

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxapram Hydrochloride 2mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxapram Hydrochloride 2mg/ml Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxapram Hydrochloride 2 mg/ml.

Each 500ml bag contains 1000mg Doxapram Hydrochloride.

Each ml of solution contains 2mg doxapram hydrochloride.

Excipient(s) with known effect

Each ml contains 50mg glucose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Infusion.

Clear, colourless, sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Doxapram Hydrochloride 2mg/ml Solution for Infusion acts as a ventilatory stimulant and is used in the following situations:

Acute respiratory failure:

1. To stimulate ventilation in patients whose blood gas status or clinical condition suggests that severe carbon dioxide retention would occur during controlled oxygen therapy.
2. To stimulate ventilation in patients showing a progressive increase in PCO₂ with mental status changes during or after controlled oxygen therapy.

Following anaesthesia:

1. To stimulate ventilation in the post-operative period as an aid to the reduction of post-operative pulmonary complications.
2. To permit use of effective doses of narcotic analgesics without associated problems of ventilatory depression.

4.2 Posology and method of administration

Posology

Adults and Elderly:

For the treatment of respiratory failure recommended dosage is 1.5 to 4mg per minute depending on the condition and response of the patient. Administer concurrently with oxygen. Whenever possible the condition of the patient should be monitored by frequent measurement of blood gas tensions.

The following dosage regimen has been shown to result in the rapid production of a steady state plasma concentration of doxapram:

0 – 15 mins 4.0 mg/min

15 – 30 mins 3.0 mg/min

30 – 60 mins 2.0 mg/min

60 mins onwards 1.5 mg/min

Following anaesthesia recommended dosage is 2–3 mg per minute, and appropriate adjustments to the administration rate should be made according to the response of the patient.

A maximum dosage of 4mg/min should not be exceeded.

Paediatric population

Not recommended.

Method of administration

Doxapram Hydrochloride 2mg/ml Solution for Infusion 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 2mg/ml Solution for Infusion 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 2mg/ml Solution for Infusion should always be used in conjunction with β_2 -adrenoceptor bronchodilator drugs in order to reduce the amount of respiratory effort.
3. As Doxapram Hydrochloride 2mg/ml Solution for Infusion is metabolised primarily by the liver, use with care in patients with hepatic dysfunction.
4. Doxapram Hydrochloride 2mg/ml Solution for Infusion should be administered cautiously to patients receiving sympathomimetic agents since an additive pressor effect may occur.
5. Doxapram Hydrochloride 2mg/ml Solution for Infusion 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 2mg/ml Solution for Infusion 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 2mg/ml Solution for Infusion administration.
7. The respiratory stimulant effect of Doxapram Hydrochloride 2mg/ml Solution for Infusion may not outlast the residual effects of the depressant drugs.
Since respiratory depression may recur after stimulation with Doxapram Hydrochloride 2mg/ml Solution for Infusion, the patient should be closely monitored until fully alert for ½ to 1 hour. Doxapram Hydrochloride 2mg/ml Solution for Infusion may temporarily mask the residual effects of curare-type muscle relaxant drugs.
8. To reduce the likelihood of local damage to a vein from 5% glucose solution, the site of administration Doxapram Hydrochloride 2mg/ml Solution for Infusion of may need to be changed periodically during prolonged therapy.

9. Doxapram Hydrochloride 2mg/ml Solution for Infusion should be administered with caution in patients with hypermetabolic states such as pheochromocytoma.
10. 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.
11. If sudden and severe hypotension or dyspnoea develops, Doxapram should be stopped.
12. Monitoring of the blood pressure and deep tendon reflexes is recommended to prevent overdosage.
13. To avoid side effects, it is advisable to use the minimum effective dosage.
14. Doxapram should not be used in conjunction with mechanical ventilation.
15. An adequate airway is essential and airway protection should be considered since Doxapram may stimulate vomiting.
16. There are a few isolated reports mentioning possible association of the prolonged use of Doxapram with delay in mental development in preterm infants.
17. Caution should be exercised when doxapram is used in patients with hypertension and is contra-indicated in cases of severe hypertension. (see section 4.3) and in patients with impaired cardiac reserve.
18. Contains 50mg glucose per ml. This should be taken into account in patients with diabetes mellitus when doses more than 100ml are administered.

4.5 Interaction with other medicinal products and other forms of interactions

Clinical data suggest that concurrent use of aminophylline/theophylline and Doxapram Hydrochloride 2mg/ml Solution for Infusion 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 2mg/ml Solution for Infusion 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 2mg/ml Solution for Infusion may be potentiated after pre-treatment with a MAOI. (see section 4.4)

Doxapram Hydrochloride 2mg/ml Solution for Infusion may potentiate the effects of sympathomimetic agents. (See section 4.4)

Doxapram 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 2mg/ml Solution for Infusion is administered to a lactating mother.

Fertility

There is currently no available data.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Adverse reactions are listed as per 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.

MedDRA System organ Class	Frequency	Undesirable Effects
Nervous system disorders:	Not known	Pyrexia ¹ Sweating ¹ Flushing ¹ Salivation ¹ Headache ¹ Dizziness ¹ Hyperactivity ¹ Confusion ¹ Hallucinations ¹ Perineal warmth ¹ Muscle fasciculation ¹ Convulsions ¹ Muscle spasticity Clonus Bilateral babinski Increased deep tendon reflexes
Cardiac disorders:	Not known	Increase in blood pressure (moderate) Arrhythmias Sinus tachycardia, Bradycardia and Extrasystoles, Chest pain or chest tightness.
Respiratory, thoracic and mediastinal disorders:	Not known	Dyspnoea, Cough Bronchospasm Laryngospasm.
Gastrointestinal Disorders:	Not known	Nausea Vomiting
Renal and Urinary disorders:	Not known	Urinary retention Stimulation of urinary bladder with spontaneous voiding.

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

¹Dopram may produce adverse effects due to general stimulation of the central, peripheral and autonomic nervous systems

Paediatric Population

Doxapram is not recommended in children (see section 4.2). The following adverse reactions have been reported in off-licence 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 bloody 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 HPR A Pharmacovigilance, Website: 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 2mg/ml Solution for Infusion 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 2mg/ml Solution for Infusion are the peripheral carotid chemoreceptors. It is considered that this site of action of Doxapram Hydrochloride 2mg/ml Solution for Infusion 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

Glucose intravenous infusion. (containing glucose and water for injections).

6.2 Incompatibilities

Doxapram Hydrochloride 2mg/ml Solution for Infusion is incompatible with alkaline solutions such as aminophylline, furosemide and thiopental sodium.

6.3 Shelf life

2 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. Keep the bag in its outer pouch until ready to use.

6.5 Nature and contents of container

Primary container: Viaflex (polyvinylchloride) bag in overpouch (High density polyethylene or polypropylene.)

Secondary container: Cardboard carton.

Presentation: Each viaflex bag contains 500 ml.

6.6 Special precautions for disposal and other handling

The VIAFLEX Plus container has an outlet port designed for an administration set with a short single connector. If an administration set with a combined air inlet/fluid path connector has to be used, ensure the air inlet tube is always clamped off.

Remove the protective overpouch by tearing down from notch and remove container.
Carefully straighten hanger and ports, if necessary.

Squeeze container and inspect for minute leaks and examine solution for visible particles or cloudiness by viewing along seam.
Discard unit if leaks, particles or cloudiness are evident.
Suspend container from base eyelet support.

Using aseptic technique prepare administration set.

Remove blue protector from outlet port and inset set connector well into port.

Prime set and regulate administration as required. If administration set becomes blocked do not pump contents back into container but replace equipment.

Discard all containers and equipment after use. Do not store partly used containers.

Cautions

Do not vent.

Do not administer unless the solution is clear and container undamaged.

Do not use in series connections as this could result in air embolism due to residual air being drawn from the primary container before administration of fluid from the secondary container is completed.

Discontinue infusion if adverse reaction occurs.

It is recommended that the intravenous administration set be replaced at least once every 24 hours.

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

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0857/003/001

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Page 6 of 7

