TOMEXA should not be used outside an Intensive Care Unit setting or surgical operating theatres. There should be continuous monitoring of vital parameters.

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

TOMEXA 200 µg/2 mL, concentrate for solution for infusion

TOMEXA 400 µg/4 mL, concentrate for solution for infusion

TOMEXA 1 000 µg/10 mL, concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of concentrate contains 100 micrograms dexmedetomidine as dexmedetomidine hydrochloride.

Each 2 mL ampoule/vial contains 200 micrograms dexmedetomidine.

Each 4 mL ampoule/vial contains 400 micrograms dexmedetomidine.

Each 10 mL ampoule/vial contains 1 000 micrograms dexmedetomidine.

The concentration of the final solution after dilution should be either 4 micrograms/mL or 8 micrograms/mL.

Sugar free.

Each mL of concentrate contains less than 1 mmol sodium (23 mg).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

The concentrate is a clear, colourless solution, pH 4,5 to 7,0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TOMEXA is an alpha$_2$ adrenoreceptor agonist sedative with analgesic properties indicated for:

- *Intensive Care Unit Sedation*

  Sedation of intubated and mechanically ventilated adult post-surgical patients during treatment in an intensive care setting.
- *Monitored Anaesthesia Care (MAC)/ Conscious sedation in a theatre or intensive care setting for*
  - Minor surgical procedures under local anaesthesia
  - Fibreoptic intubation.

Efficacy and safety have not been studied in children under 18 years of age.

4.2 Posology and method of administration

NOTE: TOMEXA should be administered only by health care professionals skilled in the management of patients in the intensive care setting. Continuous monitoring of vital signs, in particular blood pressure, heart rate and oxygen saturation is mandatory during infusion of TOMEXA.

In order to minimise undesirable pharmacologic side effects, bolus injections of TOMEXA should not be used. Clinically significant events of bradycardia and sinus arrest have been associated with dexmedetomidine hydrochloride as in TOMEXA administration in young healthy volunteers with high vagal tone, or with different routes of administration including rapid intravenous or

bolus administration of dexmedetomidine hydrochloride as in TOMEXA.

Fluid supplementation should be administered prior to and during administration of TOMEXA to ensure normovolaemia.

TOMEXA has been administered to patients requiring mechanical ventilation as well as to patients breathing spontaneously after extubation. There is no respiratory depression associated with the administration of TOMEXA. TOMEXA has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post extubation. It is not necessary to discontinue TOMEXA prior to extubation.

Posology

Adults

ICU Sedation

TOMEXA dosage should be individualised and titrated to the desired clinical effect.

Initiation: For adult patients, it is recommended to initiate TOMEXA with a loading dose of 1,0 microgram/kg over 10 minutes.

Maintenance of ICU sedation: Adult patients will generally require a maintenance infusion in the range of 0,2 to 0,7 microgram/kg/hr. The rate of the maintenance infusion can be adjusted in order to achieve the desired clinical effect. Dosages as low as 0,05 microgram/kg/hr have been used.

A dose reduction for both the loading and the maintenance infusions should be considered in

patients with impaired hepatic or renal function and in patients over 65 years of age (see section 4.3, 4.4 and 5.2).

Conscious Sedation

Monitored Anaesthesia Care (MAC) with an adequate nerve block and awake fibreoptic intubation (AFI).

TOMEXA dosing should be individualised and titrated to the desired clinical effect.

Initiation: For adult patients, TOMEXA is generally initiated with a loading infusion of 1 (one) microgram/kg over 10 minutes.

For patients over 65 years of age or those undergoing less invasive procedures such as ophthalmic surgery, a loading infusion of 0,5 microgram/kg over 10 minutes may be suitable.

Maintenance of conscious sedation:

MAC: Following the load, maintenance dosing of TOMEXA should generally be initiated at 0,6 microgram/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0,2 to 1 microgram/kg/hr for all procedures. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

AFI: Following the load in awake fibreoptic intubation, a fixed maintenance dose of 0,7 microgram/kg/hr should be used.

Dosage adjustment

Due to possible pharmacodynamic interactions a reduction in dosage of TOMEXA or other concomitant anaesthetics, sedatives, hypnotics, or opioids may be required when co-administered (see section 4.5).

Special populations

Impaired hepatic function

Dosage reductions may need to be considered for patients with hepatic impairment, as TOMEXA is metabolised primarily in the liver.

Impaired renal function

Since the majority of metabolites are excreted in the urine, dosage reductions may need to be considered for patients with renal impairment.

Elderly

Since the elderly are more sensitive to the effects of TOMEXA dosage reductions may need to be considered.

Paediatric population

Safety and efficacy of TOMEXA has not been studied in children and adolescents and is therefore not recommended for patients under 18 years of age.

Method of administration

TOMEXA should be administered by continuous intravenous infusion.

For instructions on preparation and dilution of the product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to dexmedetomidine or to any of the other excipients (see section 6.1).
- Patients with sepsis.

- Unstable trauma patients.
- Hypovolaemic patients.
- Heart block.
- Uncontrolled cardiac failure.
- Imminent hepatic failure.
- Acute cerebrovascular conditions.

4.4 Special warnings and precautions for use

TOMEXA should be administered only by health care professionals skilled in the management of patients in the intensive care setting and who have received complete training in the use of TOMEXA in the ICU setting.

Safety and efficacy of TOMEXA in non-surgical intensive care patients have not been established.

Clinical events of bradycardia and sinus arrest have been associated with TOMEXA administration in some young, healthy volunteers with high vagal tone, or with different routes of administration including rapid intravenous or bolus administration of TOMEXA. Bolus injections of TOMEXA should not be used, in order to minimise undesirable pharmacological side effects.

Elderly

The elderly are more prone to cardiovascular adverse events e.g., hypotension and bradycardia and the dose must be carefully titrated to obtain the desired effect. Close CVS monitoring is required. Elderly patients (over 65 years) often require lower doses of TOMEXA.

Special precautions

NOTE: TOMEXA should be administered only by health care providers skilled in the management of patients in the intensive care setting. Continuous electrocardiogram (ECG), blood pressure and oxygen saturation monitoring are mandatory during infusion of TOMEXA.

Caution should be exercised in patients with pre-existing severe bradycardia disorders (e.g. advanced heart block), or patients with pre-existing severe ventricular dysfunction (e.g., ejection fraction < 30 %) including congestive heart failure and cardiac failure in whom sympathetic tone is critical for maintaining haemodynamic balance (see section 4.3).

Hypotension, bradycardia, and sinus arrest

See boxed warning above. Decreased blood pressure and/or heart rate may occur with the administration of TOMEXA. Based on clinical experience with TOMEXA, if medical intervention is required, treatment may include decreasing or stopping the infusion of TOMEXA, increasing the rate of intravenous fluid administration, elevation of the lower extremities and use of pressor medicines. Because TOMEXA has the potential to augment bradycardia induced by vagal stimuli, health care professionals should be prepared to intervene. The intravenous administration of anticholinergic medicines should be considered to modify vagal tone. Atropine and glycopyrrolate were effective in the treatment of most episodes of TOMEXA-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

TOMEXA decreases sympathetic nervous activity and therefore, these effects may be expected to be most pronounced in patients with desensitised autonomic nervous system control (e.g. elderly, diabetes, chronic hypertension, severe cardiac disease).

Prevention of hypotension and bradycardia should take into consideration the haemodynamic stability of the patient and normovolaemia must be ensured prior to the administration of TOMEXA. Patients who are hypovolaemic may become hypotensive under TOMEXA therapy. Therefore, fluid supplementation should be administered prior to and during the administration of TOMEXA.

Additionally, in situations where other vasodilators or negative chronotropic medicines are administered, co-administration of TOMEXA could have an additive pharmacodynamics effect and should be administered with caution and careful titration (see section 4.5).

Clinical events of bradycardia or hypotension may be potentiated when TOMEXA is used concurrently with propofol or midazolam. Therefore, consider a dose reduction of propofol or midazolam (see section 4.5).

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

Transient hypertension

Transient hypertension has been observed primarily during the loading infusion, associated with initial peripheral vasoconstrictive effects of TOMEXA and relatively higher plasma concentrations achieved during the loading infusion. If intervention is necessary, reduction of the loading infusion rate may be considered. Following the loading infusion, the central effects of TOMEXA dominate and the blood pressure usually decreases.

Hyperthermia and lacrimation

TOMEXA may induce hyperthermia or pyrexia, which may be resistant to traditional cooling methods, such as administration of cooled intravenous fluids and antipyretic medicines. Discontinue TOMEXA if medicine-related hyperthermia or pyrexia is suspected and monitor patients until body temperature normalizes.
TOMEXA treatment is not recommended for use in malignant hyperthermia-sensitive patients.

TOMEXA may cause reduced lacrimation. Lubrication of the patient's eyes may be considered when administering TOMEXA to avoid corneal dryness.

Monitoring

The time to recovery after the use of TOMEXA 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.

When TOMEXA 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 medicines 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.

General precautions

TOMEXA should not be given as a bolus dose and in the ICU a loading 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 sedation, a small bolus of another sedative may be used if a rapid increase in sedation level is required.

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

TOMEXA normally does not cause deep sedation, and patients may be easily roused. TOMEXA is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation.

TOMEXA should not be used as a general anaesthetic induction medicine for intubation or to provide sedation during muscle relaxant use.

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

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

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 (see section 4.2).

Patients with neurological disorders

Experience of dexmedetomidine as in TOMEXA in severe neurological disorders such as head injury and after neurosurgery is limited and it should be used with caution here, especially if deep sedation is required. Dexmedetomidine as in TOMEXA may reduce cerebral blood flow and intracranial pressure and this should be considered when selecting therapy.

Withdrawal reactions

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 as in TOMEXA (see section 4.8).

Mortality in ICU patients ≤ 65 years old

It is documented that in critically ill adult ICU patients there was no overall difference in 90-day mortality between the dexmedetomidine as in TOMEXA 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 TOMEXA compared to alternative sedatives in younger patients.

Diabetes insipidus

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

Excipients with known effect

TOMEXA contains less than 1 mmol sodium (23 mg) per mL that is to say essentially “sodium free’’.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P-450

In vitro studies indicate that clinically relevant cytochrome P450 mediated interactions are unlikely.

Anaesthetics/ sedatives/ hypnotics/ opioids

Co-administration of TOMEXA is likely to lead to an enhancement of effects with anaesthetics, sedatives, hypnotics, and opioids. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine as in TOMEXA and isoflurane, propofol, alfentanil, and midazolam were demonstrated. However, due to pharmacodynamics effects, when co-administered with TOMEXA a reduction in dosage of these medicines may be required.

Neuromuscular blockers

No clinically meaningful increases in the magnitude of neuromuscular blockade and no

pharmacokinetic interactions were observed with TOMEXA and rocuronium administration.

CYP enzymes

Inhibition of CYP enzymes including CYP2B6 by dexmedetomidine as in TOMEXA 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 *in vitro* of dexmedetomidine as in TOMEXA was observed on CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4, and induction *in vivo* cannot be excluded. The clinical significance is unknown.

Medicines enhancing hypotensive and bradycardic effects

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

4.6 Fertility, pregnancy, and lactation

Pregnancy

The use of TOMEXA is not recommended in pregnancy.

Available data indicates that dexmedetomidine as in TOMEXA crosses the placenta. Animal studies have shown toxicity.

Labour and delivery

The safety of TOMEXA in labour and delivery has not been studied and it is therefore not recommended for obstetrics, including caesarean section deliveries.

Breastfeeding

There is no information regarding the effects of TOMEXA on the breastfed infant or the effects on milk production.

Dexmedetomidine as in TOMEXA is excreted in human milk, however levels will be below the limit of detection by 24 hours following treatment discontinuation. A risk to the infant cannot be excluded.

Advise women to monitor the breastfed infant for irritability. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TOMEXA and any potential adverse effects on the breastfed infant from TOMEXA or from the underlying condition.

Fertility

In the rat fertility study, dexmedetomidine as in TOMEXA 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

The patient should not drive or operate machinery or make legal decisions until 24 hours after recovery from a surgical procedure in which TOMEXA was used.

4.8 Undesirable effects

a. Summary of the safety profile

Sedation of adult ICU (Intensive Care Unit) patients

The most frequently reported adverse reactions with dexmedetomidine as in TOMEXA in ICU setting are hypotension, hypertension, and bradycardia.

Procedural/awake sedation

The most frequently reported adverse reactions with dexmedetomidine as in TOMEXA in procedural sedation are listed below.

b. Tabulated summary of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-marketing spontaneous reports with dexmedetomidine.

System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Anaemia
	Frequency unknown	Coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased prothrombin, thrombocytopenia, leukocytosis
Endocrine disorders	Frequency unknown	Diabetes insipidus
Metabolism and nutrition disorders	Frequent	Hypovolaemia, hyperglycaemia
	Less frequent	Hypocalcaemia, acidosis
	Frequency unknown	Lactic acidosis, respiratory acidosis, diabetes mellitus, hypoglycaemia, hypokalaemia, hyperkalaemia, hypoproteinaemia, increased alkaline, phosphatase, increased

		non-protein nitrogen (NPN)
Psychiatric disorders	Frequent	Agitation
	Less frequent	Hallucination
	Frequency unknown	Anxiety, confusion, delirium, depression, illusion, nervousness
Nervous system disorders	Frequency unknown	Convulsion, dizziness, headache, neuralgia, neuritis, neuropathy, paraesthesia, paralysis, paresis, speech disorder
Eye disorders	Frequency unknown	Diplopia, photopsia, abnormal vision
Cardiac disorders	Frequent	Myocardial ischaemia or infarction, bradycardia, atrial fibrillation, tachycardia
	Less frequent	Atrioventricular block, cardiac output decreased, cardiac arrest, sinus tachycardia, ventricular tachycardia
	Frequency unknown	Angina pectoris, abnormal ECG, heart disorder, dysrhythmia, atrial dysrhythmia, atrial fibrillation, AV block, bundle branch block, extrasystoles, heart block, supraventricular tachycardia, T-wave inversion, ventricular dysrhythmia

Vascular disorders	Frequent	Hypotension, hypertension
	Frequency unknown	Blood pressure fluctuation, circulatory failure, cyanosis, aggravated hypertension, postural hypotension, pulmonary hypertension, haemorrhage, cerebral haemorrhage, peripheral ischaemia, vascular disorder, vasodilation
Respiratory, thoracic, and mediastinal disorders	Frequent	Respiratory depression, atelectasis, pleural effusion, hypoxia, bradypnoea
	Less frequent	Dyspnoea, apnoea, pulmonary oedema, wheezing
	Frequency unknown	Adult respiratory distress syndrome, bronchospasm, coughing, emphysema, haemoptysis, hypercapnia, hypoventilation, pharyngitis, pleurisy, pneumonia, pneumothorax, pulmonary congestion, respiratory disorder, respiratory insufficiency, increased sputum, stridor
Gastrointestinal disorders	Frequent	Nausea, dry mouth, vomiting
	Less frequent	Abdominal distension

	Frequency unknown	Abdominal pain, diarrhoea, eructation, mucosal ulceration
Hepato-biliary disorders	Frequency unknown	Increased AG ratio, increased GGT, abnormal hepatic function, hyperbilirubinaemia, increased aspartate transaminase (AST), increased alanine transaminase (ALT), jaundice
Skin and subcutaneous tissue disorders	Frequency unknown	Rash erythematous, increased sweating
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Muscle weakness
Renal and urinary disorders	Frequency unknown	Haematuria, acute renal failure, abnormal renal function, urinary retention, increased blood urea
General disorders and administration site conditions	Frequent	Withdrawal syndrome, hyperthermia, pyrexia, chills,
	Less frequent	Medicine ineffective, thirst, peripheral oedema
	Frequency unknown	Allergic reaction, ascites, hyperpyrexia, light anaesthesia, oedema, pain, syncope, rigors
Investigations	Less frequent	Decreased urine output

Injury, poisoning and procedural complications	Frequent	Post-procedural haemorrhage
Infections and Infestations	Frequency unknown	Infection, fungal infection, sepsis

c. Description of selected adverse reactions

Withdrawal

ICU sedation: Although not specifically studied, withdrawal symptoms similar to those reported for another alpha$_2$ adrenergic medicine (clonidine) may result when TOMEXA is administered in excess of 24 hours and stopped abruptly. These symptoms include nervousness, agitation and headache accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma.

Conscious sedation: Withdrawal symptoms were not seen after discontinuation of short-term infusions of TOMEXA (< 6 hours).

Hypotension or bradycardia

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

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TOMEXA is important. It allows continued monitoring of the benefit/risk balance of TOMEXA. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.
In addition, side effects can also be reported to info@pharmacorp.co.za.

4.9 Overdose

Symptoms

Several cases of dexmedetomidine overdose have been reported both in the clinical trial and the post-marketing data. The reported highest infusion rates of dexmedetomidine as in TOMEXA in these cases have reached up to 60 micrograms/kg/h for 36 minutes and 30 micrograms/kg/h for 15 minutes in a 20-month-old child and in an adult, respectively. The most common adverse reactions reported in conjunction with overdose include bradycardia, hypotension, hypertension, oversedation, respiratory depression and cardiac arrest.

Management

In cases of overdose with clinical symptoms, TOMEXA infusion should be reduced or stopped. Expected effects are primarily cardiovascular and should be treated as clinically indicated (see section 4.4). At high concentration hypertension may be more prominent than hypotension. In

clinical studies, cases of sinus arrest reversed spontaneously or responded to treatment with atropine and glycopyrrolate. Resuscitation was required in isolated cases of severe overdose resulting in cardiac arrest.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.9 Other Analgesics

Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives

ATC code: N05CM18

Mechanism of action

Dexmedetomidine is an alpha$_2$-adrenoreceptor agonist. The sedative action of dexmedetomidine is believed to be mediated primarily by post-synaptic alpha$_2$-adrenoreceptors, which in turn act on inhibitory pertussis-toxin-sensitive G protein, thereby increasing conductance through potassium channels. The site of the sedative effects of dexmedetomidine has been attributed to the locus coeruleus. The analgesic actions are believed to be mediated by a similar mechanism of action at the brain and spinal cord level.

Alpha$_2$ selectivity is demonstrated following low and medium doses given slowly. Alpha$_2$ and alpha$_1$ activity is seen following rapid administration. Dexmedetomidine has no affinity for beta adrenergic, muscarinic, dopaminergic, or serotonin receptors.

5.2 Pharmacokinetic properties

Distribution

Following administration, dexmedetomidine exhibits the following pharmacokinetic

characteristics: rapid distribution phase with a distribution half-life ($t_{1/2\alpha}$) of about 6 minutes; terminal elimination half-life ($t_{1/2}$) of approximately two hours; steady-state volume of distribution (V_{ss}) of approximately 118 litres. Clearance has an estimated value of about 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female human subjects: the average binding was 94 % and constant across the different concentrations tested. Protein binding was similar in males and females. The fraction was dexmedetomidine that was bound to plasma proteins was statistically significantly decreased in subjects with hepatic impairment compared with healthy subjects.

Dexmedetomidine is unlikely to cause clinically significant changes in the plasma protein binding of fentanyl, ketorolac, theophylline, digoxin, lidocaine, phenytoin, warfarin, ibuprofen, and propranolol.

Biotransformation

Dexmedetomidine is eliminated by extensive metabolism in the liver. There are three types of initial metabolic reactions: direct N-glucuronidation, direct N-methylation and cytochrome P450 catalysed oxidation. The most abundant circulating dexmedetomidine metabolites are two isomeric N-glucuronides. Metabolite H-1, N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide, is also a major circulating product of dexmedetomidine biotransformation. Cytochrome P-450 catalyses the formation of two minor circulating metabolites, 3-hydroxymethyl dexmedetomidine produced by hydroxylation at the 3-methyl group of dexmedetomidine and H-3 produced by oxidation in the imidazole ring. Available data suggest that the formation of the oxidised metabolites is mediated by several CYP forms (CYP2A6, CYP1A2, CYP2E1, CYP2D6

and CYP2C19). These metabolites have negligible pharmacological activity.

Elimination

Dexmedetomidine is eliminated almost exclusively by metabolism with 95 % of a radio-labelled dose being excreted in the urine and 4 % in the faeces. Approximately 34 % of the excreted metabolites are products of N-glucuronidation.

Special populations

Hepatic impairment

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values were lower than in healthy subjects. The mean clearance values for subjects with mild, moderate, and severe hepatic impairment were 74 %, 64 % and 53 % respectively, of those observed in the normal healthy subjects. Mean clearances for free medicine were 59 %, 51 % and 32 % respectively, of those observed in the normal healthy subjects.

Although dexmedetomidine is dosed to effect, it may be necessary to consider dose reduction depending on degree of hepatic impairment (see section 4.2 and 4.4).

Renal impairment

Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2}$, CL and V_{ss}) were not different in subjects with severe renal impairment (Cr Cl: < 30 mL/min) compared with healthy subjects.

Gender

No difference in dexmedetomidine pharmacokinetics due to gender was observed.

Elderly

The pharmacokinetic profile of dexmedetomidine was not altered by age. The elderly are more sensitive to the effects of dexmedetomidine. In clinical trials, there was a higher incidence of bradycardia and hypotension in elderly patients (> 65 years of age).

Paediatrics and adolescents

The pharmacokinetic profile of dexmedetomidine has not been studied in subjects less than 18 years of age.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injection

6.2 Incompatibilities

TOMEXA must not be mixed with other medicines or diluents except those mentioned in section 6.6.

Compatibility studies have shown potential for adsorption of dexmedetomidine to some types of natural rubber. Although dexmedetomidine is dosed to effect, it is advisable to use components with synthetic or coated natural rubber gaskets.

6.3 Shelf life

48 months

After dilution: Chemical and physical in-use stability has been demonstrated for 48 hours at 25 °C and at refrigerated conditions (2 to 8 °C).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C.

See section 6.3 for storage after dilution.

6.5 Nature and contents of container

2 mL; 5 mL or 10 mL Type I colourless glass ampoules (with fill volumes of 2 mL; 4 mL and 10 mL).

2 mL; 5 mL or 10 mL Type I colourless glass vials (with fill volumes of 2 mL; 4 mL and 10 mL), closed with grey bromobutyl rubber stopper and aluminium crimp cap with plastic flip-off.

Pack sizes

5 or 25 x 2 mL ampoules

4 or 5 x 4 mL ampoules

4 or 5 x 10 mL ampoules

5 x 2 mL vials

4 or 5 x 4 mL vials

4 or 5 x 10 mL vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Directions for use

A controlled infusion device should be used to administer TOMEXA.

Parenteral products should be inspected visually for particulate matter and discolouration prior to administration. Do not use if product is discoloured or if precipitate matter is present.

Vials are intended for single patient use only.

Preparation of solution

Strict aseptic technique must always be maintained.

TOMEXA can be diluted in glucose 50 mg/mL (5 %), Ringers, mannitol, or sodium chloride 9 mg/mL (0,9 %) solution for injection to achieve the required concentration of either 4 micrograms/mL or 8 micrograms/mL prior to administration.

Please see below in tabulated form the volumes needed to prepare the infusion.

In case the required concentration is 4 micrograms/mL:

Volume of TOMEXA 100 micrograms/mL concentrate for solution for infusion	**Volume of diluent**	**Total volume of infusion**
2 mL	48 mL	50 mL
4 mL	96 mL	100 mL
10 mL	240 mL	250 mL
20 mL	480 mL	500 mL

In case the required concentration is 8 micrograms/mL:

Volume of TOMEXA 100 micrograms/mL concentrate for solution for infusion	**Volume of diluent**	**Total volume of infusion**
4 mL	46 mL	50 mL
8 mL	92 mL	100 mL
20 mL	230 mL	250 mL
40 mL	460 mL	500 mL

The solution should be shaken gently to mix well.

Administration with other fluids

TOMEXA has been shown to be compatible when administered with the following intravenous fluids and medicinal products:

Lactated ringers, 5 % glucose solution, sodium chloride 9 mg/mL (0,9 %) solution for injection, mannitol 200 mg/mL (20 %), thiopental sodium, etomidate, vecuronium bromide, pancuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, rocuronium bromide, glycopyrrolate bromide, phenylephrine HCl, atropine sulphate, dopamine, noradrenaline, dobutamine, midazolam, morphine sulphate, fentanyl citrate, and a plasma-substitute (e.g. Haemaccel).

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACORP (PTY) LTD

29 Victoria Link

Route 21 Corporate Park

Irene, 0178, RSA

8 REGISTRATION NUMBERS

TOMEXA 200 µg/2 mL: 56/2.9/0233

TOMEXA 400 µg/4 mL: 56/2.9/0234

TOMEXA 1 000 µg/10 mL: 56/2.9/0235

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 June 2024

10 DATE OF REVISION OF THE TEXT

24 February 2025