Teva Pharmaceuticals (Pty) Ltd.
Demetev, Concentrate for solution for Infusion
Each 1 ml of concentrate contains 100 µg dexmedetomidine (as hydrochloride).

APPROVED PROFESSIONAL INFORMATION

DEMETEV 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:

DEMETEV, 100 µg/ml, Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each ml of concentrate for solution for infusion contains dexmedetomidine hydrochloride equivalent to 100 micrograms of dexmedetomidine.

Each 2 ml vial contains dexmedetomidine hydrochloride equivalent to 200 micrograms of dexmedetomidine.

Each 4 ml vial contains dexmedetomidine hydrochloride equivalent to 400 micrograms of dexmedetomidine.

Each 10 ml vial contains dexmedetomidine hydrochloride equivalent to 1000 micrograms of dexmedetomidine.

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

Sugar free.

For the full list of excipients see **section 6.1**.

3. PHARMACEUTICAL FORM:

Concentrate for solution for infusion.

Clear, colourless solution. pH 4,5 -7,0.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

DEMETEV 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: DEMETEV should be administered only by health 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 DEMETEV.

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

DEMETEV should be administered by continuous intravenous infusion not to exceed 24 hours.

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

DEMETEV 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 DEMETEV. Patients receiving DEMETEV have been observed to be arousable and alert when stimulated. This is an expected component of dexmedetomidine sedation and should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms. DEMETEV has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post extubation. It is not necessary to discontinue dexmedetomidine prior to extubation.

Adults:

ICU Sedation:

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

Initiation:

For adult patients, it is recommended to initiate DEMETEV with a loading dose of 1,0 micrograms/kg over ten 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 in clinical studies.

A dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic or renal function and in patients over 65 years of age. (see **sections 4.3**; **4.4** and **5.2**).

Conscious Sedation:

Monitored anaesthesia care (MAC) with an adequate nerve block and awake fibreoptic intubation (AFI) DEMETEV dosing should be individualised and titrated to the desired clinical effect.

Initiation:

For adult patients, DEMETEV 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 DEMETEV 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.

Children:

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

Dosage Adjustment:

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

Impaired Hepatic Function:

Dosage reductions may need to be considered for patients with hepatic impairment, as DEMETEV is metabolised primarily in the liver (see **section 5.2**).

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 (see **section 5.2**).

Elderly population:

Since the elderly are more sensitive to the effects of DEMETEV dosage reductions may need to be considered (see **section 4.4**).

Directions for Use:

A controlled infusion device should be used to administer DEMETEV.

Parenteral products should be inspected visually for particulate matter and discolouration prior to administration.

Vials are intended for single patient use only.

For instructions on preparation of the solution refer to **section 6.6**.

Administration with other fluids:

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

Incompatibilities:

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

4.3 Contraindications:

- Known hypersensitivity to dexmedetomidine or to any of the excipients listed in **section 6.1**
- Patients with sepsis.
- Unstable trauma patients.
- Hypovolaemic patients.
- Uncontrolled cardiac failure.
- Imminent hepatic failure.

- Heart block
- Uncontrolled hypotension.
- Acute cerebrovascular conditions.

4.4 Special warnings and precautions for use:

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

Monitoring:

DEMETEV is intended for use in an intensive care setting or, operating room. The use in other environments is not recommended. All patients should have continuous cardiac monitoring during DEMETEV 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**).

General precautions:

DEMETEV 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 DEMETEV 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.

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

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

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

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

DEMETEV is not recommended for patient controlled sedation. Adequate data is not available.

Elderly:

Caution should be exercised when administering DEMETEV to elderly patients. Elderly patients over 65 years of age may be more prone to cardiovascular events e.g. hypotension and bradycardia with the administration of DEMETEV, including a loading dose, for procedures. A dose reduction should be considered. Close CVS monitoring is required. Refer to **section 4.2**.

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**). DEMETEV is therefore not suitable in patients with severe cardiovascular instability.

Caution should be exercised when administering dexmedetomidine to patients with pre-existing bradycardia. Data on the effects of DEMETEV 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 where needed. 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 pronounce haemodynamic changes after starting DEMETEV and so should be treated with care.

Transient hypertension has been observed primarily during the loading dose in association with the peripheral vasoconstrictive effects of DEMETEV 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 DEMETEV together with spinal or epidural anaesthesia 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 caution here, especially if deep sedation is required. Dexmedetomidine as contained in DEMETEV may reduce cerebral blood flow and intracranial pressure and this should be considered when selecting therapy.

Other:

Alpha-2 agonists, including DEMETEV, 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 DEMETEV.

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

DEMETEV contains less than 1 mmol sodium (23 mg) per ml.

4.5 Interaction with other medicines and other forms of interaction:

Interaction studies have only been performed in adults.

Anaesthetics/Sedatives/Hypnotics and Opioids:

Co-administration of DEMETEV with anaesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects, including sedative, anaesthetic 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 DEMETEV, a reduction in dosage of DEMETEV or the concomitant anaesthetic, sedative, hypnotic or opioid may be required.

Cytochrome P-450:

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 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:

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

Studies in animals have shown reproductive toxicity (see **section 5.3**). DEMETEV is not recommended during pregnancy.

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.

The use of DEMETEV is not recommended in lactating women.

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:

Patients should be advised to refrain from driving or other hazardous tasks for a suitable period of time after receiving DEMETEV for procedural sedation.

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)

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Tabulated list of adverse reactions:

The adverse reactions listed in Table 1 below with an incidence > 2 % - ICU Sedation Population and Conscious Sedation Population

Metabolism and nutrition disorders	
Frequent	Hyperglycaemia, hypoglycaemia
Less frequent	Metabolic acidosis, hypo-albuminaemia
Frequency unknown	Hypovolaemia, hypocalcaemia, acidosis
Psychiatric disorders	
Frequent	Agitation
Less frequent	Hallucination
Blood and lymphatic system disorders	
Frequency unknown	Anaemia
Cardiac disorders	
Frequent	Bradycardia[1,2], myocardial ischaemia or infarction, tachycardia
Less frequent	Atrioventricular block[1], cardiac output decreased, cardiac arrest[1]
Frequency unknown	Atrial fibrillation, sinus tachycardia, ventricular tachycardia
Vascular disorders	
Frequent	Hypotension[1,2], hypertension[1,2]
Gastrointestinal disorders	
Frequent	Nausea[2], vomiting, dry mouth[2]
Less frequent	Abdominal distension
Renal and urinary disorders	

Frequency unknown	Polyuria
General disorders and administration site conditions	
Frequent	Withdrawal syndrome, hyperthermia
Less frequent	Drug ineffective, thirst
Frequency unknown	Pyrexia, chills, peripheral oedema
Injury, poisoning and procedural complications	
Frequency unknown	Post-procedural haemorrhage
Investigations	
Frequency unknown	Urine output decreased

[1] See section on Description of selected adverse reactions

[2] Adverse reaction observed also in procedural sedation studies

[3] Incidence frequent in ICU sedation studies

Table 2 - Adverse Events Experienced During Post-Approval Use of Demetev

MedDRA SOC	*Frequency unknown:*
General disorders and administration site conditions	Allergic reaction, ascites, hyperpyrexia, light anaesthesia, oedema, pain, syncope, fever, rigors
Cardiac disorders	Blood pressure fluctuation, circulatory failure, cyanosis, abnormal ECG, heart disorder, aggravated hypertension, pulmonary hypertension, postural hypotension, dysrhythmia, atrial dysrhythmia, AV block, bundle branch block, extrasystoles, heart block, supraventricular tachycardia, T wave

	inversion, ventricular dysrhythmia, ventricular tachycardia, angina pectoris
Nervous system disorders	Haemorrhage, cerebral haemorrhage, peripheral ischaemia, convulsion, dizziness, headache, neuralgia, neuritis, neuropathy, paraesthesia, paralysis, paresis, speech disorder
Gastrointestinal disorders	Abdominal pain, diarrhoea, eructation, mucosal ulceration; nausea, vomiting
Hepato-biliary disorders	Increased AG ratio, increased GGT, abnormal hepatic function, hyperbilirubinaemia, alanine transaminase, aspartate aminotransferase, increased aspartate transaminase (AST), increased alanine transaminase (ALT), jaundice, increased alkaline phosphatase, jaundice
Metabolism and nutrition disorders	Respiratory acidosis, diabetes mellitus, hypoglycaemia, hypokalaemia, hyperkalaemia, hypoproteinaemia, increased Non-protein nitrogen (NPN); thirst
Musculoskeletal and connective tissue disorders	Muscle weakness

Blood and lymphatic system disorders	Coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased prothrombin, thrombocytopenia, leucocytosis, anaemia
Psychiatric Disorders	Agitation, anxiety, confusion, delirium, depression, illusion/hallucinations, nervousness
Renal and urinary disorders	Increased blood urea, oliguria, haematuria, acute renal failure, abnormal renal function, urinary retention
Infections and infestations	Infection, fungal infection, sepsis
Respiratory, thoracic and mediastinal disorders	Adult respiratory distress syndrome, bronchial obstruction, bronchospasm, coughing, emphysema, haemoptysis, hypercapnia, hypoventilation, pharyngitis, pleurisy, pneumonia, pneumothorax, pulmonary congestion, respiratory disorder, respiratory insufficiency, increased sputum, stridor
Skin and subcutaneous tissue disorders	Rash erythematous, increased sweating
Vascular disorders	Vascular disorder, vasodilation
Eye disorders	Diplopia, photopsia, abnormal vision

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 microgram/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 authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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 in these cases have reached up to 60 µg/kg/h for 36 minutes and 30 µg/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, DEMETEV 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 a selective alpha-2 receptor agonist with a broad range of pharmacological properties. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. The sedative effects are mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem. Dexmedetomidine has analgesic and anaesthetic/analgesic-sparing effects. The cardiovascular effects depend on the dose; with lower infusion rates the central effects dominate leading to decrease in heart rate and blood pressure. With higher doses, peripheral vasoconstricting

effects prevail leading to an increase in systemic vascular resistance and blood pressure, while the bradycardic effect is further emphasised. Dexmedetomidine is relatively free from respiratory depressive effects when given as monotherapy to healthy subjects.

5.2 Pharmacokinetic properties:

The pharmacokinetics of dexmedetomidine has been assessed following short term IV administration in healthy volunteers and long term infusion in ICU population.

Distribution:

Dexmedetomidine exhibits a two-compartment disposition model. In healthy volunteers it exhibits a rapid distribution phase with a central estimate of the distribution half-life ($t_{1/2}\alpha$) of about 6 minutes. The mean estimate of the terminal elimination half-life ($t_{1/2}$) is approximately 2 hours and the mean estimate of the steady-state volume of distribution (Vss) is approximately

118 L. Plasma clearance (Cl) has a mean estimated value of about 39 L/hr. The mean body weight associated with these Vss and Cl estimates was 69 kg. Plasma pharmacokinetics of dexmedetomidine is similar in the ICU population following infusion >24 h. The estimated pharmacokinetic parameters are: $t_{1/2}$ approximately 1,5 hours, Vss approximately 93 litres and Cl approximately 43 l/h. The pharmacokinetics of dexmedetomidine is linear in the dosing range from 0,2 to 1.4 µg/kg/h and it does not accumulate in treatments lasting up to 14 days. Dexmedetomidine is 94 % bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0,85 to 85 ng/ml. Dexmedetomidine binds to both human serum albumin and Alpha-1-acid glycoprotein with serum albumin as the major binding protein of dexmedetomidine in plasma.

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. 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:

Following IV administration of radio-labeled dexmedetomidine an average

95 % of radioactivity was recovered in the urine and 4 % in the faeces after nine days. The major urinary metabolites were the two isomeric N-glucuronides, which together accounted for approximately 34 % of the dose. Less than 1 % of unchanged parent drug was recovered in the urine.

Special Populations:

No major pharmacokinetic differences have been observed based on gender or age.

Hepatic impairment:

Dexmedetomidine plasma protein binding is decreased in subjects with hepatic impairment compared with healthy subjects. Subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C) had decreased hepatic clearance of dexmedetomidine and prolonged plasma elimination $t_{1/2}$. The mean plasma clearance values of unbound dexmedetomidine for subjects with mild, moderate, and severe hepatic impairment were 59 %, 51 % and 32 % of those observed in the normal healthy subjects, respectively. The mean $t_{1/2}$ for the subjects with mild, moderate or severe hepatic impairment was prolonged to 3,9; 5,4, and 7,4 hours, respectively. Although dexmedetomidine is administered to effect, it may be necessary to consider

initial/maintenance dose reduction in patients with hepatic impairment depending on the degree of impairment and the response (see **section 4.2** and **4.4**).

Renal impairment:

The pharmacokinetics of dexmedetomidine in subjects with severe renal impairment (creatinine clearance <30 ml/min) is not altered relative to healthy subjects.

5.3 Preclinical safety data:

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity.

In the reproductive toxicity studies, dexmedetomidine had no effect on male or female fertility in the rat, and no teratogenic effects were observed in the rat or rabbit.

In the rat, subcutaneous administration at the maximum dose, 200 µg/kg/day, caused an increase in embryofetal death and reduced the fetal body weight. These effects were associated with clear maternal toxicity. Reduced fetal body weight was noted also in the rat fertility study at dose 18 µg/kg/day and was accompanied with delayed ossification at dose 54 µg/kg/day. The observed exposure levels in the rat are below the clinical exposure range.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Sodium chloride

Water for injections

6.2 Incompatibilities:

DEMETEV must not be mixed with other medicines 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:

2 years

After dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °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 the use are the responsibility of the user and would not normally be longer than 24 hours at 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage:

Store at or below 25 °C.

Store in the original package in order to protect from light.

For storage conditions after dilution of the medicine, see **section 6.3**.

6.5 Nature and contents of container:

DEMETEV 200 micrograms/2 ml: Type I transparent, sulphur treated, glass vial (3 ml or 2R) closed with grey chlorobutyl rubber stopper and green-blue polypropylene cover.

DEMETEV 400 micrograms/4 ml: Type I transparent, sulphur treated, glass vial (6R) closed with grey chlorobutyl rubber stopper and white polypropylene cover.

DEMETEV 1 000 micrograms/10 ml: Type I transparent, sulphur treated, glass vial (10R) closed with grey chlorobutyl rubber stopper and white polypropylene cover.

Pack sizes: 1, 5, 25 x 2 ml; 4 x 4 ml and 4 x 10 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

Vials are intended for single patient use only.

Preparation of solution:

Strict aseptic technique must always be maintained during handling of DEMETEV infusion.

Preparation of infusion solutions is the same, whether for the loading dose or for the maintenance dose.

DEMETEV 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.

If required concentration is 4 micrograms/ml:

Volume of DEMETEV 100 micrograms/ml	**Volume of diluent**	**Total volume of infusion**

concentrate for solution for 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

If required concentration is 8 micrograms/ml:

Volume of DEMETEV 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	350 ml
40 ml	460 ml	500 ml

The solution should be shaken gently to mix well.

DEMETEV should be inspected visually for particulate matter and discoloration prior to administration.

DEMETEV has been shown to be compatible when administered with the following intravenous fluids and medicines:

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 sulfate, dopamine, noradrenaline, dobutamine, midazolam, morphine sulfate, fentanyl citrate, and a plasma-substitute.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

8. REGISTRATION NUMBER:

51/2.9/0984

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

18 January 2022

10. DATE OF REVISION OF THE TEXT: