PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

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

1. NAME OF THE MEDICINE

Demodinex Concentrated solution for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of concentrated solution contains dexmedetomidine hydrochloride equivalent to 100 micrograms dexmedetomidine.

Sugar free.

Contains sodium chloride: 9 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrated solution for intravenous infusion.

A clear, colourless solution, pH 4,5 – 7,0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Demodinex is an alpha2-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 has not been studied in children under 18 years of age.

4.2 Posology and method of administration

Posology

NOTE: Demodinex 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 **Demodinex**.

In order to minimise undesirable pharmacologic side effects, bolus injections of **Demodinex** 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.

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

Demodinex 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 **Demodinex**. Patients receiving **Demodinex** 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. **Demodinex** 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

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

Initiation:

For adult patients, it is recommended to initiate **Demodinex** with a loading dose of 1,0 microgram/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 micrograms/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 section 4.3, 4.4 and 5.2)

Conscious Sedation

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

Initiation

For adult patients, **Demodinex** is generally initiated with a loading infusion of 1 (one) mcg/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 mcg/kg over 10 minutes may be suitable.

Maintenance of Conscious Sedation:

MAC – Following the load, maintenance dosing of **Demodinex** should generally be initiated at 0,6 mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0,2 to 1 mcg/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 mcg/kg/hr should be used.

Paediatric population:

Safety and efficacy of **Demodinex** 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 **Demodinex** 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 **Demodinex** 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 population

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

Method of administration

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

A controlled infusion device should be used to administer **Demodinex**.

Ampoules/vials are intended for single patient use only.

See section 6.6 for the preparation of infusion solutions and administration with other fluids.

4.3 Contraindications

Demodinex is contraindicated in

- Patients with a known hypersensitivity to dexmedetomidine or to any of the excipients listed in section 6.1.
- Patients with sepsis.
- Unstable trauma patients.
- Hypovolemic patients.
- Heart block
- Uncontrolled cardiac failure.
- Imminent hepatic failure
- Uncontrolled hypotension
- Acute cerebrovascular conditions

4.4 Special warnings and precautions for use

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

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

Clinical events of bradycardia and sinus arrest have been associated with **Demodinex** administration in some young, healthy volunteers with high vagal tone, or with different

routes of administration including rapid intravenous or bolus administration of **Demodinex**. Bolus injections of **Demodinex** 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 dexmedetomidine.

Monitoring

Dexmedetomidine is intended for use in an intensive care setting, operating room and during diagnostic procedures. The use in other environments is not recommended. Continuous electrocardiogram (ECG), blood pressure and oxygen saturation monitoring are mandatory during infusion of **Demodinex**.

The time to recovery after the use of dexmedetomidine was reported to be approximately one hour.

Interference with daily activities may continue for up to 24 hours and no legal/contractual decisions should be entered into for 24 hours after receiving anaesthetic/conscious sedation. Alcohol should also be avoided for the same time period.

Some patients receiving dexmedetomidine 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.

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

Demodinex should not be used as a general anaesthetic induction medicine 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 action as additive effects may occur.

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

Hypotension, Bradycardia and Sinus arrest

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

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

Demodinex decreases sympathetic nervous activity and therefore, these effects may be expected to be most pronounced in patients with desensitised autonomic nervous system control (i.e. 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 **Demodinex**. Patients who are hypovolaemic may become hypotensive under Demodinex therapy. Therefore, fluid supplementation should be administered prior to and during the administration of **Demodinex**.

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.

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

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

Transient Hypertension

Transient hypertension has been observed primarily during the loading infusion, associated with initial peripheral vasoconstrictive effects of dexmedetomidine 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 **Demodinex** dominate and the blood pressure usually decreases.

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 anaesthesia due to possible increased risk of hypotension or bradycardia.

Patients with hepatic impariment

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

Other

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 stoppping dexmedetomidine.

Dexmedetomidine may induce hyperthermia that may be resistant to traditional cooling methods.

Dexmedetomidine treatment should be discontinued in the event of a susstained unexplained fever and is not recommended for use in malignant hyperthermia-sensitive

patients.

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

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

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P450

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

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.

Anaesthetics/Sedatives/Hypnotics/Opioids

Co-administration of **Demodinex** 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 and isoflurane, propofol, alfentanil, and midazolam were demonstrated. However, due to pharmacodynamic effects, when co-administered with **Demodinex** a reduction in dosage of these agents may be required.

Neuromuscular Blockers

No clinically meaningful increases in the magnitude of neuromuscular blockade and no pharmacokinetic interactions were observed with dexmedetomidine and rocuronium administration.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. The use of **Demodinex** is not recommended in pregnancy.

Labour and Delivery

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

Lactation

Dexmedetomidine is excreted in human milk. The use of **Demodinex** is not recommended in lactating women.

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 surgical procedure in which **Demodinex** was used.

4.8 Undesirable effects

The most frequently observed treatment-emergent adverse events include hypotension, hypertension, bradycardia, nausea, dry mouth and hypoxia. (see section 4.4)

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	*Frequency unknown*	Infection, fungal infection, sepsis
Blood and lymphatic system disorders	*Frequency unknown*	Coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased

		prothrombin, thrombocytopenia, anaemia, leukocytosis
Metabolism and nutrition disorders	*Frequent*	Hyperglycaemia, hypoglycaemia
	Less frequent	Metabolic acidosis hypoalbuminaemia
	Frequency unknown	lactic acidosis, respiratory acidosis, diabetes mellitus, hypokalaemia, hyperkalaemia, hypoproteinaemia, increased alkaline phosphatase, increased non-protein nitrogen (NPN), thirst
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*	Bradycardia, myocardial ischaemia or infarction, tachycardia
	Less frequent	Atrioventricular block, cardiac output decreased, cardiac arrest,
	Frequency unknown	abnormal ECG, heart disorder, dysrhythmia, atrial dysrhythmia, atrial fibrillation, bundle branch block, extrasystoles, heart block, hypoxia, supraventricular tachycardia, T wave inversion, tachycardia, ventricular dysrhythmia, ventricular tachycardia, angina pectoris
Vascular disorders	*Frequent*	Hypotension, hypertension
	Frequency unknown	Blood pressure fluctuation, circulatory failure, cyanosis,

		aggravated hypertension, pulmonary hypertension, postural hypotension, pulmonary hypertension, Haemorrhage, cerebral haemorrhage, peripheral ischaemia, vascular disorder, vasodilation
Respiratory, thoracic and mediastinal disorders	*Frequent*	Respiratory depression
	Less frequent	Dyspnoea, apnoea
	Frequency unknown	Adult respiratory distress syndrome, bronchial obstruction, bronchospasm, coughing, emphysema, haemoptysis, hypercapnia, hypoventilation, hypoxia, pharyngitis, pleurisy, pneumonia, pneumothorax, pulmonary congestion, pulmonary oedema, respiratory disorder, respiratory insufficiency, increased sputum, stridor

Gastrointestinal disorders	*Frequent*	Nausea, vomiting, dry mouth
	Less frequent	Abdominal distension
	Frequency unknown	Abdominal pain, abdominal distension, diarrhoea, eructation, mucosal ulceration,
Hepato-biliary disorders	*Frequency unknown*	Increase AG ratio, increased GGT, abnormal hepatic function, hyperbilirubinaemia, alanine transaminase, aspartate aminotransferase, increased aspartate transaminase (AST), increased alanine transaminase (ALT), jaundice
Skin and subcutaneous tissue disorders	*Frequency unknown*	Rash erythematous, increased sweating
Musculoskeletal and connective tissue disorders	*Frequency unknown*	Muscle weakness
Renal and urinary disorders	*Frequency unknown*	Increased blood urea, oliguria, haematuria, acute renal failure, abnormal renal function, urinary retention, polyuria

General disorders	*Frequent*	Withdrawal syndrome, hyperthermia
	Less frequent	Drug ineffective, thirst
	Frequency unknown	Allergic reaction, ascites, fever, hyperpyrexia, hypovolaemia, light anaesthesia, oedema, peripheral oedema, pain, syncope, rigors

Withdrawal

ICU Sedation

Although not specifically studied, withdrawal symptoms similar to those reported for another alpha2 adrenergic agent (clonidine) may result when **Demodinex** 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 dexmedetomidine (< 6 hours)

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**", found online under SAHPRA's publications:

https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

First-degree AV block and second-degree heart block may occur.

The most frequent adverse reactions reported in conjunction with overdose include bradycardia, hypotension, hypertension, oversedation, respiratory depression and cardiac arrest.

Because **Demodinex** has the potential to augment bradycardia induced by vagal stimuli, doctors should be prepared to intervene. In clinical trials, atropine and glycopyrrolate were effective in the treatment of dexmedetomidine-induced bradycardia

Management

In cases of overdose with clinical symptoms, dexmedetomidine 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

Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives, ATC code: N05CM18

Pharmacological classification: A 2.9 Other Analgesics.

Dexmedetomidine is an alpha2-adrenoreceptor agonist.

The sedative actions of dexmedetomidine are believed to be mediated primarily by post-synaptic alpha2-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 ceruleus. The analgesic actions are believed to be mediated by a similar mechanism of action at the brain and spinal cord level.

Alpha2, selectivity is demonstrated following low and medium doses given slowly. Alpha2 and alpha1 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 of dexmedetomidine, dexmedetomidine exhibits the following pharmacokinetic characteristics: rapid distribution phase with a distribution half-life ($t_{1/2\alpha}$) of about six minutes; terminal elimination half-life ($t_{1/2}$) of approximately two hours; steady-state volume of distribution (Vss) 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.

Biotransformation and 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 ar eproducts of N-glucuronidation.

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 of 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.

Pharmacokinetics in 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 drug 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 the degree of hepatic impairment.

Renal Insufficiency:

Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2}$, CL and Vss) 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

Demodinex must not be mixed with other medicinal product or diluents except those mentioned in section 6.6.

6.3 Shelf life

24 months

After dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 ºC. From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, 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.

6.4 Special precautions for storage

Store in the original container at or below 25 °C. Do not refrigerate.

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

6.5 Nature and contents of container

Available in colourless 3 ml glass ampoules and vials, in packs of 5.

6.6 Special precautions for disposal and other handling

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

Preparation of Solution

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

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

To prepare the infusion, withdraw 2 ml of **Demodinex** concentrate and add to 48 ml of 0,9 % sodium chloride solution to total 50 ml. Shake gently to mix well.

After dilution, **Demodinex** is intended for immediate use and should be discarded after 24 hours.

Administration with other fluids

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

Lactated Ringers, 5 % Dextrose in Water, 0,9 % Sodium Chloride in Water, 20 % Mannitol, thiopental sodium, etomidate, vercuronium bromide, pancuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, glycopyrrolate bromide, phenylephrine HCI, atropine sulphate, midazolam, morphine sulphate, fentanyl citrate and a plasma-substitute (i.e. Haemacel).

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

MYLAN (PTY) LTD

4 Brewery Street

Isando

Gauteng

Republic of South Africa

8. REGISTRATION NUMBER

50/2.9/1064

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 May 2022

10. DATE OF REVISION OF THE TEXT