

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dopram Infusion

Doxapram Hydrochloride 2mg/ml Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dopram Infusion contains 2 mg Doxapram Hydrochloride BP per ml, in 5% Glucose intravenous infusion BP.

3. PHARMACEUTICAL FORM

Sterile solution for intravenous infusion

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Doxapram acts as a ventilatory stimulant and is specifically indicated 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

Dopram infusion is recommended for intravenous use only.

Adults and Older patients

For the treatment of respiratory failure recommended dosage is 1.5 to 4 mg 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.

Children: Dopram is not recommended for use in children due to insufficient data on safety and efficacy.

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. Dopram 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, Dopram should always be used in conjunction with β -adrenoceptor bronchodilator drugs in order to reduce the amount of respiratory effort.
3. As Dopram is metabolised primarily by the liver, use with care in patients with hepatic dysfunction.
4. Dopram should be administered cautiously to patients receiving sympathomimetic agents since an additive pressor effect may occur.
5. Dopram 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 Dopram therapy should be delayed for at least 10 minutes following discontinuance of anaesthesia, since an increase in adrenaline release has been noted with Dopram administration.
7. The respiratory stimulant effect of Dopram may not outlast the residual effects of the depressant drugs. Since respiratory depression may recur after stimulation with Dopram, the patient should be closely monitored until fully alert for ½ to 1 hour. Dopram 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 of Dopram may need to be changed periodically during prolonged therapy.
9. Dopram should be administered with caution in patients with hypermetabolic states such as phaeochromocytoma.
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 hypertension or dyspnoea develops, Doxapram should be stopped.
12. Monitoring of the blood pressure and deep tendon reflexes is recommended to prevent overdose.
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 few reports mentioning possible association of the prolonged use of Doxapram with delay in mental development in preterm infants.
17. Dopram should be used with caution in hypertensive patients (Dopram is contraindicated in severe hypertension, see section 4.3) and in patients with impaired cardiac reserve.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical data suggest that concurrent use of aminophylline/theophylline and Dopram may be associated with increased CNS stimulation, agitation, muscle fasciculation and hyperactivity. Care should thus be taken when these two drugs are used concomitantly.

Dopram 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 Dopram may be potentiated after pre-treatment with a MAOI (see section 4.4)

Dopram 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. 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 Dopram 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:

Dopram 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 have been reported.

Muscle spasticity, clonus, bilateral babinski, increased deep tendon reflexes are sometimes 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:

Dopram 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:

- neurodevelopmental delay
- significant prolongation of QT interval, in some cases associated with atrio-ventricular block.
- bleeding 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 dyspnoea. 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 Dopram 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 Dopram are the peripheral carotid chemoreceptors. It is considered that this site of action of Dopram 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 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. Pre-clinical 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 (BP)

6.2. Incompatibilities

Dopram is incompatible with alkaline solutions such as aminophylline, frusemide and thiopentone sodium

6.3. Shelf-Life

2 years

6.4. Special Precautions for Storage

Store below 25°C

6.5. Nature and Content of Container

Primary container: Viaflex bag in overpouch

Secondary container: Cardboard carton

Presentation: each Viaflex bag contains 500 ml.

6.6. Instructions for Use, Handling and Disposal

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.

1. Remove the protective overpouch by tearing down from notch and remove container.
2. Carefully straighten hanger and ports if necessary
3. 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.
4. Suspend container from base eyelet support.
 5. Using aseptic technique prepare administration set.
 6. Remove blue protector from outlet port and insert set connector well into port.
 7. Prime set and regulate administration as required. If administration set becomes blocked do not pump contents back into container but replace equipment.
 8. Discard all containers and equipment after use. Do not store partly used containers.

Cautions:

1. Do not vent.
2. Do not administer unless the solution is clear and container is undamaged.
3. 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.
4. Discontinue infusion if adverse reaction occurs.
5. It is recommended that the intravenous administration set be replaced at least once every 24 hours.

7. MARKETING AUTHORISATION HOLDER

Anpharm Ltd.,
River Lane,
Roscrea,
Co. Tipperary,
Ireland.

8. MARKETING AUTHORISATION NUMBER(S)

PL 15372/0002

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

01 October 1997

10. DATE OF REVISION OF THE TEXT

14/11/2011