.2 Cholesterol biliary lithiasis

The prevalence of gallstones is 10–15% in adults in Europe and the USA and cholesterol gallstones account for about 75% in westernized countries. Precipitation of excess cholesterol in bile as solid crystals is a prerequisite for cholesterol gallstone formation. Cholesterol gallstones are composed mainly of cholesterol crystals (70%) held together in an organic matrix of glycoproteins, calcium salts, and bile pigments.

The bile chenodeoxycholic acid (CDCA) was first used in the 1970s but was associated with a dose-dependent increase in serum aminotransferases, serum low-density lipoprotein cholesterol levels, and diarrhoea. In 1975 Makino et al. first reported gallstone dissolution with the more hydrophilic UDCA. It was then postulated that UDCA could replace CDCA and may dissolve cholesterol stones given its chemical and structural relationship to CDCA without its side effects.

Since then UDCA has been used in the treatment of gallbladder stones as an alternative to cholecystectomy (Tint, 1982).

The fine mechanisms involved in UDCA-induced dissolution of cholesterol stones are rather complex.

<u>UDCA mechanism of action in cholelithiasis</u>

The proposed mechanism of action involves unsaturation of bile with UDCA by increasing its proportion in the bile acids pool inducing a decreased hepatic secretion of biliary cholesterol leading to gallstone dissolution by solubilizing cholesterol from the stone surface.

Cholesterol is only slightly soluble in aqueous media, but is made soluble in bile through mixed micelles by bile salts and phospholipids, mainly phosphatidylcholine, whose concentrations determine the degree of cholesterol saturation. The description of the ternary phase diagram by Admirand and Small (Figure 2) and later by Wang and Carey has clarified the importance of the relative amounts of bile salts and phospholipids needed to solubilize biliary cholesterol (Portincasa, 2006).

Figure 2 describes the different pathways of cholesterol solubilisation or precipitation, or both, in bile. The three axes of the triangle represent the concentrations of the three lipids.

A cholesterol-supersaturated bile of pathophysiological importance might lie in the three-phase zone (with crystals) if enriched with hydrophobic bile salts (ie, deoxycholate), but in the right two-phase zone (without crystals) if enriched with hydrophilic bile salts (ie, ursodeoxycholate). This partly explains why ursodeoxycholate prevents cholesterol crystallisation and gallstone formation and is effective for oral litholysis in a subgroup of cholesterol gallstone patients.

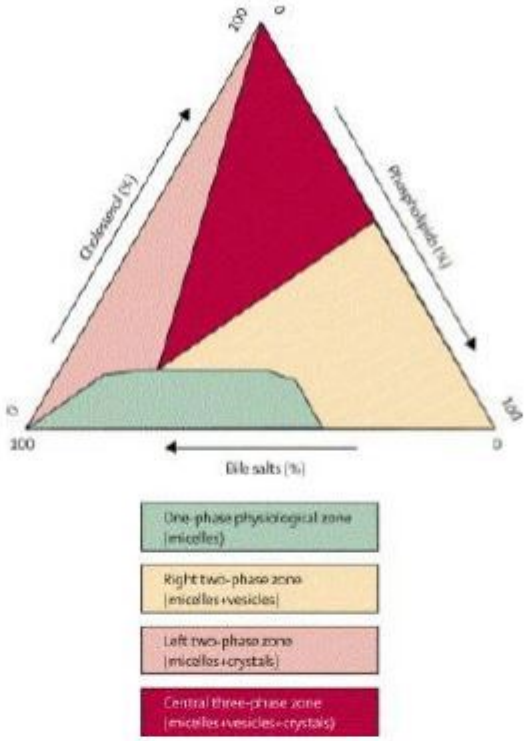

Figure 2: Schematic representation of the ternary bile salt-cholesterolphospholipid phase diagram that describes the different pathways of cholesterol solubilisation or precipitation, or both, in bile

Candidates for UDCA treatment

Most patients with symptomatic gallbladder stones are treated by elective laparoscopic cholecystectomy, which provides a permanent "cure" for nearly all individuals.

Treatment of asymptomatic gallstone patients is not routinely recommended, because of the overall low risk of biliary colic, complications, and gallbladder cancer and an expectant management (medical attention) is currently considered the most appropriate choice in patients with gallstones of any type without specific symptoms.

Candidates for dissolution therapy with oral UDCA are **symptomatic patients who are unfit for surgery** with:

- uncalcified (radiolucent) and cholesterol-enriched gallstones;
- functioning gallbladder with a patent cystic duct;
- **small stones (diameter ≤ 5 mm)**.

Therefore, only a **minority of patients** (less than 10-15% of total) is suitable for oral dissolution therapy with UDCA.

A number of diagnostic techniques provide essential information for **appropriate selection of patients**:
- gallbladder ultrasonography allows the accurate visualization of gallstone number, size, burden and explores the morphology of the gallbladder and the patency of the cystic duct;
- abdominal plain radiography or a computed tomography (CT) scan permit to exclude the presence of calcified stones (as radiopaque bodies) which are obviously unfit for dissolution because they are either calcified cholesterol stones or stones made of pigment calcium bilirubinate.

To know exactly the **composition** of gallstones is an essential step to select patients responsive to oral litholysis with bile acids. In principle, the only gallstones amenable to litholysis are cholesterol-enriched, calciumfree stones. Cholesterol gallstones represent about 75% of the gallstones in westernized countries and can be dissolved when no calcium has deposited in the stones.

An accurate selection of gallstone patients with the characteristics described above (summarized in Figure 3 below) offers a higher chance of successful oral litholysis with an expected dissolution rate of about 1 mm decrement in stone diameter per month rate following UDCA (Senior, 1990). In patients with a gallstone diameter less than 5 mm, the complete disappearance of stones assessed by ultrasonography is expected to be reached in about 90% of cases by 6 months of UDCA administration (Jazrawi 1992). The chance of dissolution is significantly lower (less than 40-50 % after 1 year of the treatment) in patients with larger or multiple stones.

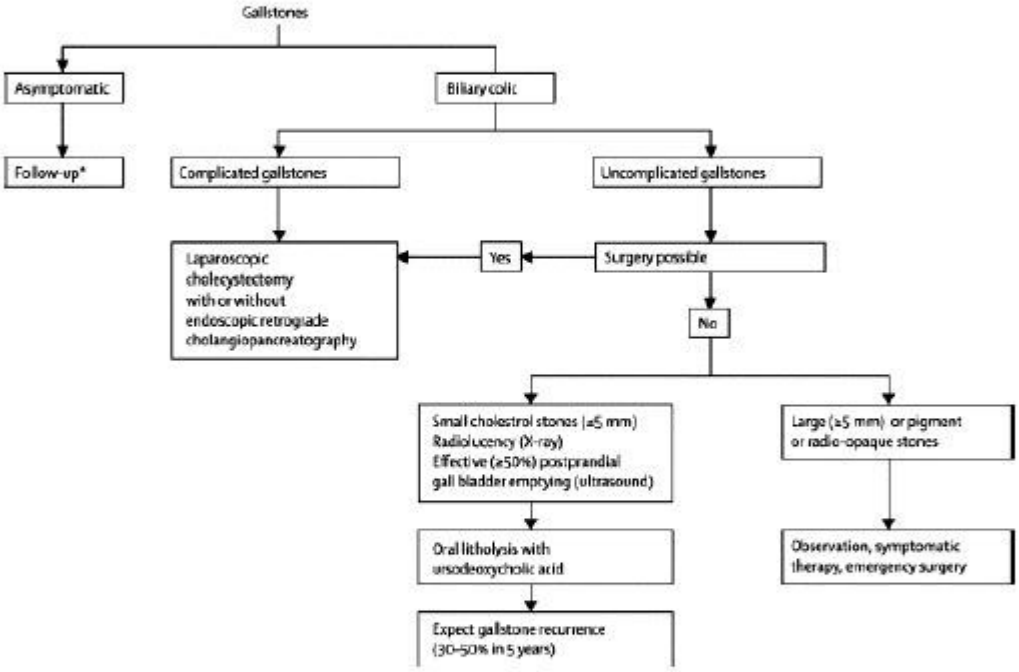

Figure 3: Algorithm for the management of cholesterol gallstone disease (Portincasa, 2006).

To conclude, only patients unsuitable for surgery with mild symptoms and small, uncalcified cholesterol gallstones should be considered for oral litholysis should be considered for oral litholysis.

Recommended dose and treatment duration

Based on empirical experience and available data, the recommended dose of oral UDCA for gallbladder stones is 8-14 mg/kg per day with higher doses not providing additional benefit in outcome (Erlinger, 1984; Rubin, 1994; Portincasa, 2012).

Bedtime administration is suggested because it maintains hepatic bile acid secretion rate overnight, thus reducing secretion of supersaturated bile and increasing the dissolution rate.

A dissolution rate of 30 to 60% has been reported at the optimal dose found in almost published studies of about 8 to 10 mg/kg/day (Ward 1984).

Absence of or minimal change in gallstone diameter within 6 to 12 months of UDCA therapy represents a poor prognostic sign for dissolution.

Recurrence

Main limits of the dissolution therapy by oral bile acids are the possibility of gallstone recurrence (about 10% per year up to 5 years and the risk of appearance of a surface calcification on cholesterol gallstones during bile acid therapy in about 10% of cases (Bateson, 1980, Petroni, 1996). Recurrence rate is higher particularly in subjects with multiple gallstones. It has to be underlined, however, that recurrent gallstones respond well to a re-treatment (Petroni, 1996).

After gallstone disappearance, the persistence of the same pathogenetic factors inducing gallstone formation is principally responsible for their recurrence and thus it is logical to speculate that such an high recurrence rate is dependent on persistent pathogenetic conditions (Di Ciaula, NIH 2010).

4.4.3 Efficacy conclusion

DOZURSO is intended for adults use only considering the uncommonness of diseases and the paucity of data in this population as well as the limitation due to the pharmaceutical form.

Primary biliary cirrhosis

Various studies (randomized trials, combined analyses, and long-term observational studies) have demonstrated consistent evidence of improved liver biochemistries and studies with extended follow-up have also shown histologic progression delay and improvement of survival without transplantation.

Therefore, on the basis of all available data, it is currently recommended to treat PBC without decompensated cirrhosis with UDCA using doses of 13-15 mg/kg/day.

Cholesterol biliary lithiasis

Considering that oral litholysis with hydrophilic bile acids have a limited role, UDCA is reserved to symptomatic patients with small radiolucent gallstones in a well functioning gallbladder with a patent cystic duct.

4.5 Clinical safety

4.5.1 UDCA safety data in patients with PBC

Most of the published trials provide few information on UDCA tolerability and adverse events.

In a Cohrane systematic review (Gong, 2008), an assessment of the adverse events compared to control groups was performed and only the MILAN trial reported one serious adverse event (SAE). Other trials reported non-serious AE. It seems that a slightly higher incidence of AE was found in patients treated with UDCA (OR 1.32, 95% CI 1.05 to 1.65, 11 trials) comparing with placebo or no intervention, including weight gain, but this last event could not be considered as an AE in this context. No adverse effect was related to the long term use of UDCA at the recommended posology in that indication.

4.5.2 Safety studies performed in patients with cholelithiasis

The studies presented in the efficacy section did not report any significant or severe adverse events. Few patients experienced diarrhoea and one maculopapular eruption was reported. Laboratory parameters did not show any adverse effect particularly on liver function tests.

The applicant provided additional studies that have limited value for the demonstration of efficacy of UDCA within the scope of the registered therapeutic indications, but may provide additional information regarding safety.

- One short duration study investigated 661 patients with dyspeptic symptoms and pain in cholelithiasis and biliary dyskinesia after 7 and 14 days of treatment (Realini, 1980). The author did not report any significant clinical or biological adverse event (including liver enzymes).

- A small study was conducted with UDCA for chemical dissolution of cholesterol gallstones in six patients with histologically confirmed HBsAg-negative chronic active hepatitis (Leuschner, 1985). The treatment with UDCA lasted 3-20 months with a daily dose of 8-11 mg/kg and demonstrated a good tolerability profile in patients with HBsAg-negative chronic active hepatitis which was confirmed recently in one large scale controlled study involving patients with chronic hepatitis C (Omata, 2007). However the usefulness of UDCA in such clinical situations was discussed in the same issue of Gut by Poupon and Serfaty (2007).

Moreover, some studies provided in order to support efficacy have also demonstrated a reassuring tolerance profile:

- Bateson 1980: 1/20 patient receiving 500 mg/day for 6 months developed diarrhœa and another patient treated with 1000 mg/day for 6 months had an extensive maculopapular symmetrical rash on her trunk ;

- Neligan 1983: Treatment with UDCA for gallstones dissolution (500 mg/d) was well tolerated and significant adverse effects were not encountered (n=84).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Most common adverse reactions reported with the use of UDCA during worldwide postmarketing and clinical experience are in alphabetical order: abdominal discomfort, abdominal pain, alopecia, diarrhea, nausea, pruritus, and rash.

However, a potential safety concern regarding **long-term high-dose UDCA use** has been identified based on recent study reports:

- A recently published study found that long-term use of high-dose UDCA (28-30 mg/kg/d) is associated with an increased risk of colorectal neoplasia in patients with ulcerative colitis (UC) and primary sclerosing cholangitis (PSC) (Eaton 2011).

- Furthermore, another study in adults receiving 28-30 mg/kg/day UDCA for PSC reported that the risk of reaching a primary endpoint of cirrhosis, varices, cholangiosarcoma, liver transplantation, or death was 2.3 times greater for patients on UDCA than for those on placebo. The authors concluded that the possibility of hepatotoxic bile acids being produced from unadsorbed UDCA may be a potential explanation (Lindor 2009).

4.5.3 Safety conclusion

The safety profile of UDCA in the proposed indications can be considered well-established and acceptable. The proposed posology is in line with current recommendations. The adverse events of UDCA are well characterized and adequately covered by the SmPCs of currently available UCDA products. A causal relationship between UDCA treatment and decompensation of liver cirrhosis in PBC stage IV was not confirmed, but can neither be excluded. The proposed posology includes a dose reduction for patients with PBC stage IV when the serum bilirubin is > 40 µg/l, which is in line with recommendations from the literature.

4.6 Pharmacovigilance System

The Pharmacovigilance system as described by the applicant was considered as fulfilling the requirements and providing adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

4.7 Risk Management Plan

UDCA has proven to be a safe medication and is associated with minimal side effects and its off-label use is well anticipated. Therefore, routine pharmacovigilance activities as planned for all important identified risks is acceptable and the RMP could be acceptable.

Table 4 - Risk management plan

<table>
<tr><th>Safety concern</th><th>Routine risk minimisation measures</th><th>Additional risk minimisation measures</th></tr>
<tr><td>Liver cirrhosis decompensation</td><td>Routine pharmacovigilance activities are sufficient for this safety concern as information is included in sections 4.4 and 4.8 of the SmPC.</td><td rowspan="3">N/A (Routine pharmacovigilance)</td></tr>
<tr><td>Diarrhea</td><td rowspan="2">Routine pharmacovigilance activities are sufficient for this safety concern as information is included in sections 4.2, 4.4, 4.8 and 4.9 of the SmPC.</td></tr>
<tr><td>Right upper quadrant pain</td></tr>
</table>

5. USER CONSULATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

V. OVERALL CONCLUSIONS

6. OVERALL DISCUSSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ursodeoxycholic acid is approved and marketed in France (since 1980) and in the EU as well as outside the EU (Argentina, Australia, Brazil, Canada, Chile, Hong Kong, India, Israel, Japan, Malaysia, Mexico, New Zealand, Russia, South Africa, Singapore, Switzerland, Thailand, USA). Following thorough review of the literature and submitted data on the use of ursodeoxycholic acid in adults is considered to be safe and effective and globally support the claimed indications.

Primary biliary cirrhosis

Available data have demonstrated consistent evidence of UDCA efficacy in PBC using doses of at least 12 mg/kg/day.
There is no remaining uncertainties since the applicant has:

- restricted the use in patients without decompensated cirrhosis;
- removed the gradual dose increase proposed to reach the optimal therapeutic dose after 4 to 8 weeks of treatment (no data could substantiate this proposal).

Cholesterol biliary lithiasis

The dissolution therapy with UDCA still remains an interesting tool in selected patients at high risk for surgical interventions. The target population has been more precisely described specifying that DOZURSO is intended only for patients unsuitable for surgery with radiolucent cholesterol gallstones not larger than 15 mm in diameter in patients with a functioning gallbladder.

Moreover, for both indications, the SmPC/PL now specified that DOZURSO is intended for adults' use only considering the uncommonness of diseases and the paucity of data in this population as well as the limitation due to the pharmaceutical form.

As far as safety is concerned, UDCA has proven to be a safe medication and is associated with minimal side effects.

The Member States, on the basis of the data submitted, considering:

- that DOZURSO has demonstrated evidence of efficacy for the two claimed indications
    - Treatment of primary biliary cirrhosis (PBC) in patients without decompensated cirrhosis;
    - Dissolution of radiolucent cholesterol gallstones not larger than 15 mm in diameter in patients with a functioning gallbladder and for whom surgical treatment is not indicated.
- that the benefice/risk profile of DOZURSO was positive;

agreed to grant a marketing authorization for DOZURSO.

The decentralised procedure was positively ended on 3rd November 2014.

VI. REVISION DATE

01/03/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From FR/H/0551/001-002 to IE/H/1136/001-002/DC			