Nanajics

Dexmedomitdine 4 mcg / ml solution for infusion,

solution for infusion

1 NAME OF THE MEDICINAL PRODUCT

Nanajics 4 micrograms/mL solution for infusion

2 Qualitative and quantitative composition

Nanajics solution for infusion 4 micrograms/ml.

Each bag of 100 ml contains 472.8 mcg Dexmedomitdine hydrochloride equivalent to 400micrograms of Dexmedomitdine.

Excipient with known effect.

Each bag of 100 ml contains 354.2 mg sodium.

3 Pharmaceutical form

Solution for infusion.

Clear, colorless solution,free from any visible particles.

4 Clinical Particulars

4.1 Therapeutic indications

For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3).

For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e., procedural/awake sedation.

4.2 Posology and method of administration

For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3).

For hospital use only. Nanajics should be administered by healthcareprofessionals skilled in the management of patients requiring intensive care.

Posology

Patients already intubated and sedated may switch to Nanajics with an initial infusion rate of 0.7 micrograms/kg/h which may then be adjusted stepwise within the dose range 0.2 to 1.4 micrograms/kg/h to achieve the desired level of sedation, depending on the patient's response. A lower starting infusion rate should be considered for frail patients. Nanajics is very potent, and the infusion rate is given per **hour**. After dose adjustment, a new steady state sedation level

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may not be reached for up to one hour.

Maximum dose

The maximum dose of 1.4 micrograms/kg/h should not be exceeded. Patients failing to achieve an adequate level of sedation with the maximum dose of Nanajics should be switched to an alternative sedative agent.

Use of a loading dose of Nanajics in ICU sedation is not recommended and is associated with increased adverse reactions. Propofol or midazolam may be administered if needed until clinical effects of Nanajics are established.

Duration

There is no experience in the use of Nanajics for more than 14 days. The use of Nanajics for longer than this period should be regularly reassessed.

For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e., procedural/awake sedation.

Nanajics should be administered only by health care professionals skilled in the anesthetic management of patients in the operating room or during diagnostic procedures. When Nanajics is administered for conscious sedation, patients should be continuously monitored by persons not involved in the conduct of the diagnostic or surgical procedure. Patients should be monitored continuously for early signs of hypotension, hypertension, bradycardia, respiratory depression, airway obstruction, apnoea, dyspnoea and/or oxygen desaturation (see section 4.8).

Supplemental oxygen should be immediately available and provided when indicated. The oxygen saturation should be monitored by pulse oximetry.

Nanajics is given as a loading infusion followed by maintenance infusion. Depending on the procedure concomitant local anesthesia or analgesia may be needed in order to achieve the desired clinical effect. Additional analgesia or sedatives (e.g., opioids, midazolam, or propofol) are recommended in case of painful procedures or if increased depth of sedation is necessary. The pharmacokinetic distribution half –life of dexmedetomidine has been estimated to be around 6 min, which can be taken into consideration, together with the effects of other administered medications, when assessing the appropriate time needed for titration to desired clinical effect of dexmedetomidine.

Initiation of Procedural Sedation:

A loading infusion of 1.0 microgram/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 micrograms/kg given over 10 minutes may be suitable.

Maintenance of Procedural Sedation:

The maintenance infusion is generally initiated at 0.6-0.7 microgram/kg/hour and titrated to

ve desired clinical effect with doses ranging from 0.2 to 1 microgram/kg/hour. The rate of maintenance infusion should be adjustedto achieve the targeted level of sedation.

Special populations

Elderly

No dose adjustment is normally required for elderly patients (see section 5.2). Elderly patients appear to have an increased risk for hypotension (see section 4.4) but the limited data available from procedural sedation do not suggest a clear dose dependency.

Renal impairment

No dose adjustment is required for patients with renal impairment.

Hepatic impairment

Dexmedetomidine is metabolized in the liver and should be used with caution in patients with hepatic impairment. A reduced maintenance dose may be considered (see sections 4.4 and 5.2).

Pediatric population

The safety and efficacy of dexmedetomidine in children aged 0 to 18 years have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Nanajics solution for infusion is supplied ready to use. It should not be diluted before use. It should not be mixed with other medicines.

Nanajics must be administered only as an intravenous infusion using a controlled infusion device.

Nanajics should not be given as a bolus dose. For General precautions, see section 4.4.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed insection 6.1.

Advanced heart block (grade 2 or 3) unless paced.

Uncontrolled hypotension.

Acute cerebrovascular conditions.

4.4 Special warnings and precautions for use

Monitoring

Nanajics is intended for use in an intensive care setting, operating room and during diagnostic procedures. Use in other environments is not recommended. All patients should have continuous cardiac monitoring during Nanajics infusion. Respiration should be monitored in

non-intubated patients due to the risk of respiratory depression and in some case apnoea (see section 4.8).

The time to recovery after the use of dexmedetomidine was reported to be approximately one hour. When used in an outpatient setting close monitoring should continue for at least one hour (or longer based on the patient condition), with medical supervision continued for at least one further hour to ensure the safety of the patient.

General precautions

Dexmedetomidine should not be given as a bolus dose and in the ICU aloading dose is not recommended. Users should therefore be ready to use an alternative sedative for acute control of agitation or during procedures, especially during the first few hours of treatment. During procedural sedationa small bolus of another sedative may be used if a rapid increase in sedation level is required.

Some patients receiving dexmedetomidine have been observed to be arousableand alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms.

Dexmedetomidine normally does not cause deep sedation, and patients may be easily roused.

Dexmedetomidine is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation.

Dexmedetomidine should not be used as a general anesthetic induction agent for intubation or to provide sedation during muscle relaxant use.

Dexmedetomidine lacks the anticonvulsant action of some other sedatives and so will not suppress underlying seizure activity.

Care should be taken if combining Dexmedetomidine with other substances with sedative or cardiovascular actions as additive effects may occur.

Dexmedetomidine is not recommended for patient-controlled sedation. Adequate data is not available.

When Dexmedetomidine is used in an outpatient setting patients should normally be discharged into the care of a suitable third party. Patients should be advised to refrain from driving or other hazardous tasks and where possible to avoid the use of other agents that may sedate (e.g., benzodiazepines, opioids, alcohol) for a suitable period of time based on observed effects of Dexmedetomidine, the procedure, concomitant medications, the age and the condition of the patient.

Elderly

Caution should be exercised when administering Nanajics to elderly patients.

Elderly patients over 65 years of age may be more prone to hypotension with the administration of Nanajics, including a loading dose, for procedures. A dose reduction should be considered. Please refer to section 4.2.

Mortality in ICU patients ≤ 65 years old

In the SPICE III pragmatic randomised controlled trial of 3 904 critically ill adult ICU patients there was no overall difference in 90-day mortality between the dexmedetomidine and usual care group (mortality 29.1% in both groups), but a heterogeneity of effect from age on mortality was observed. Dexmedetomidine was associated with an increased mortality in the age-group ≤ 65 years (odds ratio 1.26; 95% credibility interval 1.02 to 1.56) compared to alternative sedatives. While the mechanism is unclear, this heterogeneity of effect on mortality from age was most prominent in cases with early use of dexmedetomidine in high dose to achieve deep sedation in patients admitted for other reasons than postoperative care and increased with increasing APACHE II scores. The effect on mortality was not detectable when dexmedetomidine was used for light sedation. These findings should be weighed against the expected clinical benefit of dexmedetomidine compared to alternative sedatives in younger patients.

Cardio-vascular effects and precautions

Dexmedetomidine reduces heart rate and blood pressure through central sympatholysis but at higher concentrations causes peripheral vasoconstriction leading to hypertension (see section 5.1).

Nanajics is therefore not suitable in patients with severe cardiovascular instability.

Caution should be exercised when administering Nanajics to patients with pre-existing bradycardia. Data on the effects of dexmedetomidine in patients with heart rate <60 are very limited and particular care should be taken with such patients. Bradycardia does not normally require treatment but has commonly responded to anti-cholinergic medicine or dose reduction whereneeded. Patients with high physical fitness and slow resting heart rate may be particularly sensitive to bradycardic effects of alpha-2 receptor agonists and cases of transient sinus arrest have been reported. Also, cases of cardiac arrest, often preceded by bradycardia or atrioventricular block, have been reported (see section 4.8).

The hypotensive effects of Dexmedetomidine may be of greater significance in those patients with pre-existing hypotension (especially if not responsive to vasopressors), hypovolaemia, chronic hypotension or reduced functional reserve such as patients with severe ventricular dysfunction and the elderly and special care is warranted in these cases (see section 4.3). Hypotension does not normally require specific treatment but, where needed, users should be ready to intervene with dose reduction, fluids and/or vasoconstrictors.

Patients with impaired peripheral autonomic activity (e.g., due to spinal cord injury) may have more pronounced haemodynamic changes after starting Dexmedetomidine and so should be treated with care.

Transient hypertension has been observed primarily during the loading dose inassociation with the peripheral vasoconstrictive effects of Dexmedetomidine and a loading dose is not recommended in ICU sedation. Treatment of hypertension has generally not been necessary but decreasing the continuous infusion rate may be advisable.

Local vasoconstriction at higher concentration may be of greater significance in patients with ischaemic heart disease or severe cerebrovascular disease who should be monitored closely. Dose reduction or discontinuation should be considered in a patient developing signs of myocardial or cerebral ischaemia.

Caution is advised when administering Dexmedetomidine together with spinal or epidural anesthesia due to possible increased risk of hypotension or bradycardia.

Patients with hepatic impairment

Care should be taken in severe hepatic impairment as excessive dosing may increase the risk of adverse reactions, over-sedation or prolonged effect as a result of reduced Dexmedetomidine clearance.

Patients with neurological disorders

Experience of Dexmedetomidine in severe neurological disorders such as head injury and after neurosurgery is limited and it should be used with cautionhere, especially if deep sedation is required.

Dexmedetomidine may reduce cerebral blood flow and intracranial pressure, and this should be considered when selecting therapy.

Other

Diabetes insipidus has been reported in association with dexmedetomidine treatment. If polyuria occurs, it is recommended to stop Nnajics and check serum sodium level and urine osmolality.

Alpha-2 agonists have rarely been associated with withdrawal reactions when stopped abruptly after prolonged use. This possibility should be considered if the patient develops agitation and hypertension shortly after stopping dexmedetomidine.

Dexmedetomidine may induce hyperthermia that may be resistant to traditional cooling methods. Dexmedetomidine treatment should be discontinued in the event of a sustained unexplained fever and is not recommended for use in malignant hyperthermia-sensitive patients.

This medicinal product contains 354 mg sodium in each 100 ml vial to be taken in consideration for patients on restrict sodium diet.

nteraction with other medicinal products and other forms of interaction

raction studies have only been performed in adults.

Co-administration of dexmedetomidine with anesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects, includingsedative, anesthetic and cardiorespiratory effects. Specific studies have confirmed enhanced effects with isoflurane, propofol, alfentanil, and midazolam.

No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with dexmedetomidine, a reduction in dosage of dexmedetomidine or the concomitant anesthetic, sedative, hypnotic or opioid may be required.

Inhibition of CYP enzymes including CYP2B6 by dexmedetomidine has been studied in human liver microsome incubations. In vitro study suggests that interaction potential in vivo exists between dexmedetomidine and substrates with dominant CYP2B6 metabolism.

Induction of dexmedetomidine in vitro was observed on CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4, and induction in vivo cannot be excluded. The clinical significance is unknown.

The possibility of enhanced hypotensive and bradycardic effects should be considered in patients receiving other medicinal products causing these effects, for example beta blockers, although additional effects in an interactionstudy with esmolol were modest.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of dexmedetomidine in pregnant women.

Studies in animals have shown reproductive toxicity Nanajics should not be used during pregnancy unless the clinical condition of the woman requires treatment with Nanajics.

Breastfeeding

Dexmedetomidine is excreted in human milk, however levels will be below the limit of detection by 24 hours following treatment discontinuation. A risk to infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue Nanajics therapy taking into account the benefit of breastfeeding for the child and the benefit oftherapy for the woman.

Fertility

In the rat fertility study, dexmedetomidine had no effect on male or female fertility. No human data on fertility are available.

4.7 Effects on ability to drive and use machines

Dexmedetomidine has major impact on the ability to drive and use machines. Patients should be advised to refrain from driving or other hazardous tasks for a suitable period of time after receiving Nanajics for proceduralsedation.

4.8 Undesirable effects

Summary of the safety profile

Sedation of adult ICU (Intensive Care Unit) patients

The most frequently reported adverse reactions with dexmedetomidine in ICU setting are hypotension, hypertension and bradycardia, occurring in approximately 25%, 15% and 13% of patients respectively. Hypotension and bradycardia were also the most frequent dexmedetomidine -related serious adverse reactions occurring in 1.7% and 0.9% of randomised Intensive Care Unit (ICU) patients respectively.

Procedural/awake sedation

The most frequently reported adverse reactions with dexmedetomidine in procedural sedation are listed below (the protocols of phase III studies contained pre-defined thresholds for reporting changes in blood pressure, respiratory rate and heart rate as AEs).

Hypotension (55% in dexmedetomidine -group vs. 30% in placebo-group receiving rescue midazolam and fentanyl)

Respiratory depression (38% in dexmedetomidine -group vs. 35% in placebo-group receiving rescue midazolam and fentanyl)

Bradycardia (14% in dexmedetomidine -group vs. 4% in placebo-group receiving rescue midazolam and fentanyl)

Tabulated list of adverse reactions

The adverse reactions listed in Table 1 have been accumulated from pooled data of clinical trials in intensive care.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥1/10); common (≥1/100to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); veryrare (<1/10 000), not known (cannot be estimated from the available data).

Table 1. Adverse reactions

Endocrine disorders

Not Known: Diabetes insipidus

Metabolism and nutrition disorders

Common:	Hyperglycaemia, hypoglycaemia
Uncommon:	Metabolic acidosis, hypoalbuminaemia

Psychiatric disorders

Common:	Agitation
Uncommon:	Hallucination

Cardiac disorders

Very common:	Bradycardia1,2
Common:	Myocardial ischaemia or infarction, tachycardia
Uncommon:	Atrioventricular block[1], cardiac output decreased, cardiac arrest[1]

Vascular disorders

Very common:	Hypotension[1,2], hypertension[1,2]

Respiratory, thoracic and mediastinal disorders

Very common:	Respiratory depression[2,3]
Uncommon:	Dyspnoea, apnoea

Gastrointestinal disorders

Common:	Nausea[2], vomiting, dry mouth[2]
Uncommon:	Abdominal distension

Renal and urinary disorders

Not known:	Polyuria

General disorders and administration site conditions

Common:	Withdrawal syndrome, hyperthermia
Uncommon:	Drug ineffective, thirst

[1] See section on Description of selected adverse reactions

[2] Adverse reaction observed also in procedural sedation studies

[3] Incidence 'common' in ICU sedation studies

Description of selected adverse reactions

Clinically significant hypotension or bradycardia should be treated as described in section 4.4.

In relatively healthy non-ICU subjects treated with dexmedetomidine, bradycardia has occasionally led to sinus arrest or pause. The symptoms responded to leg raising and anticholinergics such as atropine or glycopyrrolate. In isolated cases bradycardia has progressed to periods of asystole in patients with pre-existing bradycardia. Also, cases of cardiac arrest, often preceded by bradycardia or atrioventricular block, have been reported.

Hypertension has been associated with the use of a loading dose and this reaction can be reduced by avoiding such a loading dose or reducing the infusion rate or size of the loading dose.

Paediatric population

Children > 1 month post-natal, predominantly post-operative, have been evaluated for treatment up to 24 hours in the ICU and demonstrated a similar safety profile as in adults. Data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to maintenance doses ≤ 0.2 mcg/kg/h. A single case of hypothermic bradycardia in a neonate has been reported in the literature.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important.