Puroxan®

Doxofylline 400 mg
BROCHODILATOR

PRESCRIPTION DRUG ONLY

INTERNATIONAL NON-PROPRIETARY NAME
Doxofylline

PRODUCT DESCRIPTION
Each tablet contains Doxofylline - 400 mg
Description: White, round, scored tablets with smooth surface.

THERAPEUTIC PROPERTIES
Doxofylline is a 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.

PHARMACODYNAMICS
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.
Doxofylline did not antagonise adenosine A1, A2B and A3 receptors; there was only a modest inhibition at the highest tested concentration (10^4 M) against A2A receptors. This may explain the improved tolerability profile of doxofylline in comparison with other xanthine based medicines.
Doxofylline does not inhibit any of the PDE enzyme subtypes, except a modest inhibition at the highest tested concentration (10^4 M) against PDE2A1.
PDE3 inhibitors are known to cause vasodilation and cardiac effects. The lack of effect of doxofylline on PDEs may help explain its improved tolerability profile on the cardiovascular system.
Doxofylline does not exert any significant inhibitory effect against any of the 11 HDAC enzymes.
Doxofylline significantly inhibited the migration of neutrophils and the release of IL-6 and TNF-α into the lung lumen, demonstrating the anti-inflammatory action of doxofylline.

PHARMACOKINETICS
The half-life of Doxofylline is greater than six hours; so as to allow effective constant plasma levels with a t.i.d. dose regimen. Single dose pharmacokinetic studies in man after oral and intravenous administration defined distribution and absorption of the drug.
After i.v. administration of 100 mg to 5 healthy volunteers, distribution of Doxofylline in plasma followed a bi-compartmental model. During the distribution phase the plasma AUC was only a modest portion of the total AUC; plasma clearance was somewhat high, ranging from 444 ml/min to 806 ml/min; apparent volume of distribution was about 1 l/kg. The mean half-life after i.v. administration was about 65 min. (from 40 min. to 96 min.).
After oral administration (tablets), 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.

Following repeated administration Doxofylline reaches the steady-state after app. 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.

CLINICAL DATA
In a multicenter, randomized clinical trial, 139 patients suffering from COPD received Doxofylline 400 mg twice daily or Theophylline 250 mg twice daily for 28 days. Doxofylline was show to be as effective as Theophylline in reducing spirometic parameters ($p<0.001$ for all tests). Doxofylline significantly decreased the daily use of Salbutamol inhaler ($p<0.001$ for both drugs). Patients treated with Doxofylline had significantly fewer adverse events than patients treated with Theophylline (Melillo et al, 1989).
The pooled-analysis of 483 patients demonstrated that both doxofylline 400 mg and theophylline 250 mg significantly increased FEV1, reduced the rate of asthma events and use of salbutamol to relieve asthma symptoms compared to placebo ($p<0.01$). No significant differences were detected between doxofylline 400 mg and theophylline 250 mg.
Doxofylline 400 mg did not significantly ($p>0.05$) increase the risk of AEs compared to placebo, conversely in patients treated with theophylline 250 mg the risk of AEs was significantly ($p < 0.05$) greater than in those that received placebo (Calzetta et al, 2018).
In a randomized clinical study performed in the USA, 263 patients with chronic reversible bronchial asthma received Doxofylline 400 mg three times daily, Theophylline 250 mg three times daily or placebo for 12 weeks. Doxofylline was demonstrated to be as effective as Theophylline. Doxofylline was better tolerated than Theophylline, as significantly more patients treated with Theophylline had to interrupt treatment because of adverse events ($p=0.001$). Doxofylline significantly reduced the number of daily asthma attacks ($p<0.05$) (Goldstein et al, 2002).
In a meta-analysis data was obtained from 998 COPD patients. When coupling relative effects for efficacy and safety, doxofylline appeared to be superior to aminophylline (comparable efficacy and significantly better safety), bamiphylline (significantly better efficacy and comparable safety) and theophylline (comparable efficacy and significantly better safety), (Cazzola et al, 2018).

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INDICATIONS
Puroxan® is indicated for the treatment of bronchial asthma and Chronic Obstructive Pulmonary Disease (COPD) associated with bronchospasm.

RECOMMENDED DOSAGE
Adults: 1 tablet (400 mg) 2 times daily.
The dosage may be increased to three times daily according to the prescribing physician.

MODE OF ADMINISTRATION
Puroxan tablets should be swallowed whole with sufficient amounts of liquid (approximately ½ a glass).

CONTRAINDICATIONS
This product is contraindicated in individuals who have shown hypersensitivity to its components. It is also contraindicated in patients with acute myocardial infarction, hypotension, and in lactating women.

WARNINGS AND PRECAUTIONS
The half-life of Doxofylline is influenced by a number of known variables. It may be prolonged in patients with liver disease, in patients with congestive heart failure, in those affected with chronic obstructive lung disease or concomitant infections. Use with caution in patients with hypertension, heart disease, hypoxemia, hyperthyroidism, chronic right ventricular failure, renal disease, in those with history of peptic ulcer, and in the elderly.
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.

DRUG INTERACTIONS
Doxofylline should not be administered together with other xanthine derivatives, including beverages and foods containing excessive amounts of caffeine. Toxic synergism with ephedrine has been documented for xanthines.
Concomitant therapy with erythromycin, troleandomycin, lincomycin, clindamycin, and other antibiotics of the same group, allopurinol, propranolol, digoxin and anti-flu vaccine may decrease the hepatic clearance of xanthines causing an increase in blood levels. 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 IN 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.

UNDESIRABLE EFFECTS
After administration occasionally nausea, vomiting, headache, irritability, insomnia, palpitations and tachycardia may occur.

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.

PRESENTATION
Aluminium blister containing 10 tablets. Box of 20 and 100 tablets.

SHELF LIFE
36 Months

STORAGE
Store below 30°C
Keep out of reach of children!

Manufactured under license for:
Eurodrug Laboratories B.V. (The Netherlands)
by ABC Farmaceutici S.p.A., Italy

eurodrug LABORATORIES

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