# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Destolit 150 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg ursodeoxycholic acid (UDCA)

Excipient(s) with known effect: Lactose

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

The dissolution of radiolucent (ie non-radio opaque) cholesterol gallstones in patients with a functioning gallbladder.

### 4.2 Posology and method of administration

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Posology

*Adults and the elderly*

Dissolution of gallstones:

A daily dose of 8 to 12mg/kg UDCA will produce cholesterol desaturation in the majority of cases. The measurement of the lithogenic index on bile-rich duodenal drainage fluid after 4-6 weeks of therapy may be useful for determining the minimum effective dose. The lowest effective dose has been found to be 4 mg/kg. The daily dose for most patients is 3 or 4 tablets, according to body weight. The dose should be divided into two administrations after meals, with one administration always after the evening meal.

The duration of treatment needed to achieve dissolution will not usually exceed 2 years, and should be monitored with regular cholecystograms. Treatment should be continued for 3-4 months after the radiological disappearance of gallstones.

Any temporary discontinuation of treatment, if prolonged for 3-4 weeks, will allow the bile to return to a state of supersaturation, and will extend the total time taken for litholysis. In some cases stones may recur after successful treatment.

*Paediatric population*

Not recommended.

Method of administration

For oral administration.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Acute inflammation of the gallbladder or biliary tract.
Occlusion of the biliary tract (occlusion of the common bile duct or a cystic duct).
Frequent episodes of biliary colic.
Radio-opaque calcified gallstones.
Impaired contractility of the gallbladder.
Non functioning gall bladder.
Inflammatory bowel disease.
Hepatic and intestinal conditions interfering with enterohepatic recirculation of bile acids:

- Extrahepatic cholestasis
- Intrahepatic cholestasis
- Ileal resection
- Regional ileitis
- Ileal stoma

Acute, chronic or severe liver disease
Active duodenal ulcer

Active gastric ulcer

## 4.4 Special warnings and precautions for use

During the first 3 months of treatment, the liver function parameters AST (SGOT), ALT (SGPT) and γ-GT should be monitored by the physician every 4 weeks, thereafter every 3 months.

When used for the dissolution of cholesterol gallstones:
In order to assess therapeutic progress and for timely detection of any calcification of the gallstones, depending on stone size, the gallbladder should be visualised (oral cholecystography) with overview and occlusion views in standing and supine positions (ultrasound control) 6-10 months after the beginning of treatment.

The active ingredient ursodeoxycholic acid is used for the treatment of primary biliary cirrhosis. DESTOLIT is not indicated for the use in the treatment of this condition.

If the gallbladder cannot be visualised on X-ray images, or in cases of calcified gallstones, impaired contractility of the gallbladder or frequent episodes of biliary colic, DESTOLIT should not be used.

If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued.

Excessive dietary intake of calories and cholesterol should be avoided; a low cholesterol diet will probably improve the effectiveness of DESTOLIT tablets.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

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- Bile acid binding resins (e.g., colestyramine, colestipol) and some antacids (e.g. aluminium hydroxide) may inhibit the absorption and efficacy of DESTOLIT. Should the use of a preparation containing one of these substances be necessary, it must be taken at least 2 hours before or after DESTOLIT.
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- Charcoal may reduce DESTOLIT absorption.
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- UDCA can increase the absorption of ciclosporin and raises ciclosporin serum levels which should therefore be checked by the physician and the ciclosporin dose adjusted if necessary.
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- In isolated cases DESTOLIT can reduce the absorption of ciprofloxacin.
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- Ursodeoxycholic acid has been shown to reduce the plasma peak concentrations ($C_{max}$) and the area under the curve (AUC) of the calcium antagonist nitrendipine. An interaction with a reduction of the therapeutic effect of dapsone was also reported. These observations together with in vitro findings could indicate a potential for ursodeoxycholic acid to induce cytochrome P450 3A enzymes.
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- It is recommended that drugs known to increase cholesterol elimination in bile, such as oestrogenic hormones, oral contraceptive agents and certain blood cholesterol lowering agents, should not be prescribed concomitantly.

## 4.6 Fertility, Pregnancy and lactation

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Pregnancy
There are no adequate data on the use of ursodeoxycholic acid, particularly in the first trimester of pregnancy. Animal studies have provided evidence of a teratogenic effect during the early phase of gestation (see section 5.3).
DESTOLIT must not be used during pregnancy unless clearly necessary. The possibility of a pregnancy must be excluded before beginning treatment.
Breast-feeding
There are no clinical data available on the safety of UDCA in women who are breast-feeding. Therefore, DESTOLIT is not recommended in this patient group.
Fertility
Women of child bearing age should use adequate non-hormonal or low oestrogen oral contraceptive measures during treatment with UDCA.
However, in patients taking DESTOLIT for dissolution of gallstones, effective non-hormonal contraception should be used, since hormonal oral contraceptives may increase biliary lithiasis.

## 4.7 Effects on ability to drive and use machines

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DESTOLIT has no effects on the ability to drive and use machines.

## 4.8 Undesirable effects

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Summary of the safety profile
DESTOLIT is normally well tolerated. No significant alterations have so far been observed in liver function.
The evaluation of undesirable effects is based on the following frequency data:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000 )
Not known (cannot be estimated from available data).

Tabulated list of adverse reactions

| System Organ Class | Frequency | Adverse Event |
|---|---|---|
| Gastrointestinal disorders | Common | Diarrhoea, Pasty stools |
| | Not known | Vomiting, nausea. |
| Hepatobiliary disorders | Very rare | Calcification of gallstones |
| Skin and subcutaneous disorders | Very rare | Urticaria |
| | Not known | Pruritus |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

## 4.9 Overdose

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

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Pharmcotherapeutic group: ATC code: A05AA02

Mechanism of action

Ursodeoxycholic acid is a gallstone dissolving agent which acts by reducing the content of cholesterol in bile.

Pharmacodynamic effects

This may be due either to a reduction in hepatic cholesterol synthesis or reduced absorption of cholesterol or both.

## 5.2 Pharmacokinetic properties

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Absorption

Intestinal absorption after an oral dose of UDCA is high, with a first-pass clearance of about 50 to 60%. Studies show that passive diffusion occurs, whereupon the drug enters the enterohepatic circulation and is subject to an efficient hepatic extraction mechanism. The 'spillover' into the systemic blood supply is therefore minimal. Plasma levels are not clinically important but may be useful in estimating patient compliance; they reach maximum concentrations at about 60 minutes after ingestion with another peak recorded at 3 hours.

Distribution

Ursodeoxycholic acid is rapidly conjugated with glycine and taurine in the liver.

Biotransformation

Microbial biotransformation of the drug and its metabolites occurs when they leave the enterohepatic circulation and is responsible for high levels of faecal lithocholic and 7-ketolithocholic acids during ursodeoxycholic acid therapy..

Elimination

Intestinal flora also hydrolyse conjugated drug back to the parent compound and interconvert ursodeoxycholic and chenodeoxycholic acids.

## 5.3 Preclinical safety data

UDCA has not shown teratogenic potential in rats and rabbits; embryotoxicity seen in the rat at high doses appears to occur early in gestation.

Bile acids act as tumour promoters in colon carcinogenesis, but there is no evidence that they are direct carcinogens. In two year carcinogenicity studies UDCA was not tumourigenic in mice. In rats an increase in adrenal

phaeochromocytomas was observed which is not considered to be clinically significant.

Ursodeoxycholic acid has low oral toxicity. However, at high doses, the liver has been shown to be a target organ in all animal species examined (due to the hepatotoxic nature of the metabolite, lithocholic acid). These effects were seen at doses 3-80 fold higher on a body weight basis than the maximum daily dose proposed for humans.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Lactose, pregelatinised maize starch, acacia gum, talc, magnesium stearate, purified water.

## 6.2 Incompatibilities

None known.

## 6.3 Shelf life

3 years.

## 6.4 Special precautions for storage

None.

## 6.5 Nature and contents of container

Aluminium/ PVC /PVdC blister pack, 60 tablets

## 6.6 Special precautions for disposal

None.

# 7 MARKETING AUTHORISATION HOLDER

Norgine Pharmaceuticals Limited

Norgine House
Widewater Place
Moorhall Road
Harefield
Uxbridge
UB9 6NS
UK

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 20011/0043

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 August 2002

## 10 DATE OF REVISION OF THE TEXT

02/10/2018