

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Doxapram Hydrochloride 20mg/ml Solution for Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains 20mg Doxapram Hydrochloride.

Each 5ml ampoule contains 100mg Doxapram Hydrochloride.

For the 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

#### Posology

#### Adults and Elderly:

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.

#### Hepatic impairment:

There are no studies to support dosage recommendations in patients with 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).

#### Renal impairment:

There are no studies to support dosage recommendations in patients with renal impairment.

#### Paediatric population:

Not recommended

#### Method of administration

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

### 4.3 Contraindications

1. Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
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 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 ½ 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.

13. 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

##### Pregnancy

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.

##### Breast-feeding

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.

##### Fertility

No data available.

#### 4.7 Effects on ability to drive and use machines

Doxapram hydrochloride 20mg/ml Solution for Injection has no or negligible influence on the ability to drive and use machines.

#### 4.8 Undesirable effects

Adverse reactions listed by System Organ Class. The following adverse reactions have been observed at the frequencies defined using the following convention:

**Not known:** cannot be estimated from the available data.

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	Not known	*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.
Cardiac disorders	Not known	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	Not known	Respiratory problems such as dyspnoea, cough, bronchospasm and laryngospasm may occur
Gastrointestinal disorders	Not known	Effects on the gastrointestinal tract such as nausea and vomiting may also occur.
Renal and urinary disorders	Not known	Urinary retention, stimulation of urinary bladder with spontaneous voiding.

\*Doxapram Hydrochloride 20mg/ml Solution for Injection may produce adverse effects due to general stimulation of the central, peripheral and autonomic nervous systems:

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

#### 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:

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

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: HPRC Pharmacovigilance Website: [www.hpra.ie](http://www.hpra.ie).

### **4.9 Overdose**

#### Symptoms

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.

#### Management

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

#### Mechanism of action

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.

#### Pharmacodynamic effects

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**

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

No special requirements for disposal.

## **7 MARKETING AUTHORISATION HOLDER**

MercuryPharm Ltd  
4045 Kingswood Road  
City West Business Park  
Co. Dublin  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA0857/003/002

## **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**

