

CARINOPHARM

Dopram®

1. Name of the drug

Dopram®,
20 mg / ml, solution for injection

Active ingredient:

Doxapram hydrochloride 1H₂O

2. Qualitative and quantitative composition

1 ampoule with 5 ml contains 100 mg doxapram hydrochloride 1 hour:O. (Auxiliary materials see under 6.1)

3. Dosage form

Solution for injection

4. Clinical information

4.1 Areas of application

Dopram® is applied:

- for mild central nervous system depression caused by medication to stimulate breathing,
- for the short-term treatment of chronic lung diseases with acute hypercapnia,
- in the case of apnea or depression of breathing after anesthesia to stimulate deeper breathing in the wake-up phase, if airway obstruction and / or hypoxia and muscle relaxant overhang are excluded,

- in the case of central apneas as a result of immaturity of the respiratory center in new and premature babies.

4.2 Dosage,

Type and duration of application

Dopram® can be combined with 5% and 10% glucose solution or physiological saline solution. A mixture of dopram® however, with alkaline solutions (e.g. 2.5% thiopental sodium, aminophylline, bicarbonate) it leads to precipitation.

For the treatment of a drug-induced depression of the central nervous system according to table 1 (method 1 or 2)

See table 1

Method 1: Intravenous injection of a single dose and / or repeated single doses

- a) Injection of an initial dose of 2.0 mg / kg body weight and repetition in 5 min.
- b) Repeat the same dose every 1 - 2 hours until the patient is breathing sufficiently spontaneously. It is important to watch out for falling back into respiratory depression, as doxapram does not affect the metabolism of the drugs that lead to respiratory depression.
- c) In the event of a relapse, the injections must be resumed every 1 to 2 hours until sufficient spontaneous breathing can be restored or a total daily dose of 3 g has been administered. If necessary, assisted ventilation can be provided.
- d) Repeat the specified treatment until the patient breathes spontaneously or until the maximum daily dose of 3 g has been administered.

Table 1

Degree of depression	<i>Method 1</i> Initial dose + repeated i. v. - injection [mg / kg]	<i>Method 2</i> speed intermittent IV infusion [mg / kg / h]
easy ¹⁾	1.0	1.0-2.0
moderate ²⁾	2.0	2.0-3.0

1) mild depression

Class 0: in the sleep state, but waking up possible, questions can be answered Class 1: comatose, defensive movement to painful stimuli, reflexes preserved

2) moderate depression

Class 2: comatose, no defensive movement to painful stimuli, reflexes preserved Class

3: comatose, reflexes cannot be triggered, no circulatory or respiratory depression

Table 2: Intravenous use

	recommended dose [mg / kg]	Maximum dose for single injection [mg / kg]	Maximum dose all in all [mg / kg]
Single injection	0.5 - 1.0	1.5	1.5
repeated injection, 5 min interval	0.5 - 1.0	1.5	2.0
infusion	0.5 - 1.0	-	4.0

e) Repeated doses should only be administered to patients who have responded to the loading dose.

f) If there is no corresponding positive reaction, this is an indication of a necessary neurological examination as to whether the cause of the respiratory depression can lie in the CNS.

Method 2: Intermittent intravenous infusion

- a) Injection of a loading dose as in method 1.
- b) If the patient breathes spontaneously enough, watch out for relapse. If there is no response, general supportive care should be continued for 1-2 hours and the doxapram injection repeated. If breathing is stimulated, an intravenous infusion must be prepared by adding 250 mg (12.5 ml) doxapram hydrochloride 1 hour to 250 ml of physiological saline or glucose solution. The speed should be set to 1 - 3 mg / min (60 - 80 ml / h) depending on the patient's weight and the degree of respiratory depression. Dopram® must be discontinued as soon as the patient is spontaneously breathing sufficiently or after 2 hours.
- c) Supportive treatment should be continued for ½-2 hours and step b) should be repeated.
- d) The maximum daily dose of 3 g doxapram hydrochloride 1 hour:O must not be exceeded.

Use after anesthesia intravenous injection according to table 2

Close monitoring of cardiovascular and respiratory parameters is essential during treatment with dopram® and required until sufficient spontaneous breathing occurs.

Intravenous infusion:

To prepare the solution, 250 mg (12.5 ml) of doxapram are added to 250 ml of glucose or

given physiological saline solution. The infusion is initiated at approximately 5 mg / min until satisfactory breathing is observed. Then it is set to 1 - 3 mg / min. The rate of infusion should be set so that the desired stimulation of breathing is maintained with a minimum of side effects. The recommended total dose per infusion is 4 mg / kg. 300 mg should not be exceeded per treatment situation.

Chronic obstructive pulmonary disease with acute hypercapnia

- a) 400 mg doxapram hydrochloride (20 ml) are mixed with 180 ml of the infusion solution (concentration 2.0 mg / ml). The infusion should be initiated at 1 - 2 mg / min (0.5 - 1 ml / min). If necessary, it can be increased to a maximum of 3 mg / min. Before using dopram® the arterial blood gas values should be determined. To oppose the creeping development of a CO₂- To ensure retention and acidosis, the determination should be repeated at least every ½ hour during the 2-hour infusion. A change in the oxygen concentration or a change in the drip rate may cause the dopram infusion rate to be readjusted® make necessary.
- b) If the blood gas levels show signs of deterioration, the dopram should® -Infusion should be discontinued.
- c) Additional infusions that exceed the individual maximum amount within 2 hours are not recommended.

Dopram for newborn and premature infant apnea® can be used as an alternative or supplement to xanthine derivative treatment for newborn and premature infant apnea.

Various dosage regimens have been tested and have been found to be effective. A bolus injection of 2 - 2.5 mg /

kg body weight intravenously over 15 - 30 min is a guideline. You should start with the lowest dosage and slowly increase your titration. A continuous infusion of 1 mg / kg / h can then be carried out. The effective keto metabolite should also be taken into account when assessing plasma levels. Various authors see the limit to risky levels at 9 µg / ml or 4 µg / ml doxapram + metabolite (in very small premature infants).

4.3 Contraindications

- hypersensitivity to doxapram hydrochloride,
- severe hypertension, coronary disease, decompensated heart failure, thyrotoxicosis, pheochromocytoma; Disturbances of the respiratory mechanics, such as mechanical obstruction in the airways, serial rib fractures, pneumothorax, pulmonary embolism, neuromuscular blockages, pulmonary fibrosis, bronchial asthma, or other conditions that restrict the respiratory mechanics and respiratory muscles,
- cerebral spasms, status after head trauma, cerebral edema, apoplexy.

4.4 Special warnings and precautions for use

1. A clear airway must be ensured prior to using dopram® be guaranteed because dopram® Can induce vomiting.
2. If the arterial blood gas values deteriorate, dopram should be used ® discontinued and mechanical ventilation initiated. Dopram® should not be used in conjunction with mechanical ventilation.
3. Paravenous injection or the choice of the same injection site over a long period of time could lead to thrombophlebitis or local skin irritation. Too fast an infusion can cause hemolysis.
4. In case of sudden hypotension or dyspnea, dopram should be used
• be dropped off; be discontinued; be deducted; be dismissed.
5. Arrhythmias in acute respiratory failure secondary to chronic obstructive pulmonary disease are probably due to hypoxia; in this case it should be dopram® should only be used with caution.
6. In the case of seriously ill patients, the pCO₂ to reduce the rate of infusion of dopram® should not be increased, as this would be associated with an increase in the work of breathing.

4.5 Interactions with other drugs and others Interactions

Patients receiving a sympathomimetic drug or a monoamine oxidase inhibitor should use dopram® should only be given with caution, as an additive pressor effect can set in.

Dopram® leads to an increase in the release of adrenaline. Volatile anesthetics that sensitize the myocardium to catecholamines (e.g. halothane, isoflurane and enflurane) should therefore be used for at least 10 min

before dopram® Application to be discontinued.

There have been reports of interactions with theophylline manifesting as agitation and increased skeletal tone.

4.6 Use during pregnancy and lactation

For the safe use of dopram® Insufficient clinical documentation is available during pregnancy and breastfeeding. It is not known whether doxapram hydrochloride 1 H₂O crosses the placental barrier or is excreted in breast milk. The benefits and possible risks for the mother and for the unborn or breast-fed child must therefore be carefully weighed against each other. If use during breastfeeding is absolutely necessary, breastfeeding should be stopped.

4.7 Effects on ability to drive and use machines

Patients should be allowed to take dopram after they have been given dopram® do not actively participate in road traffic. This warning is more related to the underlying diseases to be treated.

4.8 Side effects

1. Disorders of the nervous system:

Headache, dizziness, anxiety, confusion, dilated pupils, hyperactivity, uncontrolled movements, cramps, spasticity, increase in deep tendon reflexes, clonus, Babinski's bilateral reflex, feverish states, feeling hot, sweating; Itching and paraesthesia (sensation of warmth, burning sensation or sensation of heat, especially in the genital region or in the perineum).

2. Respiratory system:

Cough, shortness of breath, rapid breathing, laryngeal and bronchospasm, singultus and reactive hypoventilation.

3. Cardiovascular system:

Phlebitis, heart rate fluctuations, flat T-wave, arrhythmia, chest pain, chest tightness. Mild to moderate increases in blood pressure are usually observed. The increase in blood pressure can only be of importance in patients with hypertension (see contraindications).

4. Gastrointestinal tract:

Nausea, vomiting, diarrhea, urge to defecate.

5. Kidney and urinary tract:

urinary retention, bladder irritation with spontaneous urination.

6. Investigations:

A decrease in hemoglobin, hematocrit, or erythrocyte count was seen postoperatively. With existing leukopenia it can be after anesthesia and dopram®-Application leads to a further decrease in leukocytes. Increases in blood urea and albuminuria were observed. However, the causal link has not been established because, in some cases, several drugs were administered at the same time.

Reporting suspected side effects

Reporting suspected side effects after approval is of great importance. It enables continuous monitoring of the benefit-risk balance of the medicinal product. Health professionals are requested to report any suspected side effects to the Federal Institute for Drugs and Medical Devices, Dept. Pharmacovigilance, Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn, website: www.bfarm.de to display.

4.9 Overdose

Early signs of intoxication include a rise in blood pressure, tachycardia, skeletal muscle hyperactivity, and an increase in deep tendon reflexes. Therefore, blood pressure, pulse rate and deep tendon reflexes should be monitored periodically and the dosage or infusion rate adjusted accordingly. At the recommended doses, seizures are unlikely, but intravenous anticonvulsants, oxygen, and the equipment necessary for possible cardiopulmonary resuscitation should be available.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

respiratory stimulant

ATC code: R07A B01

Doxapram hydrochloride stimulates breathing via the peripheral chemoreceptors in the carotid body. The relatively specific breathing stimulation after therapeutic doses is based on this. Only after administration of higher doses does the respiratory centers in the medulla become stimulated with increasing excitation of other centers of the CNS.

The onset of respiratory stimulation is usually observed after 20-40 seconds. The effect reaches a maximum after about 1 - 2 minutes; the duration of action varies between 5 and 12 minutes after a single injection.

Dopram® can reverse respiratory depression caused by medication. Doxapram does not antagonize the analgesic effects of opioids.

5.2 Pharmacokinetic properties

After intravenous bolus injection or short infusion, the plasma concentration of doxapram falls according to a multi-exponential function. The mean half-life is 3.4 hours (range 1.4-4.1 hours), the mean volume of distribution 1.5 l / kg and the clearance (based on the whole body) 370 ml / min. Doxapram is extensively metabolized; Less than 5% of an iv dose is excreted unchanged in the urine over 24 hours. A metabolite (ketodoxapram), comparable in concentration to the original substance, was detectable in the plasma with a similar half-life.

5.3 Preclinical Safety Data

The mean lethal dose in animal experiments with a single intravenous administration was in the range of the maximum total daily dose used in human therapy. Signs of intoxication were tonic-clonic convulsions.

In experiments on rats, after intravenous administration of 20 mg / kg body weight for 10 weeks and oral administration of 40 mg / kg body weight orally for 4.5 weeks, hypoxia-related petechial cerebral hemorrhage and loss of Purkinje cells in the cerebellum were observed.

In vitro Doxapram blocks expressed hERG channels in micromolar concentrations that are in the upper range of plasma concentrations used in human therapy. These channels are responsible for repolarization in the heart. Therefore, Doxapram has the potential to trigger certain types of irregular heartbeat (torsades de pointes).

In animal studies that do not meet current standards, no reproductive toxicological or teratogenic effects were observed.

In vitro- Investigations on genetic toxicology did not provide any indications of a clinically relevant mutagenic potential. Long-term studies to clarify a carcinogenic potential were not carried out.

6. Pharmaceutical particulars

6.1 Auxiliary materials

Water for injections.

6.2 Incompatibilities

Chemical incompatibilities in the form of precipitates are when mixing dopram® with alkaline solutions (e.g. 2.5% thiopental sodium, aminophylline, bicarbonate) have been observed. Since no further compatibility studies have been carried out, Dopram® not be mixed with other medicinal products.

6.3 Shelf life

4 years.

6.4 Special storage instructions

No.

6.5 Nature and content of the container

Packs of 5 or 10 ampoules, each with 5 ml of solution for injection

6.6 Instructions for use

For single use. Remaining quantities are to be discarded.

7. Authorization holder

CARINOPHARM GmbH

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* 0.06 € per call from the German landline network; Maximum cell phone price: 0.42€ per minute

8. Approval number

6743066.00.00

9. Date of approval

05/30/2005

10. State of information

February 2016

11. Prescription status / pharmacy requirement

Prescription only.

Requirement to:

Sentence computing center Berlin

Specialized information service

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