

## **1 NAME OF THE MEDICINAL PRODUCT**

Dopram Injection

Doxapram Hydrochloride 20mg/ml Solution for Injection

## **2. Qualitative and Quantitative Composition**

Dopram Injection contains 20mg Doxapram Hydrochloride BP per ml.

## **3. Pharmaceutical Form**

Sterile solution for intravenous injection.

## **Clinical Particulars**

### **4.1 Therapeutic Indications**

Doxapram acts as a ventilatory stimulant and Dopram 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. Dopram 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**

Dopram Injection is recommended for intravenous use only.

#### 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. 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  $\beta$ -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 a 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  $\frac{1}{2}$  to 1 hour. Dopram may temporarily mask the residual effects of curare-type muscle relaxant drugs.
8. Dopram should be administered with caution in patients with hypermetabolic states such as phaeochromocytoma.
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 overdose.
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. 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

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 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 pretreatment 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, muscle spasticity, clonus, bilateral babinski, increased deep tendon reflexes and convulsions 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:**

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 atrioventricular 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.

**Pharmacological Properties**

**5.1. Pharmacodynamic Properties**

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. Preclinical Safety Data**

Reproduction studies have been performed in rats at doses 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.

## **Pharmaceutical Particulars**

### **6.1. List of Excipients**

Water for Injections

### **6.2. Incompatibilities**

Dopram is incompatible with alkaline solutions such as aminophylline, furosemide and thiopental sodium.

### **6.3. Shelf Life**

4 years.

### **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 one point-cut (OPC) glass ampoules

Secondary container: Cardboard carton

Presentation: Each ampoule contains 5ml

**6.6. Special precautions for disposal**

Not applicable

**Administrative Data**

**7. Marketing Authorisation Holder**

Anpharm Limited

Roscrea

Co. Tipperary

Ireland

**8. Marketing Authorisation Number(s)**

PL 15372/0001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

20/03/2006

**10 DATE OF REVISION OF THE TEXT**

July 2010