

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

**Ursodeoxycholzuur Strides 250 mg, capsules, hard
Strides Arcolab International Ltd., United Kingdom**

ursodeoxycholic acid

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/2516/001/DC
Registration number in the Netherlands: RVG 111238**

2 April 2014

Pharmacotherapeutic group:	bile acid preparations
ATC code:	A05AA02
Route of administration:	oral
Therapeutic indication:	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.
Prescription status:	prescription only
Date of authorisation in NL:	10 January 2014
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, EL, HU, IE, NO, PL, PT, RO, SE, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ursodeoxycholzuur Strides 250 mg, capsules, hard from Strides Arcolab International Ltd. The date of authorisation was on 10 January 2014 in the Netherlands.

The product is indicated 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.

A comprehensive description of the indications and posology is given in the SmPC.

Ursodeoxycholic acid (UDCA) is a bile acid which effects a reduction in cholesterol in biliary fluid primarily by dispersing the cholesterol and forming a liquid-crystal phase. UDCA affects the enterohepatic circulation of bile salts by reducing the reabsorption in the intestine of endogenous more hydrophobic and potentially toxic salts such as cholic and chenodeoxycholic acids.

In-vitro studies show that UDCA has a direct hepatoprotective effect and reduces the hepatotoxicity of hydrophobic bile salts.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of UDCA capsules. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. "Medicinal use" does not exclusively mean "use as an authorised medicinal product", so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

UDCA in general has been used in clinical practice for over 20 years. In the Netherlands, Ursochol tablets and Ursofalk capsules have been registered since 1979 and 1980, respectively. Also in the CMS countries, UDCA has been registered for 10-20 years. The use of UDCA in the proposed indications has been sufficiently substantiated and can be considered well-established. Additionally the MAH provided a bioequivalence study with Ursodeoxycholzuur Strides 250 mg versus Ursofalk 250 mg capsules from the Australian market. The acceptability of a bioequivalence study in the context of a well-established use application was questioned by one CMS, as well as the relevance of a reference product from the Australian market. These issues were resolved through a CMD(h) referral, discussed on page 13-14 of this report.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application. The results of a bioequivalence study were however provided in support of this application.

The marketing authorisation was granted based on article 10a of Directive 2001/83/EC.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, which is acceptable for this kind of application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is ursodeoxycholic acid (UDCA), an established active substance described in the European pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white powder, which is practically insoluble in water, freely soluble in ethanol, slightly soluble in acetone and practically insoluble in methylene chloride. The product does not exhibit polymorphism and is not hygroscopic.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. and the additional requirement of the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches of the drug substance.

Stability of drug substance

The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

Ursodeoxycholic Strides 250 mg is a white hard gelatin capsule (size '0') containing a white to off white powder.

The capsules are packed in blister packs consisting of a colourless PVC film sealed to plain aluminium blister foil.

The excipients are:

Capsule content - povidone (kollidon K-30) (E1201), sodium lauryl sulphate (E487), maize starch, magnesium stearate (E572)

Capsule shell - gelatin (E441), titanium dioxide (E 171)

Pharmaceutical development

The development of the product has been described, the choice of excipients justified and their functions

explained. All excipients used are well known. The choices of the packaging and manufacturing process are justified. This product concerns an abridged, bibliographic application for UDCA 250 mg capsules submitted under Article 10a (Well-established use) of Directive 2001/83/EC for which bioequivalence studies are not required. However, the MAH submitted the results of a bioequivalence study comparing Ursodeoxycholic acid Strides 250 mg capsules to Ursofalk 250 mg capsules from the Australian market.

Comparative dissolution studies between Ursodeoxycholic acid Strides 250 mg capsules and Ursofalk from the European market were conducted. The results show that the dissolution profiles of test and reference are comparable. A CMS questioned whether a bioequivalence study is acceptable in the context of a well-established use application. Moreover, the relevance of the Australian reference product was questioned. These issues were resolved through a CMD(h) referral, discussed below under section II.3 'Clinical aspects'.

Overall, the development of the product has been adequately performed.

Manufacturing process

The manufacturing process includes sifting, wet mixing and granulation, drying, sifting and milling of the granules, blending and lubrication, filling and polishing of the capsules, inspection and metal detection, and packaging.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two full-scale batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with their respective Ph.Eur monographs. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification, average weight of the capsules, average fill weight of capsules, uniformity of fill weight, locking length, disintegration time, dissolution, uniformity of dosage units, moisture content, assay, impurities, residual solvents and microbiological limits. The specifications are in line with the BP Monograph. The release and shelf-life limits for all tests are the same. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two full-scale batches, demonstrating compliance with the release specifications.

Stability of drug product

Stability data on the product has been provided for two full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in blister pack consisting of a colourless PVC film sealed to plain aluminium blister foil. Stability results showed that no significant changes or trends occur in the parameters tested when the capsules are stored at long-term conditions during 24 months and at accelerated conditions during 6 months. Additional long term and accelerated stability data were provided on two batches stored for 36 months and 6 months respectively. All data remained within the specification, so based on the submitted data a shelf life of 36 months is considered to be acceptable.

The product was demonstrated to be photostable. The proposed shelf-life of 36 months and the proposed storage conditions of "This medicinal product does not require any special storage conditions" are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Gelatin is the only excipient of animal origin. It is of bovine origin. A relevant TSE Certificate of Suitability of the gelatin supplier used in the manufacture of the capsules is provided.

II.2 Non-clinical aspects

According to Article 10a of Directive 2001/83/EC, it is possible to replace results of pre-clinical trials by detailed references to published scientific literature (information available in the public domain), if it can be demonstrated that the active substance has been in well-established medicinal use within the Community for at least 10 years for the same indication, with recognized efficacy and an acceptable level of safety.

The active compound of UDCA Tramedico tablets is ursodeoxycholic acid. This compound is a gallstone dissolving agent, which acts by reducing the content of cholesterol in bile, due either to a reduction in hepatic cholesterol synthesis or reduced absorption of cholesterol or both. The provided non-clinical overview is adequate.

In the Netherlands, ursodeoxycholic acid is a well-known active substance in medicinal products for treatment of biliary cirrhosis and for the dissolution of small and medium sized cholesterol-rich gallstones. These products include, among others, Ursochol 150, 300, 450 mg, tablets (NL License RVG 07718, 09307, 29828) and Ursofalk capsules 250 mg (RVG 08384). Both are registered products in the Netherlands for more than ten years.

The provided literature data justify why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

Environmental risk assessment

The approval of this product will not result in an increase in the total quantity of ursodeoxycholic acid released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

UDCA is a well-known active substance with established efficacy and tolerability.

The dossier is based on well-established use of UDCA. The MAH submitted a clinical overview for the justification of the proposed indications and posology. Sufficient literature references were provided.

Pharmacokinetics

The 250 mg capsule is an immediate release form of UDCA.

After administration of the pharmacological dose, UDCA is absorbed through passive non-ionic diffusion, mostly in the small intestine and to a small extent in the colon. UDCA is taken up from the portal blood during its first hepatic passage in a proportion of 50%, is conjugated especially with glycine and to a lesser extent with taurine, and is actively secreted into the bile. Conjugated UDCA is absorbed mainly in the distal ileum and undergoes an enterohepatic circulation. Unabsorbed conjugated UDCA is deconjugated and converted in part to lithocholic acid by intestinal bacteria. About 15 % of the total faecal bile acids is excreted unchanged in faeces (Paumgartner 2002¹/2004², AHFS 2010³, Trauner 1999⁴, Arenas 2008⁵). These pharmacokinetic properties described in literature are well known.

UDCA is considered to be a low solubility drug and a low permeability drug. In the provided literature data, reference is made to several UDCA formulations. Ursodeoxycholic acid is marketed in Europe in different dosage forms which include capsules, tablets and suspension by the innovator Ursofalk. All UDCA formulations are indicated for dissolution of cholesterol gallstones in the gall bladder and in the treatment of primary biliary cirrhosis (PBC). Based on the submitted literature data, Ursofalk tablet and suspension showed comparable pharmacokinetics, despite the considerable difference in formulation and excipients. In contrast, the study of Williams et al.⁶ in which different commercial available tablet and capsule UDCA formulations, marketed in the US and Canada, were used, showed significantly higher AUCs and C_{max} and

¹ Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. *Hepatology* 2002; 36(3):525-31

² Paumgartner G, Beuers U. Mechanisms of action and therapeutic efficacy of ursodeoxycholic acid in cholestatic liver disease. *Clin Liver Dis* 2004; 8(1):67-81;

³ AHFS Monograph: Ursodiol, 2010; The Pharmaceutical Press

⁴ Trauner M, Graziadei IW. Review article: mechanisms of action and therapeutic applications of ursodeoxycholic acid in chronic liver diseases. *Aliment Pharmacol Ther* 1999; 13(8):979-96;

⁵ Arenas F, Hervias I, Uriz M, Joplin R, Prieto J, Medina JF. Combination of ursodeoxycholic acid and glucocorticoids upregulates the AE2 alternate promoter in human liver cells. *J Clin Invest* 2008; 118(2):695-709;

⁶ C.N. Williams*, B. Al-Knawy & W. Blanchard; Bioavailability of four ursodeoxycholic acid preparations; *Aliment Pharmacol Ther* 2000; 14: 1133±1139.

shorter t_{max} for the tablet formulations compared to the UDCA capsule formulations for the standardized 500 mg dose. However all formulations are marketed and considered to be effective and safe.

The MAH used *in vitro* comparison with Ursofalk formulation, to further substantiate the bridging of the UDCA Strides formulation to literature. The UDCA Strides formulation is comparable regarding excipients with Ursofalk 250 mg capsule, except for the addition of povidone. Dissolution profiles have been provided at pH 1.2, 4.5, 6.8 and 7.5 using Ursofalk 250 mg capsules as reference. At pH 1.2 and 4.5 both UDCA Strides and Ursofalk did not dissolve. At pH 6.8 about 68% dissolved after 45 min and dissolution profiles were comparable ($f_2 > 50$). Comparability has also been shown at pH 7.5. Therefore the low solubility and low permeability of the UDCA formulations will not lead to different absorption characteristics, which may be a clinically relevant difference.

Bioequivalence study

To further substantiate bridging, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ursodeoxycholzuur Strides 250 mg (Strides Arcolab International Ltd., United Kingdom) is compared with the pharmacokinetic profile of the reference product Ursofalk 250 mg capsules (Dr Falk Pharma GmbH, Germany, obtained from Australia).

The choice of the reference product

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. Relevance of the Australian Ursofalk reference capsule is sufficiently supported by *in vitro* dissolution data comparing the Australian reference product and the European Ursofalk.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 64 healthy subjects. Each subject received a single dose (250 mg) of one of the 2 UDCA formulations. A washout period of 28 days was applied between the 2 periods.

Blood samples were collected pre-dose at -24 h, -18 h, -12 h, -6 h, 0 h and up to 72 h after administration of the products. The analytical method was fully validated and proved to be accurate and precise. The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

UDCA given orally is rapidly and completely absorbed. It is 96-98% bound to plasma proteins and efficiently extracted by the liver and excreted in the bile as glycine and taurine conjugates. In the intestine, some of the conjugates are deconjugated and reabsorbed. This pharmacokinetic behaviour of UDCA led to the assessment of the total amount of drug (free or parent UDCA plus the two metabolites) as an overall measure of the rate of absorption.

Results

Two subjects were withdrawn for drug abuse. Two subjects did not report for period II and one subject discontinued from the study on medical grounds on check-in day of period II. Data of 59 subjects were included in the analysis.

Table 1: Test and Reference Product Baseline Corrected Total Ursodeoxycholic acid Arithmetic Means:

Variable	N	Reference		Test	
		Mean	Std. Dev	Mean	Std. Dev
C_{max} (ng/mL)	58	6055.550	2742.255	7027.136	2920.763
AUC_t (ng/mL. hr)	59	91367.164	34420.155	101282.08	36445.827
AUC_{inf} (ng/mL. hr)	58	130453.19	121288.35	124891.52	63904.404

T_{max} (hr)	59	3.780	1.796	3.229	1.633
T_{half} (hr)	58	35.621	77.926	24.560	20.717

Table 2: Summary of Statistical Analysis of Baseline Corrected Total Ursodeoxycholic acid Data:

Parameter	Least Square Means Log Data		Ratio of Geometric Mean	90% CI of Log Transformed data
	Reference	Test		
C _{max} (ng/mL)	8.637	8.788	1.16	1.08 – 1.25
AUC _t (ng/mL. hr)	11.361	11.468	1.11	1.04 – 1.19
AUC _{inf} (ng/mL. hr)	11.610	11.648	1.04	0.93 – 1.15

Table 3: Test and Reference Product Baseline Corrected Parent (free) Ursodeoxycholic acid Arithmetic Means:

Variable	CORRECTED PARENT URSODEOXYCHOLIC ACID			
	Test		Reference	
	Mean	Std. Dev	Mean	Std. Dev
AUC _{0-72hr} (ng.h/mL)	21659.512	11272.511	17669.078	8497.591
AUC _{0-∞} (ng.h/mL))	27783.400	15260.073	25441.220	21829.607
C _{max} (ng/mL)	5471.874	2571.468	4415.706	2333.646
T _{max} (hr)	2.559	1.063	2.915	1.018
T _{half} (hr)	10.179	11.442	13.159	0.150

Table 4: Summary of Statistical Analysis of Baseline Corrected Parent Ursodeoxycholic acid Data:

Parameter	Least Square Means Log Data		Ratio of Geometric Mean	90% CI of Log Transformed data
	Reference	Test		
C _{max} (ng/mL)	8.297	10.101	1.26	1.17 – 1.36
AUC _t (ng/mL. hr)	9.697	9.875	1.19	1.10 – 1.30
AUC _{inf} (ng/mL. hr)	9.979	8.527	1.13	0.99 – 1.29

Bioequivalence was demonstrated for total UDCA. One subject was excluded from the statistical analysis for AUC_{0-inf}, as the extrapolated area was very high (>90%) which is considered acceptable. In addition, one subject was excluded from the statistical analysis for C_{max} as an outlier. The C_{max} of test for this subject was 2.6-fold higher than the reference, which was agreed.

Based on free UDCA (parent) pharmacokinetics, UDCA Strides showed higher AUC (about 13-19%) and C_{max} values (about 26%) compared to Ursolfalk capsules. This resulted in 90% CI outside the 0.80-1.25 criteria.

For a well-established use application, comparability in pharmacokinetics can be considered sufficiently demonstrated. The higher AUC and C_{max} of free UDCA observed in the bioequivalence study are considered not clinically relevant. Furthermore, the pharmacokinetic data obtained for the UDCA Strides formulation showed that the UDCA C_{max} of 5472 ng/ml, i.e. 13.9 nmol/ml, fits well within the published C_{max}

data and Ursofalk product information.

Overall, the data indicate comparable bioavailability of UDCA Strides and Ursofalk, and, with regard to C_{max} , comparable bioavailability based on literature data. Bridging to literature data is considered justified.

Pharmacodynamics

Several studies have shown that treatment with UDCA could change the bile acid composition in bile and reduce cholesterol, so that bile became unsaturated with cholesterol. In PBC patients, it has been shown that UDCA induced changes in the circulating pool of endogenous bile acids together with improvement of liver function test values.

Clinical efficacy

To substantiate clinical efficacy of this application based on well-established use, the MAH submitted a literature overview, which was updated during the procedure in accordance with comments raised by the member states. The updated overview contains a total of 39 references between 1992 and 2012 to substantiate clinical efficacy. This also included references related to different indications, which were not assessed as they are not related to the sought indication.

Efficacy of UDCA in the dissolution of gallstones

To substantiate the proposed indication of “dissolution of radiolucent gallstones in patients with a functioning gallbladder” the MAH submitted an updated overview with 84 publications between 1982 and 2012.

These include 2 randomized, double-blind, placebo-controlled studies (Salvioli et al 1983⁷ and Schoenfield et al 1990⁸). The study by Salvioli et al is considered most relevant as this study showed that UDCA, given at the relevant dose of 12 mg/kg/day, was superior to placebo in the dissolution of radiolucent biliary duct stones. After treatment with UDCA, stones completely disappeared in 50% of subjects, while stone number and size remained unchanged in the placebo group. This study, however, was limited in size with only 14 subjects in each treatment arm. The study by Schoenfield et al was much larger (600 subjects), but investigated the effect of UDCA as adjuvant therapy to lithotripsy, which was not applied for as an indication. A total of 600 patients with three or fewer radiolucent gallstones, 5 to 30 mm in diameter, were randomly assigned to receive UDCA (10-12 mg/kg/day) or placebo, starting one week before lithotripsy and continuing for 6 months after the procedure. Of the 600 patients, 21% receiving UDCA and 9% receiving placebo ($p < 0.0001$) were free of stones after 6 months. Among those with completely radiolucent solitary stones < 20 mm in diameter, respectively 35% and 18% of patients receiving UDCA and placebo ($p < 0.001$) were free of stones after 6 months.

The 2 other studies submitted (Boscaini et al 1994⁹ and Petroni et al 2001¹⁰) are not considered useful in the substantiation of the proposed indication. The study of Boscaini also investigated the effect of UDCA as adjuvant therapy to lithotripsy, but –in contrast to Schoenfield et al- lacked a placebo arm (lithotripsy without UDCA) and therefore the effect of UDCA was difficult to assess. The study of Petroni compared UDCA monotherapy to a combination therapy, which is less relevant for the current application.

With their update, the MAH chose to add papers by Ward et al (1984)¹¹, May et al (1993)¹², Meredith et al (1982)¹³ and Tuncer et al (2012)¹⁴. Although all four papers substantiate the use of UDCA in the

⁷ Salvioli G et al. Medical treatment of biliary duct stones: effect of ursodeoxycholic acid administration. Gut 1983; 24(7): 609-14

⁸ Schoenfield LJ et al. The effect of ursodiol on the efficacy and safety of extracorporeal shock-wave lithotripsy of gallstones. The Dornier National Biliary Lithotripsy Study. N Engl J Med 1990; 323(18): 1239-45

⁹ Boscaini M et al. Gall stone pulverisation strategy in patients treated with extracorporeal lithotripsy and follow up results of maintenance treatment with ursodeoxycholic acid. Gut 1994; 35(1): 117-21

¹⁰ Petroni ML et al. Ursodeoxycholic acid alone or with chenodeoxycholic acid for dissolution of cholesterol gallstones: a randomized multicentre trial. The British-Italian Gallstone Study group. Aliment Pharmacol Ther 2001; 15(1): 123-8

¹¹ Ward A, Brogden RN, Heel RC, Speight TM, Avery GS. Ursodeoxycholic acid: a review of its pharmacological properties and therapeutic efficacy. Drugs 1984; 27(2):95-131

¹² May GR, Sutherland LR, Shaffer EA. Efficacy of bile acid therapy for gallstone dissolution: a meta-analysis of randomized trials. Aliment Pharmacol Ther 1993; 7(2):139-48

¹³ Meredith TJ, Williams GV, Maton PN, Murphy GM, Saxton HM, Dowling RH. Retrospective comparison of 'Cheno' and 'Urso' in the medical treatment of gallstones. Gut 1982; 23(5):382-9

dissolution of gallstones, the paper by May et al is considered most useful and relevant. This paper concerns a meta-analysis of published randomized trials from January 1966 to September 1992. A total of 23 trials were included with 819 patients exposed to UDCA. High-dose UDCA (≥ 7 mg/kg/day) was given to 539 patients in 16 studies with stone dissolution seen in 31.9% (95% CI: 28-37%). In studies of >6 months duration (12 studies, $n=415$), high-dose UDCA completely dissolved stones in 37.3% (95% CI 33-42%). Low dose UDCA (<7 mg/kg/day) dissolved stones in 20.6%. Rates for placebo treatments were close to zero. UDCA was also shown to be more effective than both low and high dose CDCA (chenodeoxycholic acid).

Overall, it can be considered that the updated overview sufficiently substantiates the efficacy of UDCA in the treatment of gallstones.

Efficacy of UDCA in primary biliary cirrhosis

To substantiate the proposed indication of "primary biliary cirrhosis", the MAH submitted an updated overview with 11 original studies between 1991 and 2005, and 4 meta-analyses.

Five papers concerned randomized, double-blind, placebo-controlled studies and are considered most relevant:

Poupon et al (1991)¹⁵: PBC patients were treated with UDCA ($n=73$ and at the relevant dose of 13-15 mg/kg/day) or placebo ($n=73$) for 2 years. The UDCA treated group had a lower risk of treatment failure as compared to the placebo group (0.32 (95% CI: 0.11, 0.88)). Also, the proportion of patients with clinically overt disease decreased in the UDCA group ($p<0.02$), but not in the placebo group. The UDCA group also had significant improvements in liver enzymes and relevant biochemical variables. The mean Mayo risk score, reflecting the overall severity of the disease, was significantly reduced after 2 years of treatment with UDCA. Liver biopsy showed a significant improvement in the mean histological score ($p<0.002$) in all the characteristic histological features except fibrosis in the UDCA group. After the 2-year double-blind period, this study was extended into an open phase for 2 more years (Poupon et al, 1994¹⁶), in which all patients were treated with UDCA (including those who had received placebo in the double-blind period). The results showed that patients in the UDCA group had a lower probability of liver transplantation and liver transplantation or death as compared to the group initially assigned to placebo.

Lindor et al (1994)¹⁷: In this study, 180 PBC patients were given UDCA (13-15 mg/kg/day) or placebo. In patients receiving UDCA, treatment failure was delayed compared with the placebo-treated group ($p = 0.0003$, log rank test). During the 4 years of the study, there were 21 treatment failures (24%) in the 89 patients in the UDCA group and 43 treatment failures (48%) of the 91 subjects in the placebo group. Seven patients receiving UDCA died or required transplantation compared with 12 in the placebo group ($p = 0.18$).

Combes et al (1995)¹⁸: In this study, 150 PBC patients were given UDCA (10-12 mg/kg/day) or placebo. UDCA induced major improvements in biochemical tests of the liver and affected histology favourably in less advanced PBC, but had less effect in more advanced PBC. UDCA treated patients tended to develop a treatment failure less frequently than those who received placebo, particularly in less advanced PBC (UDCA 42%, placebo 60%, $p = 0.078$). Development of severe symptoms (fatigue/pruritus) and doubling of serum bilirubin were reduced significantly in UDCA-treated patients.

¹⁴ Tuncer I, Harman M, Colak Y, Arslan I, Turkdogan MK. Effect of ursodeoxycholic Acid alone and ursodeoxycholic Acid plus domperidone on radiolucent gallstones and gallbladder contractility in humans. *Gastroenterol Res Pract* 2012; 2012:159438

¹⁵ Poupon RE et al. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. *N Engl J Med* 1991; 324(22): 1548-54

¹⁶ Poupon RE et al. Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC Study Group. *N Engl J Med* 1994; 330(19): 1342-7

¹⁷ Lindor KD, Dickson ER, Baldus WP et al. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. *Gastroenterology* 1994; 106(5):1284-90

¹⁸ Combes B, Carithers RL Jr, Maddrey WC et al. A randomized, double-blind, placebo-controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology* 1995; 22(3):759-66

Heathcote et al (1994)¹⁹: In this study, 222 PBC patients were treated with UDCA (14 mg/kg/day) or placebo for 2 years. Although treatment was not associated with any improvement in symptoms, UDCA caused the bilirubin to fall significantly within the first 3 months of therapy ($p < 0.001$). Significant falls in serum alkaline phosphatase, aminotransferases, cholesterol and IgM levels were also noted in the treated group. Improvement in some histological features was observed, but there was no difference between the groups in the number of patients who reached the endpoints of death or liver transplantation. It was concluded that UDCA given to patients with PBC leads to an improvement in serum markers of cholestasis.

Pares et al (2000)²⁰: In this study, 192 PBC patients were treated with UDCA (14-16 mg/kg/day) or placebo. UDCA treatment was associated with decreases in alkaline phosphatase, γ -glutamyl transferase, alanine aminotransferase, and cholesterol levels, effects which were conspicuous after 3 months of treatment and remained similar during the follow-up. Times to death or liver transplantation and to clinical complications were not significantly different in patients receiving UDCA or placebo. Histological analysis indicated that UDCA improved portal inflammation and prevented histological stage progression. By contrast, histological stage as well as ductular proliferation and ductopenia progressed in patients receiving placebo. It was concluded that although UDCA treatment did not significantly affect time to death or liver transplantation and to clinical complications, the effects on both cholestasis and liver histology suggest that UDCA may be useful for preventing the progression of primary biliary cirrhosis.

The MAH also submitted papers by Bateson et al (1998)²¹ and Chan et al (2005)²², in which PBC patients who were treated with UDCA or who were untreated, were followed up for up to 10 and 12 years. The results of Bateson et al showed that survival rates were better for UDCA-treated patients. In the study of Chan et al, the unadjusted Kaplan-Meier analyses showed benefit of UDCA treatment, but rates adjusted for baseline differences showed no significant differences between UDCA and placebo groups. The remaining 3 publications are considered of low relevance. Papers by Almasio et al (2000)²³ and Battezzati et al (2001)²⁴ compared UDCA monotherapy to a combination therapy of UDCA and colchicine, while the paper by Van Hoogstraten et al (1998)²⁵ compared 2 different UDCA doses. These papers do not contribute to the substantiation of the proposed indication.

The MAH submitted 4 meta-analyses:

Poupon et al (1997)²⁶: This meta-analysis combined data from 3 clinical trials (Poupon 1991, Lindor 1994 and Heathcote 1994). In total 273 patients received UDCA and 275 patients received placebo. In two studies (Poupon 1991 and Heathcote 1994) treatment was given for 2 years, in the remaining study (Lindor 1994) treatment was given for 4 years. The results showed that survival free of liver transplantation was significantly improved in the patients treated with UDCA compared with the

¹⁹ Heathcote EJ, Cauch-Dudek K, Walker V *et al*. The Canadian Multicenter Double-blind Randomized Controlled Trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology* 1994; 19(5):1149-56

²⁰ Pares A, Caballeria L, Rodes J *et al*. Long-term effects of ursodeoxycholic acid in primary biliary cirrhosis: results of a double-blind controlled multicentric trial. UDCA-Cooperative Group from the Spanish Association for the Study of the Liver. *J Hepatol* 2000; 32(4):561-6

²¹ Bateson MC *et al*. Ursodeoxycholic acid therapy for primary biliary cirrhosis. A 10-year British single-centre population-based audit of efficacy and survival. *Postgrad Med J* 1998; 74(874): 482-5

²² Chan CW *et al*. Long-term ursodeoxycholic acid therapy for primary biliary cirrhosis: a follow-up to 12 years. *Aliment Pharmacol Ther* 2005; 21(3): 217-26

²³ Almasio PL *et al*. Multicentre randomized placebo-controlled trial of ursodeoxycholic acid with or without colchicine in symptomatic primary biliary cirrhosis. *Aliment Pharmacol Ther* 2000; 14(12): 1645-52

²⁴ Battezzati PM *et al*. Ten-year combination treatment with colchicine and ursodeoxycholic acid for primary biliary cirrhosis: a double-blind, placebo-controlled trial on symptomatic patients. *Aliment Pharmacol Ther* 2001; 15(9): 1427-34

²⁵ Van Hoogstraten *et al*. A randomized trial in primary biliary cirrhosis comparing ursodeoxycholic acid in daily doses of either 10 mg/kg or 20 mg/kg. Dutch Multicentre PBC Study Group. *Aliment Pharmacol Ther* 1998; 12(10): 965-71

²⁶ Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. *Gastroenterology* 1997; 113(3):884-90

patients originally assigned to placebo ($p < 0.001$; relative risk, 1.9; 95% CI: 1.3-2.8). Subgroup analyses showed that survival free of liver transplantation was significantly improved in medium- and high-risk groups (serum bilirubin level, 1.4 to 3.5 or > 3.5 mg/dl; $p < 0.0001$ and $p < 0.03$, respectively) and histological stage IV subgroup ($p < 0.01$). It was concluded that long-term UDCA therapy improves survival free of liver transplantation in patients with moderate or severe disease. An effect in patients with mild disease is probably not found because they do not progress to end-stage disease in 4 years.

Goulis et al (1999)²⁷: This meta-analysis was done for randomised and switch-over phases of trials comparing UDCA with placebo in PBC from 1987 to 1998. Eleven randomised controlled trials, including 1272 patients and six reports of switch-over phases were identified. UDCA had a favourable effect on liver biochemistry in most of the studies, but not on symptoms or the progression of histological stage; two studies did not assess survival, liver transplantation, or complications of liver disease. Meta-analysis showed no difference between UDCA and placebo in the incidence of death (odds ratio 1.21, 95% CI 0.71-2.04), liver related death (0.72, 0.22-2.32), liver transplantation (1.27, 0.78-2.07), death or liver transplantation (1.26, 0.87-1.82), and in the development of complications of liver disease (1.11, 0.64-1.92). With the primary end point defined by the authors (a combined end point in three studies, and death or liver transplantation in the others) an odds ratio of 1.53 (0.97-2.42) was obtained.

Shi et al (2006)²⁸: The aim of this study was to assess the long-term efficacy of mid-dose (10-16 mg/kg/day) UDCA treatment for PBC as compared to placebo. Seven randomised controlled trials and six reports of their extended follow-up including 1,038 patients were assessed. UDCA could significantly improve liver biochemistry, but had no effect on pruritus and fatigue. UDCA could delay the progression of PBC, especially for early-stage patients. Meta-analysis of the seven trials including their extended follow-up showed a significant reduction of the incidence of liver transplantation (OR 0.65, $p = 0.01$), and a marginally significant reduction of the rate of death or liver transplantation (fixed-effect model: OR 0.76, $p = 0.05$; random-effect model: OR 0.77, $p = 0.3$) in the UDCA group, except death (OR 1.01, $p = 1$). In the sensitivity analyses, which included studies administering placebo as control, long-term studies (≥ 48 months), or large size studies (total number of patients ≥ 100), it was found that long-term treatment with UDCA could significantly reduce the incidence of liver transplantation, and death or liver transplantation. The authors concluded that long-term treatment with mid-dose UDCA can improve liver biochemistry and survival free of liver transplantation in patients with PBC. In addition, UDCA therapy can delay the histological progression in the early-stage patients.

Gong et al (2007)²⁹: This meta-analysis included 15 randomized clinical trials (1447 patients) evaluating UDCA versus placebo or no intervention. In 9 trials the average UDCA dose was lower than 12 mg/kg/day (thus not in line with current recommendation and the proposed posology). In 4 trials treatment duration was ≤ 12 months, in 8 trials 12 - 24 months, and in 3 trials ≥ 24 months. The trials also differ significantly in PBC severity, ranging from 15% to 83% of included patients with stage III or IV PBC. The results showed that comparing with placebo or no intervention, UDCA did not significantly affect mortality (RR 0.97, 95% CI 0.67–1.42) and mortality or liver transplantation (RR 0.92, 95% CI 0.71–1.21). UDCA did not improve pruritus, fatigue, autoimmune conditions, liver histology, or portal pressure. UDCA seemed to improve biochemical variables, such as serum bilirubin, and ascites and jaundice, but the findings were based on few trials with sparse data.

Upon request of the member states, the MAH provided additional, relevant literature data. Most studies consistently showed that UDCA significantly decreased plasma levels of relevant liver parameters in PBC patients. However, the effect of UDCA on liver histology, and the reduction in the risk of liver transplantation and death has yielded variable results. This could be related to the limited follow-up time

²⁷ Goulis J, Leandro G, Burroughs AK. Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis. *Lancet* 1999; 354(9184):1053-60

²⁸ Shi J, Wu C, Lin Y, Chen YX, Zhu L, Xie WF. Long-term effects of mid-dose ursodeoxycholic acid in primary biliary cirrhosis: a meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2006; 101(7):1529-38

²⁹ Gong Y et al. Ursodeoxycholic acid for patients with primary biliary cirrhosis: an updated systematic review and meta-analysis of randomized clinical trials using Bayesian approach as sensitivity analyses. *Am J Gastroenterol* 2007; 102(8): 1799-807

and lower UDCA doses used in some studies, as is applicable to several studies included in the Gong et al meta-analysis. The meta-analysis of Shi et al, which was focused on the long-term efficacy of mid-dose UDCA (10-16 mg/kg/day; SmPC proposed dose is 12-16 mg/kg/day) showed favorable effects on liver transplantation and death or liver transplantation.

Overall, it can be considered that the overview sufficiently substantiates the efficacy of UDCA in the treatment of PBC.

The approved indication for UDCA with regard to PBC differs across EU countries. In some countries, the approved indication is the treatment of PBC without further specification (i.e. stage IV PBC) is included, while in other countries the indication is PBC stages I-III or PBC provided there is no decompensated cirrhosis. The MAH was therefore requested to motivate the inclusion of PBC stage IV in the indication. The MAH has provided the available efficacy and safety literature data for PBC stage IV. For efficacy, the MAH refers to studies by Poupon, Lindor and Heathcote. All three studies included patients with PBC stage IV. In Lindor et al (1994)¹¹, results were reported for each histological subgroup. For patients with PBC stage IV, a significant lower number of patients had treatment failure in the UDCA group as compared to the placebo group (6/26 and 14/28 for UDCA and placebo, respectively, p=0.015). In Poupon et al (1997)²⁰, data of the three studies were combined. In the combined analysis, a total of 68 (25.5%) of patients had PBC stage IV in the UDCA group versus 65 (24.2%) PBC stage IV patients in the placebo group. Subgroup analyses showed that survival free of liver transplantation was significantly improved in patients with histological stage IV (p<0.01). Overall, it can be considered that there is sufficient evidence that UDCA is also effective in PBC stage IV. Data on safety in PBC stage IV is included below under the Clinical Safety section.

Conclusion on clinical efficacy

UDCA has been used and is registered for the requested indications in the RMS and the CMS countries for 10-20 years. Based upon clinical data and the longstanding clinical experience, the use of UDCA in the proposed indications can be considered well-established with demonstrated efficacy. The proposed dose is in line with current recommendations. On the basis thereof, the efficacy of Ursodeoxycholic Acid Strides 250 mg capsules can be considered acceptable. The MAH has updated the overview and has added relevant and recent publications as required by the member states. The updated clinical overview sufficiently reflects the well-established efficacy of UDCA in the dissolution of radiolucent gallstones and in the treatment of PBC. In addition, the MAH provided literature data showing that UDCA is also effective in PBC stage IV.

Clinical safety

The MAH submitted a summary of clinical safety based on the systematic review of Hempfling et al (2003)³⁰. Diarrhoea was the single most frequent adverse event during UDCA treatment in patients with gallstone disease, and has been reported at an incidence of 2–9%. In patients with PBC, diarrhoea was rarely observed and was only incidentally reported. On rare occasions, right upper quadrant pain has been reported in PBC patients after UDCA treatment.

Liver toxicity has not been shown for UDCA in controlled clinical trials. Decompensation of liver cirrhosis has been observed in single cases during UDCA treatment of PBC stage IV, although a causal relationship has not been confirmed. Hempfling et al (2003) recommended a lower UDCA dosage in icteric patients with PBC stage IV with regular monitoring of serum bilirubin levels. The exacerbation of pruritus in patients with primary biliary cirrhosis at different stages has been described, although UDCA improved pruritus in about 40% of pruritic primary biliary cirrhosis patients in some trials. No evidence exists for a mutagenic or carcinogenic potential of UDCA in humans.

UDCA should not be administered concomitantly with cholestyramine, colestipol or antacids containing aluminium hydroxide and/or smectite (aluminium oxide), because these preparations bind ursodeoxycholic acid in the intestine and thereby inhibit its absorption and efficacy. Should the use of a preparation containing one of these substances be necessary, it should be taken at least 2 hours before or after UDCA intake. UDCA can increase the absorption of cyclosporine and decrease the absorption of

³⁰ Hempfling W et al. Systematic review: ursodeoxycholic acid--adverse effects and drug interactions. *Aliment Pharmacol Ther* 2003; 18(10):963-72

ciprofloxacin. UDCA can reduce the C_{max} and AUC of nitrendipine. Also, an interaction with a reduction of the therapeutic effect of dapsone has been reported. Oestrogenic hormones and blood cholesterol lowering agents such as clofibrate may increase biliary lithiasis, which is a counter-effect to UDCA used for dissolution of gallstones.

There is no evidence to suggest a need for dose alteration in the elderly. The UDCA dose in children should be related to bodyweight.

Conclusion on clinical safety

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 UDCA 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 $> 40 \mu\text{g/l}$, which is in line with recommendations from the literature and the approved posology in the RMS for UDCA containing products. Furthermore, the MAH proposed to exclude patients with decompensated liver cirrhosis from the PBC indication. This is in line with the approved PBC indication in several member states and is considered acceptable.

Risk management plan

The MAH provided a statement that this application is based on well-established use where no safety concerns requiring additional risk minimization activities have been identified compared with the innovator product Ursofalk, 250 mg hard capsules.

There are no new safety concerns and the labelling for the product reflects that of the innovator product. Accordingly, only routine pharmacovigilance activities are considered necessary for post authorization safety monitoring of this product. At the time of this application, the pharmacovigilance legislation did not require a Risk Management Plan. Therefore, the absence of an RMP is acceptable.

CMD(h) referral

Grounds for referral

At the end of the decentralised procedure, agreement could not be reached between member states. The procedure was referred to the CMD(h) because it was questioned by one CMS whether the submission of the results of a bioequivalence study could be accepted to support bridging to the product described in literature for an application based on Article 10a of Directive 2001/83/EC (well-established use).

Furthermore, it was questioned whether a medicinal product obtained from the Australian market could be used as the reference product in the bioequivalence study for this application, and to what extent this Australian product was comparable to the European reference product.

Outcome

The positive benefit-risk for ursodeoxycholic acid has been demonstrated by reference to and submission of literature data only, as required by the legislation with regard to well-established use applications. The submitted *in vivo* data are considered to be a supportive study which has been submitted to allow bridging from the literature data to the proposed product. In view of the current legislation this was considered to be acceptable.

Furthermore, sufficient proof was provided for the relevance of the Australian reference product for the EU situation. Therefore, with the submitted supportive *in vivo* data, sufficient data have been submitted to bridge the product applied for to literature data.

Consensus was reached before the CMD(h) meeting and the procedure was closed with a positive outcome.

Product information

SmPC

The content of the SmPC approved during the decentralised procedure is in accordance with those accepted for comparable UDCA containing products.

Readability test

The package leaflet 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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. No problems were identified regarding comprehensibility and usefulness of the information and thus no amendments were made during the process. Overall, each and every question met the criterion of 81% correct answers. Altogether the testing has been performed in line with the requirements. The final leaflet is considered readable, with patients/users being able to act properly upon the information that it contains.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ursodeoxycholzuur Strides 250 mg, capsules, hard has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

In the Board meeting of 16 July 2013, the application for UDCA Strides supported by literature data was discussed. The well-established use of UDCA has been sufficiently substantiated based on the literature overview provided. Additionally the MAH presented the results of a bioequivalence study which indicate comparable bioavailability of UDCA Strides with Ursofalk from the Australian market, and comparable bioavailability with data reported in literature. Moreover, relevance of the Australian Ursofalk capsule used in the study was sufficiently supported by *in vitro* data. Therefore, bridging to literature data is considered adequately justified.

From a clinical point of view, the proposed indications of dissolution of radiolucent gallstones and PBC, as well as the proposed posology are in line with current UDCA use and recommendations in the RMS and CMS countries, in which UDCA has been registered for 10-20 years. Based upon clinical data and the longstanding clinical experience, the use of UDCA in the proposed indications can be considered well-established with demonstrated efficacy and acceptable safety.

As the approved indication for UDCA with regard to PBC differs across EU countries, the MAH was requested to motivate the inclusion of PBC stage IV. Based on the available efficacy and safety data of UDCA in the treatment of PBC stage IV, it can be concluded that inclusion of PBC stage IV, in conjunction with a dose reduction and exclusion of patients with decompensated liver cirrhosis, is acceptable.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC is consistent with that of the innovator's product, Ursofalk capsules. The SmPC, package leaflet and labelling are in the agreed templates.

Agreement could however not be reached during the decentralised procedure. A CMD(h) referral was initiated because of concerns with regard to the bioequivalence study. The issues were then resolved: a bioequivalence study can be considered supportive in the context of a well-established use application, and the Australian reference product used has been demonstrated to be relevant for the EU market. The CMD(h) referral was finalised with a positive outcome on 21 October 2013. Ursodeoxycholzuur Strides 250 mg, capsules, hard was authorised in the Netherlands on 10 January 2014.

The date for the first renewal will be: 21 October 2018

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to manufacture and validate one additional batch.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OR	Odds Ratio
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PBC	Primary Biliary Cirrhosis
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
UDCA	Ursodeoxycholic Acid
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached