DOXOFYLLINE

DoxoFix™

400 mg Tablet

Anti-asthma

FORMULATION

Each tablet contains:

Doxofylline ..... 400 mg

PRODUCT DESCRIPTION

Doxofylline (DoxoFix™) 400 mg tablet is a white, ½" diameter round, flat tablet, bisected on one side, plain on the other side.

CLINICAL PHARMACOLOGY

Doxofylline (7-(1,3-dioxolan-2-ylmethyl) theophylline) is a methylxanthine derivative characterized by the presence of a dioxolane group in position 7. It has potent bronchodilator activity equal or superior to theophylline.

Doxofylline's activity is due to its ability to inhibit phosphodiesterase enzymes followed by an increase in cyclic-3',5' adenosine monophosphate (cAMP) resulting in smooth muscle relaxation. The decreased affinity of doxofylline for adenosine A_1 and A_2 receptors has been suggested to account for its better safety profile compared with theophylline.

Pharmacodynamic investigations in animals showed that doxofylline has the ability to overcome bronchoconstriction, inflammatory events (pleurisy) and thromboxane A_2 release when challenged with platelet-activating factor.

The pharmacokinetics of oral and intravenous doxofylline was evaluated in adults with chronic bronchitis. Doxofylline has a very short distribution phase following intravenous administration of 100 mg doxofylline given as a single dose over 10 minutes, with a sustained elimination phase (half-life 1.83 ± 0.37 hours). After oral administration of 400 mg doxofylline twice daily for 5 days, the peak serum doxofylline concentration at steady state was 5.78 - 20.76 mcg/mL (mean ± SD 15.21 ± 1.73 mcg/mL), with time to reach maximum concentration of 1.19 ± 0.19 hours. The total clearance was 555.2 ± 180.6 mL/min and the mean elimination half-life was 7.01 ± 0.80 hours.

The absolute bioavailability of doxofylline was reported to be 63 ± 25 % after oral administration at a dose of 400 mg given in healthy subjects, with only one metabolite (ß-hydroxymethyltheophylline), which was devoid of any significant pharmacological activity, being detected in the serum and urine.

DOSAGE AND ADMINISTRATION

AGE GROUP	ORAL DOXOFYLLINE DOSE
ADULT	1 Tablet two to three times daily
ELDERLY	½ Tablet two to three times daily
	Or, as prescribed by a physician.

INDICATIONS

For the treatment of bronchial asthma, pulmonary disease with spastic bronchial component and chronic obstructive pulmonary disease (COPD).

CONTRAINDICATIONS

- Hypersensitivity to any ingredient in the product or to other methylxanthines.
- Patients with acute myocardial infarction, hypotension, and in breastfeeding women.

WARNINGS AND PRECAUTIONS

Xanthine clearance may be altered by different variables affecting its half-life. In patients with cardiovascular failure, renal or hepatic dysfunction, in those with chronic obstructive pulmonary disease, in patients undergoing influenza immunization or who have an active influenza infection and in patients taking other drugs (e.g., cimetidine, allopurinol, propranolol, erythromycin, troleandomycin, lincomycin, and ciprofloxacin), clearance may be decreased and its half-life increased. The dose of doxofylline may be reduced in these conditions. In patients who are taking phenytoin and other anticonvulsants and in those who are smoking, clearance may be increased and its half-life decreased. In these cases, a higher dose of doxofylline may be required.

Use with caution in patients with the following conditions:

- Peptic ulcer
- Hyperthyroidism
- Hypoxemia
- Renal or hepatic dysfunction
- Cardiovascular disorders including cardiac arrythmias, angina pectoris, acute myocardial injury, or hypertension
- Convulsive disorders

INTERACTION WITH OTHER MEDICAMENTS

- Doxofylline should not be administered concomitantly with other methylxanthines, including beverages and foods containing caffeine.
- Xanthine clearance may be decreased by interaction with cimetidine, allopurinol, propranolol, erythromycin, troleandomycin, lincomycin, ciprofloxacin, and anti-flu vaccine.
- Phenytoin and other anticonvulsants may increase xanthine clearance.
- Xanthines may also potentiate hypokalemia caused by hypoxia or associated with the use of $ß_2$- adrenoceptor stimulants ($ß_2$-agonist). Synergistic toxicity with ephedrine and other sympathomimetics have also been reported for xanthines.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: The safe use of doxofylline during pregnancy has not been established. Doxofylline should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation: Methylxanthines are distributed into all body compartments. They cross the placenta and are distributed into breast milk. Doxofylline is contraindicated in breastfeeding mothers.

Use in Children: Doxofylline should be administered cautiously to young children.

Use in the Elderly: Doxofylline should be administered cautiously to elderly patients particularly those with conditions such as cardiac failure, pulmonary edema or hepatic dysfunction. Dosage may be reduced and careful monitoring of doxofylline plasma concentrations may be required to avoid severe toxicity.

ADVERSE EFFECTS

After xanthine administration, nausea, vomiting, abdominal pain, epigastric distress, insomnia, headache, nervousness, and dizziness may occur. Adverse cardiovascular effects include tachycardia, extrasystoles, and palpitation. Albuminuria and hyperglycemia may also occur.

OVERDOSAGE AND MANAGEMENT

Common clinical manifestations of xanthine overdosage include nausea, vomiting, gastrointestinal bleeding, metabolic acidosis, hypokalemia, hypotension, cardiac arrythmias, and seizures, often ending in death.

Treatment of xanthine overdosage is symptomatic and supportive. It includes withdrawal of the drug. If seizures have not occurred following acute overdosage, the stomach should be emptied immediately by inducing emesis or by gastric lavage, followed by administration of activated charcoal and cathartic. If the patient is having seizures, an adequate airway should first be established and maintained. Seizures may be treated with intravenous diazepam, phenobarbital or in combination. There is no adequate evidence to support the use of dialysis in the treatment of doxofylline overdose.

STORAGE CONDITIONS

STORE AT TEMPERATURES NOT EXCEEDING 30^{0}C

Keep the product out of reach and sight of children

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

AVAILABILITY

Doxofylline 400 mg Tablet in box of 50's (in blister pack of 10's)

Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

Trusted Quality Healthcare

Date of Revision: 09/2012
P30000012164