

IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA1140/005/001

Case No: 2026068

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Taro Pharmaceuticals (Ireland) Limited

Lourdes Road, Roscrea, Co. Tipperary, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Doxapram Injection BP 20 mg/ml

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **17/12/2006** until .

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxapram Injection BP 20mg/ml
Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of sterile solution for injection contains 20 mg doxapram hydrochloride
Each 5 ml of sterile solution for injection contains 100 mg doxapram hydrochloride.
For excipients see 6.1

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Doxapram acts as a ventilatory stimulant and Doxapram Injection BP 20 mg/ml is used following anaesthesia to stimulate ventilation in the post-operative period as an aid to the reduction of post-operative pulmonary complications, and to permit the use of effective doses of narcotic analgesics without associated problems of ventilatory depression. Doxapram Injection BP 20 mg/ml is also used to increase CNS arousal and spontaneous activity from inhalational anaesthesia when this would be beneficial.

4.2 Posology and method of administration

Route of administration:

Intravenous administration only.

Adults and older patients:

The recommended dosage is 1.0 to 1.5 mg/kg body weight, administered over a period of 30 seconds or more, which may be repeated at one-hour intervals, if necessary.

Children:

Not recommended.

4.3 Contraindications

Known hypersensitivity to doxapram or to any of the excipients
 Severe hypertension
 Status asthmaticus
 Coronary artery disease
 Epilepsy or other convulsive disorders
 Cerebral oedema
 Cerebrovascular accident
 Hyperthyroidism
 Physical obstruction of respiratory tract, or conditions resulting in restriction of chest wall, muscles of respiration or alveolar expansion.

4.4 Special warnings and precautions for use

Doxapram should be administered concurrently with oxygen to patients with severe irreversible airways obstruction or severely decreased lung compliance, due to the increased work of breathing in these patients.

In patients presenting with bronchoconstriction, doxapram should always be used in conjunction with beta-adrenoreceptor bronchodilator drugs in order to reduce the amount of respiratory effort.

As doxapram is metabolised primarily by the liver, use with care in patients with hepatic dysfunction.

Doxapram should be administered cautiously to patients receiving sympathomimetic agents since an additive pressor effect may occur.

Doxapram should be used with great care in patients who are being treated concurrently with monoamine oxidase inhibiting drugs. Animal studies have shown that the action of doxapram is potentiated after treatment with a Monoamine Oxidase Inhibitor (MAOI).

In patients who have received anaesthetics known to sensitise the myocardium to catecholamines, such as halothane, cyclopropane, and enflurane, initiation of doxapram therapy should be delayed for at least 10 minutes following discontinuance of anaesthesia, since an increase in adrenaline release has been noted with doxapram administration.

The respiratory stimulant effect of doxapram may not outlast the residual effects of the depressant drugs. Since respiratory depression may recur after stimulation with doxapram, the patient should be closely monitored until fully alert for one half to one hour. Doxapram may temporarily mask the residual effects of curare-type muscle relaxant drugs.

Doxapram should be administered with caution in patients with hypermetabolic state such as phaeochromocytoma.

The administration of doxapram does not diminish the need for continuous monitoring of all aspects of patient response, including frequent analysis of arterial-blood gases.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical data suggest that concurrent use of aminophylline and doxapram may be associated with agitation, muscle fasciculation and hyperactivity. Care should be taken when these two drugs are used concomitantly.

Doxapram should also be administered with great care to patients being treated concurrently with monoamine oxidase-inhibitors (MAOIs). Animal studies have shown that the action of doxapram may be potentiated after pretreatment with an MAOI.

Doxapram may potentiate the effects of sympathomimetic agents.

4.6 Pregnancy and lactation

Animal studies are insufficient with respect to effects on pregnancy and embryonal/foetal development. The potential risk for humans is unknown. Doxapram Injection BP 20 mg/ml should not be used during pregnancy unless clearly necessary

It is not known whether this drug is excreted in human milk. Therefore, caution should be exercised when prescribing doxapram to a lactating mother.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Doxapram may produce adverse effects due to general stimulation of the central, peripheral, and autonomic nervous systems. Pyrexia, sweating, flushing, headache, dizziness, hyperactivity, confusion, hallucinations, perineal warmth, muscle fasciculation, and convulsions have been reported.

Respiratory problems such as dyspnoea, cough, bronchospasm, and laryngospasm may occur.

Cardiovascular effects have been observed and include a moderate increase in blood pressure, arrhythmias, sinus tachycardia, bradycardia and extrasystoles, chest pain, or chest tightness.

Effects on the gastrointestinal tract such as nausea and vomiting may also occur.

4.9 Overdose

Overdosage may result in hypertension, tachycardia and other arrhythmias, skeletal muscle hyperactivity including enhanced deep tendon reflexes, and dyspnoea. Serious symptoms of overdosage may include chronic and generalised seizures. Intravenous diazepam, phenytoin, and short acting barbiturates, oxygen and resuscitative equipment should be readily available to manage overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The principle pharmacological action of doxapram is an increase in minute volume produced primarily by an increase in tidal volume and to a lesser extent by changes in respiratory rate. Neuropharmacological studies have shown that the primary sites of action of doxapram are the peripheral carotid chemoreceptors. It is considered that this site of action of doxapram is responsible for its relative specificity of action; it is only following large doses of doxapram hydrochloride that non-specific central nervous system stimulation occurs.

5.2 Pharmacokinetic properties

Following an IV bolus injection of 1.5 mg/kg doxapram, the plasma concentration of doxapram declined in a multiexponential manner. The mean half-life from 4 to 12 hours was 3.4 hours (range 2.4 to 4.1 hours). The mean apparent volume of distribution was 1.5 l/kg and the whole body clearance was 370 ml/min. Renal clearance was not related to urine flow or pH, but increased progressively with time over the first 12 hours. The mean 0 -24 hour renal clearance values for individual volunteers ranged from 1.1 to 14.1 ml/min. The rate of decline of plasma concentration appeared to decrease after 12 hours. Doxapram was extensively metabolised, and less than 5% of an IV dose was excreted unchanged in the urine in 24 hours.

5.3 Preclinical safety data

Reproduction studies have been performed in rats at doses of up to 1.6 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus associated with the use of the doxapram. Acute toxicity studies in several animal species suggest impairment of the central nervous system at high doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

Doxapram is incompatible with alkaline solutions such as aminophylline, furosemide and thiopentone sodium.

Do not mix with any other solutions for infusion/injections

6.3 Shelf Life

Unopened: 3 years.

The product should be used immediately after opening.

6.4 Special precautions for storage

Do not store above 25°C.

Do not refrigerate or freeze.

6.5 Nature and contents of container

Clear glass ampoules type I, 5 ml.

Pack size: 10 x 5 ml ampoules

6.6 Special precautions for disposal

For single use only.

Discard any unused contents.

Do not mix and/or co-administer with other solutions for injection or infusion.

7 MARKETING AUTHORISATION HOLDER

Taro Pharmaceuticals Ireland Limited,
Lourdes Rd.,
Roscrea,
County Tipperary.
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1140/5/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22nd December 2005

10 DATE OF REVISION OF THE TEXT

March 2007