**Summary of Product Characteristics for Pharmaceutical Products**

## 1. Name of the medicinal product:

DONET 800SR (Doxofylline Sustained Release Tablets 800 mg)

## 2. Qualitative and quantitative composition

Each uncoated sustained release tablet contains: Doxofylline 800 mg

For a full list of excipients, see section 6.1.

## 3. Pharmaceutical form

A white colored, caplet shaped, biconvex, uncoated tablet, plain on both sides.

## 4. Clinical particulars

### 4.1 Therapeutic indications

Bronchial asthma.
Pulmonary disease associated with bronchospasm.

### 4.2 Posology and method of administration

400 mg tablets – adults: 1 tablet two/three times daily

100 mg ampoules – adults: 2 ampoules by slow intravenous injection to patients in supine position (15-20 minutes), preferably diluted, during the acute phase.
Administration can be repeated at 12 hour intervals, at the physician's discretion.

200 mg sachets - children aged 6-12 years
1-3 sachets per day (12-18 mg/kg) dissolved in plenty of water.

2% syrup: - adults: one 20 ml measures two/three times a day (one 20 ml measure corresponds to 400 mg of Doxofylline)

At the recommended posology, the plasma levels of Doxofylline do not generally exceed 20 µg/ml, so it is not essential to check these levels periodically.
If the dosage is increased, the blood levels of the drug must be measured (the therapeutic value is about 10 µg/ml, the value bordering on toxicity is 20 µg/ml).

## 4.3 Contraindications

DONET 800SR is contraindicated in individuals with known hypersensitivity to the drug or other xanthine derivatives. It is also contraindicated in patients with acute myocardial infarction, hypotension and during lactation.

## 4.4 Special warnings and precautions for use

Numerous factors may reduce the hepatic clearance of xanthine derivatives with increased plasma levels of the drug. These factors include age, congestive cardiac decompensation, chronic obstructive pulmonary disease, severe liver disease, concomitant infections, the concurrent administration of several drugs such as: erythromycin, TAO, lincomycin, clindamycin, allopurinol, cimetidine, influenza vaccine and propranolol. In these cases, it may prove necessary to reduce the dosage of the drug.
Phenytoin, other anticonvulsants and cigarette smoking may increase the clearance of xanthine derivatives with a reduction of plasmatic half-life. In these cases, it may prove necessary to increase the dosage of the drug.
In case of factors that may influence the clearance of xanthine derivatives, monitoring of the concentration of the blood levels of the drug is recommended for the control of the therapeutic range.
Caution should be observed in administering the product to patients with cardiac disease, hypertension, in the elderly, in patients with severe hypoxemia, hyperthyroidism, chronic cor pulmonale, congestive heart failure, liver disease, peptic ulcer and in those with renal impairment. In particular, it is to be used with caution in patients with congestive heart failure, since the clearance of the drug is considerably slower in these patients in which high blood levels may persist for long periods even after discontinuation of the treatment.
There is no risk of addiction or any other form of dependence.

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

DONET 800SR should not be administered with other xanthine preparations. It is recommended to limit consumption of beverages and food containing caffeine.
Caution should be exercised in administering DONET 800SR together with ephedrine or other sympathomimetic drugs.

The concurrent administration of many drugs such as erythromycin, TAO, lincomycin, clindamycin, allopurinol, cimetidine, influenza vaccine and propranolol may reduce the hepatic clearance of xanthine derivatives with an increase in the plasmatic levels of the drug.

Phenytoin, other anticonvulsants and cigarette smoking may increase the clearance of xanthine derivatives with a reduction of plasmatic half-life. In these cases, it may prove necessary to increase the dosage of the drug.

## 4.6 Fertility, pregnancy, and lactation

Animal tests have shown that the active ingredient of DONET 800SR does not interfere with pre-and postnatal growth.

However, as there is not sufficient clinical evidence about the effects of the drug during pregnancy, use of the drug during pregnancy should be evaluated carefully case by case on the basis of the risk-benefit ratio. The drug is contraindicated during lactation.

## 4.7 Effects on ability to drive and use machines.

The product does not affect the patient's alertness and therefore does not interfere with his/her ability to drive and use machines.

## 4.8 Undesirable effects

Patients treated with xanthine derivatives may suffer nausea, vomiting, epigastric pain, headache, irritability, insomnia, tachycardia, extrasystoles, tachypnea, and in rare cases, hyperglycemia or albuminuria. In case of overdose severe cardiac arrhythmias and tonic-clonic seizure may occur. These effects may represent the first signs of intoxication.

The appearance of side effects may require discontinuation of the treatment which, if necessary, at the physician's discretion, may be resumed at lower doses after all signs and symptoms of toxicity have subsided.

Reporting of suspected adverse reactions:

Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

## 4.9 Overdose

As there is no specific antidote, in case of overdose a symptomatic

treatment of cardiovascular collapse should be instituted.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Doxofylline directly relaxes the smooth muscles of the bronchi and pulmonary vessels. In this way, it acts mainly as a bronchodilator, pulmonary vasodilator and as a relaxant of the bronchial muscle. The action of Doxofylline may be mediated, at least in part, by inhibition of the phosphodiesterase leading to an increase in intracellular cyclic AMP which results in smooth-muscle relaxation.
At higher concentrations, Doxofylline may inhibit the release of histamine by the cells. Prolonged use of the drug does not lead to addiction.

### 5.2 Pharmacokinetic properties

Doxofylline half-life is more than 6 hours, so constant effective plasma levels may be maintained with three administrations a day.
The kinetics after a single i.v. and oral administration have been studied in man to define the distribution and absorption of the drug.
After intravenous administration of 100 mg of Doxofylline to 5 volunteers, the distribution of the unchanged substance in the serum follows a bi-compartmental model.
The area under the curve of the concentration of the drug in the serum during the distribution phase represents a small fraction of the total area.

Plasmatic clearance is high, with values ranging from 444 to 806 ml/min, whereas distribution volume is about 1 l/kg.

The mean half-life after intravenous administration was calculated to be 65 minutes (from 40 to 96).

### 5.3 Preclinical safety data

Acute toxicity
The LD50 in rats and mice following oral, intraperitoneal and intravenous administration of the drug:

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|---|---|---|
| Oral administration: | in the rat | = 1022.4 mg/kg |
| | in the mouse | = 841.0 mg/kg |

Intraperitoneal administration: in the rat = 444.7 mg/kg

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|---|---|---|---|---|
| Intravenous administration: | in m. rats | = 360 mg/kg | | |
| | in f. rats | = | 310 | mg/kg |
| | in m. mice | = | 245 | mg/kg |
| | in f. mice | = | 238 | mg/kg |

Oral and i.p. acute toxicity in beagle dogs
Oral administration: over 800 mg/kg
I.p. administration : 400 mg/kg

Subacute toxicity (three months) - per os
In male and female rats at doses of:
7.21 mg/kg - 57.66 mg/kg - 288.40 mg/kg per os;

in male rats at doses of:
3.625 mg/kg - 29 mg/kg - 145 mg/kg i.p.;

in female rats at the dose of:
3.625 mg/kg i.p.;

in male and female beagle dogs at doses of:
180 mg/kg - 60 mg/kg - 20 mg/kg per os

no appreciable changes were observed.

Chronic toxicity (six months) -
In male rats at doses of:
7.21 mg/kg - 57.66 mg/kg - 288.4 mg/kg per os;

in female rats at doses of:
7.21 mg/kg - 288.4 mg/kg per os;

in male rats at doses of:
3.625 mg/kg - 29 mg/kg - 145 mg/kg i.p.;

in female rats at the dose of:
145 mg/kg i.p.;

in male and female beagle dogs, at doses of:
180 mg/kg - 60 mg/kg - 20 mg/kg

the product was well tolerated and had no toxic effects.

Subacute toxicity (1 month) - i.v.
In male and female rabbits at doses of:

57.68 mg/kg - 28.84 mg/kg - 7.21 mg/kg i.v.

the product proved suitable for prolonged i.v. administration.

The product was found to be free of fetal toxicity following tests carried out on rats and rabbits at the following doses:

in rats: 57.66 mg/kg per os
29 mg/kg i.p.

- in rabbits: 7.21 mg/kg - 28.84 mg/kg - 115.36 mg/kg via oral route.

The product was found to have no effect on fertility, pre or post-natal growth and no teratogenic effect on rats.

Doxofylline was also found to have no mutagenic effect.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Microcrystalline Cellulose (PH 102),
HydroxypropylMethylcellulose K100M,
Polyvinyl pyrrolidone K30,
Purified water,
PEG 6000
Talc,
Magnesium Stearate

### 6.2 Incompatibilities

No incompatibility with other substances has been reported for any of the available pharmaceutical forms.

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage:

Store below 30°C. Store in the original carton to protect from light.

### 6.5 Nature and contents of container

DONET 800SR mg tablets:

1 X 10 Tablet Alu-Alu Blister

## 6.6 Special precautions for disposal and other handling:

No particular precautions need be taken in handling the product. See Posology and method ofadministration.

## 7. Marketing authorization holder and manufacturing site addresses

**Marketing authorization holder:**

OMILIFE LIMITED
Address: P.O. BOX 524-00200 CITY SQUARE, NAIROBI, KENYA.
Telephone: +254 723353615
E-Mail: omilifebio@gmail.com

**Manufacturing site address:**

4Care life Science (P) Limited SurveyNo.23/3P&24, Opp. Jeans Factory, Daduram Vistar, Village-Bagdol, Tal- Kathlal, Dist- Kheda - 387630, Gujarat, India.

## 8. Marketing authorization number

CTD9863

## 9. Date of first registration

02-08-2022

## 10. Date of revision of the text:

15-09-2023

## 11. Dosimetry:

Not Applicable

## 12. Instructions for Preparation of Radiopharmaceuticals:

Not Applicable