

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxapram Hydrochloride 20mg/ml Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxapram Hydrochloride 20 mg/ml.

Each 5ml ampoule contains 100mg Doxapram Hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Doxapram acts as a ventilatory stimulant and Doxapram Hydrochloride 20mg/ml Solution for Injection 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 Hydrochloride 20mg/ml Solution for Injection is also used to increase CNS arousal and spontaneous respiratory activity from inhalational anaesthesia when this would be beneficial.

4.2 Posology and method of administration

Doxapram Hydrochloride 20mg/ml Solution for Injection is recommended for intravenous use only.

There are no studies to support dosage recommendations in patients with renal or hepatic impairment. However, as Doxapram is metabolized primarily by liver it should be used with care in patients with hepatic dysfunction (see section 4.4).

Adults and older patients:

The recommended dosage is 1.0 to 1.5mg/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

1. Hypersensitivity to any of the ingredients in the product.
2. Severe hypertension.
3. Status asthmaticus.
4. Coronary artery disease.
5. Epilepsy and other convulsive disorders
6. Cerebral oedema
7. Cerebrovascular accident
8. Hyperthyroidism/Thyrotoxicosis
9. Physical obstruction of the respiratory tract, or conditions resulting in restriction of chest wall, muscles of respiration or alveolar expansion.

10. Head injury
11. Proven/suspected pulmonary embolism

4.4 Special warnings and precautions for use

1. Doxapram Hydrochloride 20mg/ml Solution for Injection 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.
2. In patients presenting with bronchoconstriction, Doxapram Hydrochloride 20mg/ml Solution for Injection should always be used in conjunction with β -adrenoceptor bronchodilator drugs in order to reduce the amount of respiratory effort.
3. As Doxapram Hydrochloride 20mg/ml Solution for Injection is metabolised primarily by the liver, use with care in patients with hepatic dysfunction.
4. Doxapram Hydrochloride 20mg/ml Solution for Injection should be administered cautiously to patients receiving sympathomimetic agents since an additive pressor effect may occur.
5. Doxapram Hydrochloride 20mg/ml Solution for Injection 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 pre-treatment with an MAOI.
6. In patients who have received anaesthetics known to sensitize the myocardium to catecholamines, such as halothane, cyclopropane, and enflurane, initiation of Doxapram Hydrochloride 20mg/ml Solution for Injection therapy should be delayed for at least 10 minutes following discontinuance of anaesthesia, since an increase in adrenaline release has been noted with Doxapram Hydrochloride 20mg/ml Solution for Injection administration.
7. The respiratory stimulant effect of Doxapram Hydrochloride 20mg/ml Solution for Injection may not outlast the residual effects of the depressant drugs. Since respiratory depression may recur after stimulation with Doxapram Hydrochloride 20mg/ml Solution for Injection, the patient should be closely monitored until fully alert for $\frac{1}{2}$ to 1 hour. Doxapram Hydrochloride 20mg/ml Solution for Injection may temporarily mask the residual effects of curare-type muscle relaxant drugs.
8. Doxapram Hydrochloride 20mg/ml Solution for Injection should be administered with caution in patients with hypermetabolic states such as pheochromocytoma.
9. If sudden hypertension or dyspnoea develops, Doxapram should be stopped.
10. Monitoring of the blood pressure and deep tendon reflexes is recommended to prevent overdosage.
11. To avoid side effects, it is advisable to use the minimum effective dosage.
12. Doxapram should not be used in conjunction with mechanical ventilation.
12. An adequate airway is essential and airway protection should be considered since Doxapram may stimulate vomiting.
14. Doxapram should be used with caution in hypertension (it is contraindicated in severe hypertension), and in patients with impaired cardiac reserve.
15. The administration of this agent 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/theophylline and Doxapram Hydrochloride 20mg/ml Solution for Injection may be associated with increased CNS stimulation, agitation, muscle fasciculation and hyperactivity. Care should thus be taken when these two drugs are used concomitantly.

Doxapram Hydrochloride 20mg/ml Solution for Injection 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 Hydrochloride 20mg/ml Solution for Injection may be potentiated after pretreatment with a MAOI (see section 4.4).

In patients who have received anaesthetics known to sensitize the myocardium to catecholamines, initiation of Doxapram Hydrochloride 20mg/ml Solution for Injection therapy should be delayed for at least 10 minutes following discontinuance of anaesthesia (see section 4.4).

Doxapram Hydrochloride 20mg/ml Solution for Injection may potentiate the effects of sympathomimetic agents (see section 4.4).

Doxapram Hydrochloride 20mg/ml Solution for Injection may temporarily mask the residual effects of curare-type muscle relaxant drugs (see section 4.4).

4.6 Fertility, pregnancy and lactation

Although there is no recognised hazard, this product is not recommended for use in pregnancy unless there are compelling clinical reasons to do so. The physician must weigh the benefit to the risk.

It is not known whether this drug is excreted in human milk. Therefore, caution should be exercised when Doxapram Hydrochloride 20mg/ml Solution for Injection is administered to a lactating mother.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Nervous system disorders:

Doxapram Hydrochloride 20mg/ml Solution for Injection may produce adverse effects due to general stimulation of the central, peripheral and autonomic nervous systems: Pyrexia, sweating, flushing, salivation, headache, dizziness, hyperactivity, confusion, hallucinations, perineal warmth, muscle fasciculation and convulsions, muscle spasticity, clonus, bilateral babinski, increased deep tendon reflexes have been reported.

Doxapram can induce a significant decrease in maximal cerebral blood flow velocity.

Cardiac disorders:

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

Respiratory, thoracic and mediastinal disorders:

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

Gastrointestinal Disorders:

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

Renal and Urinary disorders:

Genitourinary: Urinary retention, stimulation of urinary bladder with spontaneous voiding.

Paediatric Population:

Doxapram is not recommended in children (see section 4.2). The following adverse reactions have been reported in off-license use of doxapram in preterm neonates and infants:

- neurodevelopmental delay
- significant prolongation of QT interval, in some cases associated with atrioventricular block.
- blood in stools, abdominal distension and necrotizing enterocolitis and multiple gastric perforations
- early teeth eruption involving lower central incisors

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Respiratory stimulants

ATC code: R07AB01

The principal pharmacological action of Doxapram Hydrochloride 20mg/ml Solution for Injection 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 Hydrochloride 20mg/ml Solution for Injection are the peripheral carotid chemoreceptors. It is considered that this site of action of Doxapram Hydrochloride 20mg/ml Solution for Injection is responsible for its relative specificity of action; it is only following large doses of doxapram hydrochloride that non-specific central nervous stimulation occurs.

5.2 Pharmacokinetic properties

Following an I.V. bolus injection of 1.5mg/kg doxapram, the plasma concentration of doxapram declined in a multi-exponential manner. The mean half-life from 4 – 12 hours was 3.4 hours (range 2.4 – 4.1 hours). The mean apparent volume of distribution was 1.5 litres/kg and the whole body clearance was 370ml/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 14.1ml/min. The rate of decline of plasma concentration appeared to decrease after 12 hours. Doxapram was extensively metabolised, and less than 5% of an I.V. 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 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 injection.

6.2 Incompatibilities

Doxapram Hydrochloride 20mg/ml Solution for Injection is incompatible with alkaline solutions such as aminophylline, furosemide and thiopental sodium.

6.3 Shelf Life

4 years.

The product should be used immediately after opening. Any unused portion must be discarded.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate.

6.5 Nature and contents of container

Primary container: Clear type I glass ampoules.

Secondary container: Cardboard carton.

Presentation: Each ampoule contains 5ml.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any remaining contents after use.

7 MARKETING AUTHORISATION HOLDER

Anpharm Limited
Roscrea
Co Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 857/3/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1980

Date of last renewal: 01 April 2010

10 DATE OF REVISION OF THE TEXT

November 2010