SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxapram hydrochloride 20 mg/ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 20 mg doxapram hydrochloride.
Each 5 ml ampoule contains 100 mg doxapram hydrochloride.

3 PHARMACEUTICAL FORM

Sterile solution for intravenous injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Doxapram acts as a ventilatory stimulant and Doxapram hydrochloride 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 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.

Paediatric population
Not recommended

Hepatic impairment
There are no studies to support dosage recommendations in patients with hepatic impairment. However, as Doxapram hydrochloride 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.

Method of administration
Doxapram hydrochloride is recommended for intravenous use only.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Severe hypertension
- Status asthmaticus
- Coronary artery disease
- Epilepsy and other convulsive disorders
- Cerebral oedema
- Cerebrovascular accident
- Hyperthyroidism /Thyrotoxicosis
- Physical obstruction of the respiratory tract, or conditions resulting in restriction of chest wall, muscles of respiration or alveolar expansion.
- Head injury
- Proven/suspected pulmonary embolism

4.4 Special warnings and precautions for use

- Doxapram hydrochloride 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.
- In patients presenting with bronchoconstriction, Doxapram hydrochloride should always be used in conjunction with β-adrenoceptor bronchodilator drugs in order to reduce the amount of respiratory effort.
- As Doxapram hydrochloride is metabolised primarily by the liver, use with care in patients with hepatic dysfunction.
- Doxapram hydrochloride should be administered cautiously to patients receiving sympathomimetic agents since an additive pressor effect may occur.
- Doxapram hydrochloride 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.
- In patients who have received anaesthetics known to sensitize the myocardium to catecholamines, such as halothane, cyclopropane, and enflurane, initiation of doxapram hydrochloride 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 administration.
- The respiratory stimulant effect of Doxapram hydrochloride may not outlast the residual effects of the depressant drugs. Since respiratory depression may recur after stimulation with Doxapram hydrochloride, the patient should be closely monitored until fully alert for ½ to 1 hour. Doxapram hydrochloride may temporarily mask the residual effects of curare-type muscle relaxant drugs.

- Doxapram hydrochloride should be administered with caution in patients with hypermetabolic states such as phaeochromocytoma.
- If sudden hypertension or dyspnoea develops, Doxapram hydrochloride should be stopped.
- Monitoring of the blood pressure and deep tendon reflexes is recommended to prevent overdosage.
- To avoid side effects, it is advisable to use the minimum effective dosage.
- Doxapram should not be used in conjunction with mechanical ventilation.
- An adequate airway is essential and airway protection should be considered since doxapram may stimulate vomiting.
- Doxapram should be used with caution in hypertensive patients (Doxapram hydrochloride is contraindicated in severe hypertension, see section 4.3) and in patients with impaired cardiac reserve
- 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 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 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 may be potentiated after pre-treatment with a MAOI (see section 4.4)

Doxapram hydrochloride 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.

Breastfeeding

It is not known whether this drug is excreted in human milk. Therefore, caution should be exercised when Doxapram hydrochloride is administered to a lactating mother.

Fertility

There are no human data available on fertility.

4.7 Effects on ability to drive and use machines

Doxapram hydrochloride 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.

Nervous system disorders:

Doxapram hydrochloride 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:

Urinary retention, stimulation of urinary bladder with spontaneous voiding.

Paediatric population

Doxapram hydrochloride 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

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 the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

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.

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 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 are the peripheral carotid chemoreceptors. It is considered that this site of action of Doxapram hydrochloride 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 1.5 mg/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 370 ml/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 14.1 ml/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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

6.2 Incompatibilities

Doxapram hydrochloride is incompatible with alkaline solutions such as aminophylline, frusemide and thiopentone sodium.

6.3 Shelf life

36 months

The product should be used immediately after opening.

6.4 Special precautions for storage

Do not refrigerate.
For single use only.
Discard any unused contents.
Do not mix and/or co-administer with other solutions for injection or infusion.

6.5 Nature and contents of container

Colourless type I glass ampoule of 5 ml.

Carton box with 5 ampoules.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Synchrony Pharma Limited
3 Bunhill Row
London
EC1Y 8YZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 39280/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/11/2020

10 DATE OF REVISION OF THE TEXT

04/08/2023