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, Doxofylline 400 mg Tablet, 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 of Doxofylline 400 mg Tablet is prescribed by the attending physician, depending on the patient's age, weight and the characteristics of the body.
On average it is recommended to take:
- 400 mg Tablets: 1 tablet two/three times a day in adults.

At the recommended dosage, doxofylline plasma levels generally do not exceed 20 µg/ml, therefore it is not essential to periodically check these levels.
In the event of an increase in this dosage it is necessary to resort to monitoring the blood levels of the drug (therapeutic values around 10 µg/ml, values at the toxicity limits of 20 µg/ml)

4.3 Contraindications

Individual hypersensitivity to the product components and chemically related substances (e.g. xanthine derivatives).

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

4.4 Special warnings and special precautions for use

Numerous factors can reduce the hepatic clearance of xanthine derivatives with increases in plasma levels of the drug. These include age, congestive heart failure, chronic obstructive lung diseases, severe liver disease, infections
concomitant, the simultaneous administration of many drugs such as: erythromycin, TAO, lincomycin, clindamycin, allopurinol, cimetidine, influenza vaccine, propranolol. In these cases it may be necessary to reduce the dosage of the drug.
Phenytoin, other anticonvulsants and cigarette smoking can increase the clearance of xanthine derivatives with a reduction in plasma half-life. In these cases it may be 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 blood levels of the drug is recommended in order to control the therapeutic range.
The administration of the product must be done with caution in heart patients, in hypertensive patients, in the elderly and in patients with severe hypoxemia, hyperthyroidism, chronic cor pulmonale, congestive heart failure, liver disease, peptic ulcer and in patients with poor renal function. In particular, it should be used with caution in patients with congestive heart failure as in these patients there is a notable slowdown in drug clearance, with persistence of high blood levels for long periods, even after suspension of treatment.
There is no risk of addiction, dependence or otherwise.

4.5 Drug Interactions

Puroxan tablets must not be administered together with other xanthine preparations. Moderate use of drinks and foods containing caffeine is recommended.
The association between Puroxan tablets and ephedrine or other sympathomimetics requires caution.
The simultaneous administration of many drugs such as erythromycin, TAO, lincomycin, clindamycin, allopurinol, cimetidine, influenza vaccine, propranolol can reduce the hepatic clearance of xanthine derivatives with an increase in plasma levels of the drug.
Phenytoin, other anticonvulsants and cigarette smoking can increase the clearance of xanthine derivatives with a reduction in plasma half-life. In these cases it may be necessary to increase the dosage of the drug.

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.

5. PHARMACOLOGICAL PROPERTIES

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 10270, Thailand.

8. MARKETING AUTHORISATION HOLDER

PharmaTech CJSC
111 Raffi str, Yerevan,
Republic of Armenia

9. DATE OF FINAL REVISION OF THE DOCUMENTS

May 2024