1. NAME OF THE MEDICINAL PRODUCT
Puroxan

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Doxofylline 400 mg

For excipients, see 6.1.

3. DOSAGE FORM
Tablets

4. CLINICAL CHARACTERISTICS

4.1 Therapeutic indications
PUROXAN is indicated for the treatment of chronic respiratory disease, such as Bronchial Asthma and Chronic Obstructive Pulmonary Disease (COPD).

4.2 Dosage and method of administration
The dose is prescribed by the attending physician, depending on the patient's age, weight and the characteristics the body.
On average it is recommended to take:
- adults and children over 12 years old - 1 tablet 2-3 times a day;
- for children over 6 and up to 12 years old – 0,5 tablets (200 mg) 2-3 times a day.

4.3 Contraindications
It is not applicable if you have an increased sensitivity (allergy) with respect to one of the components that are part of the medication.

Contraindicated in:
- acute myocardial infarction;
- if you are breast feeding.
- arterial hypotension.

4.4 Special warnings and special precautions for use
The half-life of xanthine derivatives is influenced by a number of known variables. It may be prolonged in patients with severe hepatic insufficiency, in patients with end stage congestive heart failure, in those affected with chronic obstructive lung disease or concomitant infections, and in those patients taking certain other drugs (erythromycin, troleandomycin, lincomycin and other antibiotics of the same group, allopurinol, cimetidine, propanolol, and anti-flu vaccine). In these cases, a lower dose of Doxofylline may be needed.
Phenytoin, other anticonvulsants and smoking may cause an increase in clearance with a shorter mean half-life: in these cases higher doses of Doxofylline may be needed.
Laboratory monitoring of plasma concentration of Doxofylline is recommended in all the above situations.
Use with caution in patients with hypertension, heart disease, hypoxemia, hyperthyroidism, chronic right ventricular failure, congestive heart failure, liver

disease, renal disease, in those with history of peptic ulcer, and in the elderly with impaired hepatic function.
Frequently, patients with congestive heart failure have markedly prolonged drug plasma levels following discontinuation of the drug.
Doxofylline does not cause any risk of tolerance or addiction.

4.5 Drug Interactions

Doxofylline should not be administered together with other xanthine derivatives, including beverages and foods containing caffeine. Toxic synergism with ephedrine has been documented for xanthines.
Like other xanthines, concomitant therapy with erythromycin, troleandomycin, lincomycin, clindamycin, allopurinol, cimetidine, ranitidine, propanolol and anti-flu vaccine may decrease the hepatic clearance of xanthines causing an increase in blood levels. No evidence of a relationship between Doxofylline serum concentrations and toxic events has been reported.
See also section 4.4.

4.6 Pregnancy and lactation

Animal reproduction studies indicate that Doxofylline does not cause foetal harm when administered to pregnant animals nor can affect reproduction capacity.
However, since there is limited experience in humans during pregnancy, xanthines should be given to a pregnant woman only if clearly needed. Doxofylline is contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines

Driving and other activities related with the use of machines are not affected by Doxofylline.

4.8 Adverse Drug Reactions

After xanthine administration nausea, vomiting, epigastric pain, cephalalgia, irritability, insomnia, tachycardia, extrasystole, tachypnea, and occasionally hyperglycemia and albuminuria may occur.
If a potential oral overdose is established, the patient may present with severe arrhythmias and seizure; these symptoms could be the first sign of intoxication.
Adverse reactions may cause the withdrawal from treatment; a lower dose rechallenge may start only after the advice of a physician.

4.9 Overdosage

Although no major arrhythmias have been documented with doxofylline, the occurrence of major cardiac rhythm disturbances cannot be excluded in case of overdosage of xanthine compounds. If a potential oral overdose is established, the patient may present seizures; these symptoms could be the first sign of intoxication. Adverse reactions may cause the withdrawal from treatment. A lower dose re-challenge may start only after the advice of the physician.

APPROVED BY SCDMTE JSC
Expert / Date 19.02.19
Applicant / Date 20.02.19

5. PHARMACOLOGICAL PROPERTIES

ATC code R03DA11

5.1 Pharmacodynamic properties

Doxofylline is a novel bronchodilator structurally classified as a xanthine derivative.
Doxofylline directly relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels, thus acting mainly as a bronchodilator and smooth muscle relaxant. The exact mode of action remains unknown, although doxofylline does cause inhibition of phosphodiesterase with a resultant increase in intracellular cyclic AMP. At high concentrations, doxofylline is also able to inhibit the cellular release of histamine.

5.2 Pharmacokinetic properties

The half-life of Doxofylline is greater than seven hours.

After **oral** administration, peak plasma levels were reached after one hour.
Absolute bioavailability is about 62.6%; at a pH 7.4 plasma protein binding of the compound is about 48%. Less than 4% of an orally administered dose is excreted unchanged in the urine.
Doxofylline is almost completely metabolized in the liver (90% of the total drug clearance). Hydroxyethyltheophylline is the only detectable circulating metabolite of Doxofylline.

After repeated administrations Doxofylline reaches the steady-state in about 4 days; the elimination half-life during long-term treatment is 8-10 hours: this allows a twice daily dose regimen. No accumulation of the drug was noted after one week of treatment.

5.3 Preclinical safety data

Acute toxicity

LD_{50} in the rat and in the mouse:

Oral administration:	rat	1022.4 mg/kg
	mouse	841.0 mg/kg
Intraperitoneal administration:	rat	444.7 mg/kg
Intravenous administration:	male rat	360 mg/kg
	female rat	310 mg/kg
	male mouse	245 mg/kg
	female mouse	238 mg/kg

Acute toxicity in the beagle dog:
Oral administration: greater than 800 mg/kg
Intraperitoneal administration: 400 mg/kg.

Subacute toxicity (3 months)

Male and female rats: 7.21 mg/kg, 57.66 mg/kg, 288.4 mg/kg orally.
Male rat: 3.625 mg/kg, 29 mg/kg, 145 mg/kg intraperitoneally.
Female rat: 3.625 mg/kg given intraperitoneal
Male and female beagle dogs: 180 mg/kg, 60mg/kg, 20mg/kg orally.
Effects worth noting were not observed.

Chronic toxicity (6 months)

Male and female rat: 7.21 mg/kg, 57.66 mg/kg, 288.4 mg/kg

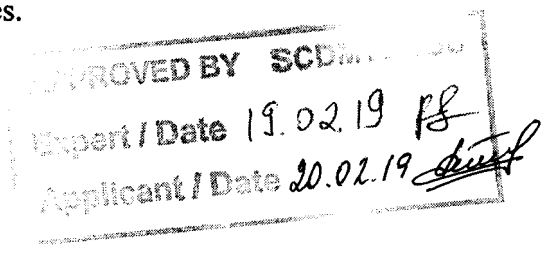
per os;
Female rat: 7.21 mg/kg, 288.4 mg/kg per os;
Male rats: 3.625 mg/kg, 29 mg/kg, 145 mg/kg intraperitoneal;
Female rats 145 mg/kg intraperitoneal;
Male and female beagle dog: 180 mg/kg, 60mg/kg,
20 mg/kg, orally.
The drug was well tolerated and lacking toxic effects.

Subacute toxicity (1 month) in the rabbit
Male and female rabbits, intravenous doses:
57.68 mg/kg, 28.84 mg/kg, 7.21 mg/kg.
The preparation was suitable for prolonged i.v. administration.
The preparations were without fetal toxicity following trials in the rat and in the rabbit at the following doses:
Rat 57.66 mg/kg per os, 29 mg/kg intraperitoneal;
Rabbit 7.21 mg/kg, 28.84 mg/kg, 115.36 mg/kg orally.
The drug did not affect fertility, on the pre- and post-natal development and was devoid of teratogenic effects in the rat.
Doxofylline was also devoid of mutagenic activity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Colloidal silicone dioxide, Corn starch, Mannitol, Povidone, Microcrystalline Cellulose, Talc, Magnesium stearate.

6.2 Incompatibilities
No known incompatibilities.



6.3 Shelf life
2 years

6.4 Storage Conditions
Store below 25°C.

6.5 Packaging
Alufoil blister containing 10 tablets.
Carton box containing 10 or 20 tablets.

6.6 Instructions for use and handling
No special requirements

7. MANUFACTURER
M&H Manufacturing Co. Ltd.,
Samutprakarn, Thailand.

8. OWNER OF THE LICENSE
PharmaTech CJSC
111 Raffi str, Yerevan,

Republic of Armenia

9. DATE OF FINAL REVISION OF THE DOCUMENTS

February 2019