

 **29 January 2024**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**for**

**Rafaject, solution for injection in a pre-filled pen**

**0. D.SP.NO.**

32071

**1. NAME OF THE MEDICINAL PRODUCT**

Rafaject

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

One pre-filled pen contains 1.67 mg atropine in 0.7 ml solution.

Excipient(s) with known effect:

This medicine contains less than 1 mmol sodium (23 mg) per 0.7 mL (see section 4.4).

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Solution for injection in a pre-filled pen

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Rafaject is indicated for symptomatic therapy for poisoning with organophosphorus cholinesterase inhibitors in adults.

**4.2 Posology and method of administration**

Posology

This medicinal product is intended to be given:

* as part of self-medication and first aid by (non-medical) caregiver.

Adults:

The initial dose is 1.67 mg atropine (content of one pre-filled pen); can be repeated after 5 minutes and subsequently as required, until the muscarinic signs and symptoms disappear or until signs and symptoms of atropinisation appear (this dose may be repeated up to three times).

Method of administration

Rafaject pre-filled pen is administered by intramuscular injection.

1. Remove yellow safety cap

2. Aim and firmly jab green tip against the outer thigh. The autoinjector will inject the solution.

3. Wait 10 seconds.

4. Remove the needle from the outer thigh.

Paediatric population

Rafaject is not in a presentation suitable for paediatric use, as the auto-injector of the pre-filled pen does not permit accurate measurement of the doses for paediatric population.

Special populations:

No specific studies have been conducted to investigate whether hepatic or renal impairment relevantly affects the clearance of atropine. Due to the emergency setting, an alteration of the dose even in case of pre-existing renal or hepatic impairment is not recommended.

**4.3 Contraindications**

Contraindications are not relevant in acute poisoning (see also 4.4).

**4.4 Special warnings and precautions for use**

Use only in cases of suspicion of poisoning with organophosphorus cholinesterase inhibitors.

Misuse can result in in health damage (poisoning and injuries).

Signs of atropinisation

Atropine should be used in doses large enough to reverse the cholinergic signs of organophosphorus poisoning. In cases of severe intoxication, where the signs and symptoms persist, atropine may be given until signs of atropinisation appear. These signs include warm, dry, flushed skin, dilated pupils and an increased heart rate.

Precautions

Atropine blocks vagal inhibition of the sino-atrial nodal pacemaker and should thus be used with caution in patients with tachyarrhythmias, congestive heart failure or coronary heart disease.

Atropine should be used with caution in patients with hyperthyroidism or hypertension and in patients with high temperature or fever since it reduces the ability to sweat, thus increasing the risk of hyperthermia.

Parenterally administered atropine should be used cautiously in patients with chronic pulmonary disease since a reduction in bronchial secretions may lead to formation of bronchial plugs.

Antimuscarinics should be used with caution in patients with autonomic neuropathy.

Atropine decreases gastric motility, relax the lower oesophageal sphincter and may delay gastric emptying; it should therefore be used with caution in patients with gastric ulcer, oesophageal reflux or hiatus hernia associated with reflux oesophagitis, diarrhoea or gastrointestinal infection.

Atropine should be used with caution in patients with ileostomy or colostomy.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per 0.7 mL, that is to say essentially ‘sodium-free’.

**4.5 Interaction with other medicinal products and other forms of interaction**

The effects of atropine may be enhanced by the concomitant administration of other medicinal agents with anticholinergic activity e.g. tricyclic antidepressants, antispasmodics, anti-parkinsonian drugs (e.g. amantadine), some antihistamines, phenothiazines, class Ia antiarrythmic agents (e.g. disopyramide and quinidine), antiemetics, muscle relaxants.

By delaying gastric emptying, atropine may alter the absorption of other drugs.

Data regarding interactions are only available for adults.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of atropine.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Atropine rapidly crosses the placental barrier.

After iv administration, peak concentrations of atropine in foetal cord blood were reached 5 min post-dose with maximum effect on foetal heart rate 25 min post-dose. During pregnancy or at term systemic exposure of atropine may cause tachycardia in the foetus.

As a precautionary measure, it is preferable to avoid the use of Rafaject during pregnancy.

**Lactation**

Atropine is excreted in trace amounts in human milk. Atropine may cause antimuscarinic effects in the suckling infant.

Breast-feeding should be discontinued during treatment with Rafaject.

**Fertility**

Atropine has been associated with disturbance of fertility in animals (see section 5.3).

**4.7 Effects on ability to drive and use machines**

No traffic warning.

Disorders of eye accommodation and effects on the central nervous system can impair the ability to use machines, as well as your ability to drive.

**4.8 Undesirable effects**

The following adverse reactions have been observed with the administration of atropine, not only in organophosphorus poisoning, but also in other indications and clinical settings. The frequency of the undesirable effects cannot be determined for the proposed indication because no controlled data are available.

The occurrence, frequency and severity of adverse reactions are, however dose-related and may be influenced by the age of the patient, the level of poisoning, and the environment (e.g. hot environment).

|  |  |
| --- | --- |
| System Organ Class | Adverse reaction |
| Cardiac disorders | Tachycardia |
| Cardiac arrythmia |
| Atrial arrhythmias (incl. atrial fibrillation) |
| ECG changes (prolonged P wave, shortened PR segment, R on T phenomenon, shortened RT duration, prolonged QT interval, widening of QRS Complex, flattened T wave, repolarization abnormalities, ST segment elevation, retrograde conduction) |
| Ventricular arrhytmias |
| Heart failure |
| Hypertension |
| Eye disorders | Mydriasis |
| Blurred vision |
| Inhibition of accommodation |
| Photophobia |
| Gastrointestinal disorders | Xerostomia |
| Parasympathetic inhibition of the GI tract (incl. constipation, reflux, nausea, vomiting, bloating, abdominal pain) |
| General disorders | Hyperthermia |
| Immune reactions | Allergic reactions (incl. anaphylaxis) |
| Nervous system disorders | Irritability |
| Agitation |
| Confusion |
| Lethargy |
| Ataxia |
| Hallucinations |
| Abnormal EEG |
| Psychotic reactions |
| Seizures |
| Headache  |
| Renal and urinary disorders | Inhibition of the parasympathetic control of the urinary bladder |
| Urinary retention  |
| Respiratory, thoracic and mediastinal disorders | Reduced bronchial secretion |
| Skin and subcutaneous tissue disorders | Anhydrosis |
| Rash |
| Urticaria |
| Pain and swelling at the injection site |
| Vascular disorders | Flushing |

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:

Lægemiddelstyrelsen

Axel Heides Gade 1

DK-2300 København S

Website: www.meldenbivirkning.dk

**4.9 Overdose**

Symptomes of an overdose after using Atopine AI Auto-Injector are:

* dry mouth,
* decreased sweat secretion,
* erythema, skin rash,
* tachycardia (rapid heartbeat),
* arrhythmia,
* decrease of blood pressure following a evantualy brief increase in blood pressure,
* urinary retention,
* mydriasis (dilation of the pupil),
* paralysis of accommodation (disorder of near vision),
* pressure increase in the eye (risk of glaucoma),
* ataxia (movement coordination disorders),
* restlessness and arousal,
* hallucinations (illusions),
* confusion to delirium,
* memory and concentration disorders,
* drowsiness,
* loss of consciousness.

These symptoms are dose dependent. They can occur in particular after repeated dosing, in the absence of nerve agent poisoning, at high outside temperatures and caused by heavy physical exertion.

Antidote for unsubstantiated use or overdose:

1 - 4 mg physostigmine slowly intravenously (if necessary, repeat after 1 - 2 h)

or:

5 - 10 mg pilocarpine subcutaneously.

For central cramps: 10 to 20 mg diazepam i.v.

If necessary, artificial respiration.

Suppression of sweat secretion can cause heat caused stress and hyperthermia, which must be treated by physical measures.

**4.10 Legal status**

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**5. PHARMACOLOGICAL PROPERTIES**

**5.0 Therapeutic classification**

 Pharmacotherapeutic group: Belladonna alkaloids, tertiary amines.
ATC code: A 03 BA 01.

Mechanism of action

Atropine is a competitive antagonist for the M-cholinoceptors. Ganglionic and neuromuscular transmission of arousal is only inhibited in very high concentrations.

Atropine competitively blocks the effects of acetylcholine, including excess acetylcholine due to organophosphorus poisoning, at muscarinic cholinergic receptors on smooth muscle, cardiac muscle, secretory gland cells, and in peripheral autonomic ganglia and the central nervous system.

Pharmacodynamic effects

Atropine reduces secretions in the mouth and respiratory passages, relieves the constriction and spasm of the respiratory passages, and may reduce the paralysis of respiration, which results from actions of the toxic agent on the central nervous system. Although mild vagal excitation occurs, the increased respiratory rate and occasionally increased depth of respiration produced by atropine are more probably the result of bronchiolar dilatation. Accordingly, atropine is an unreliable respiratory stimulant and large or repeated doses may depress respiration.

Adequate doses of atropine abolish various types of reflex vagal cardiac slowing or asystole. Atropine-induced parasympathetic inhibition may be preceded by a transient phase of stimulation, especially on the heart where small doses first slow the rate before characteristic tachycardia develops due to paralysis of vagal control.

The drug also prevents or abolishes bradycardia or asystole produced by injection of choline esters, anticholinesterase agents or other parasympathomimetic drugs, and cardiac arrest produced by stimulation of the vagus. Atropine may also lessen the degree of partial heart block when vagal activity is an etiologic factor. In some individuals with complete heart block, the idioventricular rate may be accelerated by atropine; in others, the rate is stabilized.

Occasionally, a large dose may cause atrioventricular block and nodal rhythm.

Atropine in clinical doses counteracts the peripheral dilatation and abrupt decrease in blood pressure produced by choline esters. However, when given by itself, atropine does not exert a uniform effect on blood vessels or blood pressure. Systemic doses slightly raise systolic and lower diastolic pressures and can produce significant postural hypotension. Such doses also slightly increase cardiac output and decrease central venous pressure. Occasionally, therapeutic doses dilate cutaneous blood vessels (atropine flush).

Atropine may also cause increased body temperature due to suppression of sweat gland activity. This effect is, however, more common in infants and small children.

**5.2 Pharmacokinetic properties**

Absorption

Atropine is rapidly absorbed after intramuscular administration. Peak plasma concentrations of atropine after intramuscular administration are reached after approximately 20 - 30 minutes. Auto-injector devices as used in this medicinal product, lead to a faster absorption and shorter time to reach peak plasma concentrations.

Distribution

The volume of distribution is approximately 1.7 - 4 L/kg and the protein binding level is 40 – 50 %.

Biotransformation

Atropine is metabolised by the microsomal mono-oxygenase enzymes and atropine esterase to four major metabolites. Following i.v. administration of atropine sulfate approximately 50 % will be metabolised, while approximately 30-50 % of the administered dose is excreted as unchanged atropine.

Elimination

The elimination of atropine is biphasic with half-live in the plasma of 2-3 h or 12-38 h and is mainly renal. About 50 % are excreted unchanged, some are metabolized (ester cleavage, demethylation and glucoronidation).

**5.3 Preclinical safety data**

Studies with rats demonstrated that chronic intraperitoneal administration of 80 mg/kg atropine sulfate resulted in reduced weight gain and damage to the liver and kidneys.

**Genotoxicity, Carcinogenicity**

In conventional studies on genotoxicity (in vitro) and carcinogenicity atropine has shown no mutagenic or carcinogenic potential.

**Reproductive and developmental toxicity**

In conventional studies in rodents no teratogenic effects could be demonstrated.

A study in mice demonstrated that administration of 50 mg/kg of atropine sulfate on the eighth or ninth day of gestation led to delayed ossification (phalanges, sternebrae, skull) of the foetus with 1/60 instance of exencephaly and 1/32 instance of exencephaly at doses > 100 x the human equivalent dose. Studies concerning pre-/postnatal development were not conducted.

After repeat dosing of high doses of atropine, fertility was reduced in male (i. a. reduction in mating frequency, oligospermia, dysfunction of seminal emission and/or ejaculation, low pregnancy rates. decrease in the number of implantations) and female (delay in implantation) rats in a dose dependent manner. All findings were reversible.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Glycerol

Citric acid monohydrate

Sodium citrate dihydrate

Phenol

Water for injections

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

36 months

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

Each pre-filled pen contains 0.7 ml solution for injection.

The solution is contained in a stainless-steel cartridge cylinder, sealed with bromobutyl rubber stopper and bromobutyl rubber piston. In each cartridge a needle with a polypropylene needle guide is included.

The 0.7 ml cartridge is sealed in a disposable pen injector with a green injector cap and a yellow injector safety plug.

Each pre-filled pen is packed in a polyethylene bag.

The following pack sizes are available:

Carton containing 1, 3, 35, 40, 136 or 144 pre-filled pens.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

Attention! Rafaject is ready for injection after removing the yellow safety cap, accidental release of injection has to be avoided.

After the injection, avoid contact with blood or the needle by carefully bending the needle back against the autoinjector using a hard surface.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

actrevo GmbH

Großer Burstah 25

20457 Hamburg

Tyskland

**8. MARKETING AUTHORISATION NUMBER(S)**

64462

**9. DATE OF FIRST AUTHORISATION**

4 October 2021

**10. DATE OF REVISION OF THE TEXT**

29 January 2024