1.3.1.1 PROPOSED PI

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S 4

1 NAME OF THE MEDICINE

DESREM 100 mg/vial Lyophilized Powder for Injection for IV Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of remdesivir.

Each ml of concentrate contains 5 mg of remdesivir.

DESREM 100 mg vial contains 3 g sulfobutylether-β-cyclodextrin sodium salt (SBECD). For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lyophilized powder for injection for IV infusion.

White to off-white to yellow lyophilized powder or lumps or solid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DESREM is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia requiring supplemental oxygen (see section 5.1).

4.2 Posology and method of administration

Use of DESREM is confined to healthcare facilities in which patients can be monitored closely (see section 4.4).

Posology

The recommended dosage of DESREM is:

• Day 1 – single loading dose of DESREM 200 mg given by intravenous infusion.

• Day 2 onwards – 100 mg given once daily by intravenous infusion.

The total duration of treatment should be at least 5 days and not more than 10 days.

Special populations

Elderly

No dose adjustment of DESREM is required in patients over the age of 65 years (see sections 5.1 and 5.2).

Renal impairment

The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Patients with eGFR ≥ 30 ml/min have received remdesivir for treatment of COVID-19 with no dose adjustment. DESREM should not be used in patients with eGFR < 30 ml/min (see sections 4.4 and 5.2).

Hepatic impairment

The pharmacokinetics of remdesivir have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment (see section 4.4 and 5.2).

Paediatric population

The safety and efficacy of DESREM in children under the age of 18 years have

not yet been established. No data are available.

Method of administration

For intravenous use.

DESREM is for administration by intravenous infusion after further dilution.

It must not be given as an intramuscular (IM) injection.

Table 1: Recommended rate of infusion – for diluted remdesivir concentrate for solution for infusion

Infusion Bag	Volume Infusion Time	Rate of Infusion
250 ml	30 min	8,33 ml/min
	60 min	4,17 ml/min
	120 min	2,08 ml/min
100 mL	30 min	3,33 mL/min
	60 min	1,67 mL/min
	120 min	0,83 mL/min

4.3 Contraindications

- Hypersensitivity to remdesivir or to any of the excipients of DESREM (see section 6.1).

4.4 Special warnings and precautions for use

Hypersensitivity including infusion-related and anaphylactic reactions

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of DESREM. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia,

hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of DESREM and initiate appropriate treatment.

Transaminase elevations

Transaminase elevations have been observed in the remdesivir clinical trials, including in healthy volunteers and patients with COVID-19. Liver function should be determined in all patients prior to starting DESREM and should be monitored while receiving it as clinically appropriate. No clinical studies with remdesivir have been conducted in patients with hepatic impairment.

DESREM should not be initiated in patients with Alanine Aminotransferase (ALT) ≥ 5 times the upper limit of normal at baseline

- DESREM should be discontinued in patients who develop:
    - ALT ≥ 5 times the upper limit of normal during treatment with remdesivir. It may be restarted when ALT is <5 times the upper limit of normal.

OR

- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR) (see sections 4.8 and 5.2).

Renal impairment

In animal studies on rats and monkeys, severe renal toxicity was observed. The mechanism of this renal toxicity is not fully understood. A relevance for humans cannot be excluded.

All patients should have eGFR determined prior to starting DESREM and while receiving it as clinically appropriate. Remdesivir should not be used in patients with eGFR < 30 ml/min.

Risk of reduced antiviral activity when co-administered with chloroquine or hydroxychloroquine

Co-administration of DESREM and chloroquine phosphate or hydroxychloroquine sulphate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir (see section 4.5, 5.1).

Excipients

DESREM contains sulfobutylether-β-cyclodextrin sodium salt (SBECD), which is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function. Therefore, DESREM should not be used in patients with eGFR < 30 ml/min (see sections 4.2 and 5.2).

4.5 Interaction with other medicines and other forms of interaction

No clinical interaction studies have been performed with remdesivir. The overall potential for interactions is currently unknown; patients should remain under close observation during the days of remdesivir administration. Due to antagonism

observed *in vitro*, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulphate is not recommended.

Effects of other medicines on DESREM

In vitro, DESREM is a substrate for esterases in plasma and tissue, metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters.

The potential of interaction of DESREM with inhibitors/inducers of the hydrolytic pathway (esterase) or CYP2C8, 2D6 or 3A4 has not been studied. The risk of clinically relevant interaction is unknown.

Strong inhibitors may result in increased DESREM exposure. The use of strong inducers (e.g. rifampicin) may decrease plasma concentrations of remdesivir and is not recommended.

Dexamethasone is reported to be a moderate inducer of CYP3A and P-gp. Induction is dose-dependent and occurs after multiple doses. Dexamethasone is unlikely to have a clinically significant effect on DESREM as DESREM has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19.

Effects of DESREM on other medicines

In vitro, DESREM is an inhibitor of CYP3A4, OATP1B1 and OATP1B3. The clinical relevance of these *in vitro* interactions has not been established. DESREM may transiently increase plasma concentrations of medicines that are substrates of

CYP3A or OATP 1B1/1B3. No data is available, however it can be suggested that medicines that are substrates of CYP3A4 or substrates of OATP 1B1/1B3 should be administered at least 2 hours after DESREM. DESREM induced CYP1A2 and potentially CYP3A *in vitro*. Co-administration of DESREM with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy. Dexamethasone is a substrate of CYP3A4 and although DESREM inhibits CYP3A4, due to remdesivir's rapid clearance after I.V administration, DESREM is unlikely to have a significant effect on dexamethasone exposure.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in males and females

Women of child-bearing potential have to use effective contraception during treatment.

Pregnancy

There are no or limited amount of data from the use of DESREM in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. DESREM should not be used during pregnancy.

Breast-feeding

It is unknown whether DESREM is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production.

In animal studies, the nucleoside analog metabolite GS-441524 has been detected in the blood of nursing rat pups of mothers given remedesivir. Therefore, excretion of remdesivir and/or metabolites into the milk of lactating animals can be assumed.

Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the medicine in breast-feeding infants, mothers receiving DESREM should not breast-feed their infants.

Fertility

No human data on the effect of remdesivir on fertility are available. In male rats, there was no effect on mating or fertility with remdesivir treatment. In female rats, however, an impairment of fertility was observed. The relevance for humans is unknown.

4.7 Effects on ability to drive and use machines

Patients receiving DESREM must not drive or use machines until all side effects of the medicine and the symptoms of SARS-CoV-2 infection, have resolved.

4.8 Undesirable effects

a. Summary of the safety profile

The most common adverse reaction in healthy volunteers is increased transaminases (14 %). The most common adverse reaction in patients with COVID-19 is nausea (4 %).

b. Tabulated summary of adverse reactions

The adverse reactions in the table are listed below by system organ class and frequency.

System organ class	**Frequency**	**Adverse reactions**
Immune system disorders	Less frequent Frequency hot known	Hypersensitivity Anaphylactic reaction
Nervous system disorders	Frequent	Headache
Cardiac disorders	Frequency not known	Sinus bradycardia
Gastrointestinal disorders	Frequent	Nausea
Hepatobiliary disorders	Frequent	Transaminases increased
Skin and subcutaneous tissue disorders	Frequent	Rash
Injury, poisoning and procedural complications	Less frequent	Infusion-related reaction
Investigations	Frequent	Prothrombin time prolonged

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

Treatment of overdose with DESREM should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with DESREM.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, other antivirals, ATC code: J05AB16.

Mechanism of Action

Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolized to form the pharmacologically active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent

RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA.

As an additional mechanism, remdesivir triphosphate can also inhibit viral RNA synthesis following its incorporation into the template viral RNA as a result of read-through by the viral polymerase that may occur in the presence of higher nucleotide concentrations. When remdesivir nucleotide is present in the viral RNA template, the efficiency of incorporation of the complementary natural nucleotide is compromised, thereby inhibiting viral RNA synthesis.

Antiviral Activity

Remdesivir exhibited cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial (HAE) cells with a 50 % effective concentration (EC_{50}) of 9,9 nM after 48 hours of treatment. The EC_{50} values of remdesivir against SARS-CoV-2 in Vero cells was 137 nM at 24 hours and 750 nM at 48 hours post-treatment. The antiviral activity of remdesivir was antagonised by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC50 values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in normal human bronchial epithelial cells.

Resistance

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified 2 substitutions (F476L and V553L) in the viral RNA-dependent RNA

polymerase at residues conserved across CoVs that conferred 5.6-fold reduced susceptibility to remdesivir. Introduction of the corresponding substitutions (F480L and V557L) into SARS-CoV resulted in 6-fold reduced susceptibility to remdesivir cell culture and attenuated SARS-CoV pathogenesis in a mouse model.

The cell culture development of SARS-CoV-2 resistance to remdesivir has not been assessed to date. No clinical data are available on the development of SARS-CoV-2 resistance to remdesivir.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of remdesivir has been investigated in healthy volunteers. No pharmacokinetic data is available from patients with COVID-19.

Absorption

The pharmacokinetic properties of remdesivir and the predominant circulating metabolite GS-441524 have been evaluated in healthy adult subjects. Following intravenous administration of remdesivir adult dosage regimen, peak plasma concentration was observed at end of infusion, regardless of dose level, and declined rapidly thereafter with a half-life of approximately 1 hour. Peak plasma concentrations of GS-441524 were observed at 1.5 to 2.0 hours post start of a 30 minutes infusion.

Distribution

Remdesivir is approximately 93 % bound to human plasma proteins (ex-vivo data) with free fraction ranging from 6,4 % to 7,4 %. The binding is independent of drug concentration over the range of 1 to 10 µM, with no evidence for saturation of remdesivir binding. Protein binding of GS-441524 was low (2 %

bound) in human plasma. After a single 150 mg dose of [14C]-remdesivir in healthy subjects, the blood to plasma ratio of 14C-radioactivity was approximately 0,68 at 15 minutes from start of infusion, increased over time reaching ratio of 1,0 at 5 hours, indicating differential distribution of remdesivir and its metabolites to plasma or cellular components of blood.

Biotransformation

Remdesivir is extensively metabolized to the pharmacologically active nucleoside analog triphosphate GS-443902 (formed intracellularly). The metabolic activation pathway involves hydrolysis by esterases, which leads to the formation of the intermediate metabolite, GS-704277. Phosphoramidate cleavage followed by phosphorylation forms the active triphosphate, GS-443902. Dephosphorylation of all phosphorylated metabolites can result in the formation of nucleoside metabolite GS-441524 that itself is not efficiently re-phosphorylated. The human mass balance study also indicates presence of a currently unidentified major metabolite (M27) in plasma.

Elimination

Following a single 150 mg IV dose of [14C]-remdesivir, mean total recovery of the dose was 92 %, consisting of approximately 74 % and 18 % recovered in urine and feces, respectively. The majority of the remdesivir dose recovered in urine was GS-441524 (49 %), while 10 % was recovered as remdesivir.

These data indicate that renal clearance is the major elimination pathway for GS-441524. The median terminal half-lives of remdesivir and GS-441524 were approximately 1 and 27 hours, respectively.

Specific Populations

Gender, Race and Age

Pharmacokinetic differences based on gender, race, and age have not been evaluated.

Renal Impairment

The pharmacokinetics of remdesivir and GS-441524 in renal impairment has not been evaluated. Remdesivir is not cleared unchanged in urine to any substantial extent, but its main metabolite GS-441524 is renally cleared and the metabolite levels in plasma may theoretically increase in patients with impaired renal function. The excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function. Remdesivir should not be used in patients with eGFR <30 ml/min.

Hepatic impairment

The pharmacokinetics of remdesivir and GS-441524 in hepatic impairment has not been evaluated. The role of the liver in the metabolism of remdesivir is unknown.

Paediatric Patients

The pharmacokinetics of remdesivir in paediatric patients has not been evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid and/or sodium hydroxide (for pH adjustment)

Sulfobutylether-β-cyclodextrin sodium salt (SBECD).

6.2 Incompatibilities

DESREM must not be mixed or administered simultaneously with other medicines in the same dedicated line except those mentioned in section 4.2.

6.3 Shelf life

Unopened vials: 24 months.

For storage conditions after dilution of DESREM, see section 6.4.

6.4 Special precautions for storage

Store at or below 30 °C.

After reconstitution, vials can be stored up to 4 hours at room temperature (20°C to 25°C) prior to administration or 24 hours at refrigerated temperature (2°C to 8°C). Dilute within the same day as administration.

IMPORTANT:

This medicine contains no preservative. Any unused portion of a single-dose DESREM vial should be discarded after a diluted solution is prepared. Maintain adequate records showing receipt, use, and disposition of DESREM. For unused intact vials, maintain adequate records showing disposition of DESREM; do not discard unused intact vials.

6.5 Nature and contents of container

DESREM is packed in 30 ml/20 mm flint moulded glass vial, Type I, USP & Ph. Eur, plugged with 20 mm grey/dark grey bromobutyl lyo stopper and 20 mm white flip off aluminium seal. Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

Prepare solution for infusion under aseptic conditions and on the same day as administration.

DESREM should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Should either be observed, the solution should be discarded and fresh solution prepared.

DESREM must be reconstituted with 19 ml sterile water for injections and diluted in sodium chloride 9 mg/ml (0,9 %) solution for injection before being administered via intravenous infusion over 30 to 120 minutes.

Preparation of DESREM solution for infusion

Reconstitution

Remove the required number of single-use vial(s) from storage. For each vial:

- Aseptically reconstitute DESREM powder for concentrate for solution for infusion by addition of 19 ml of sterile water for injections using a suitably sized syringe and needle per vial.
- Discard the vial if a vacuum does not pull the sterile water for injections into the vial.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result.
- If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved.

- Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
- Dilute immediately after reconstitution.

Dilution

Care should be taken to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this medicine, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medicines immediately after preparation when possible.

- Using Table 2, determine the volume of sodium chloride 9 mg/ml (0,9 %) solution for injection to withdraw from the infusion bag.

Table 2: Recommended dilution instructions – Reconstituted DESREM powder for concentrate for solution for infusion

DESREM dose	Sodium chloride 9 mg/ml (0,9 %) infusion bag volume to be used	Volume to be withdrawn and discarded from sodium chloride 9 mg/ml (0,9 %) infusion bag	Required volume of reconstituted DESREM
200 mg (2 vials)	250 ml	40 ml	2 × 20 ml
	100 ml	40 ml	2 × 20 ml
100 mg (1 vial)	250 ml	20 ml	20 ml
	100 ml	20 ml	20 ml

NOTE: 100 ml should be reserved for patients with severe fluid restriction, e.g. with ARDS or renal failure.

- Withdraw and discard the required volume of sodium chloride 9 mg/ml from the bag using an appropriately sized syringe and needle per Table 2. Withdraw the required volume of reconstituted DESREM powder for concentrate for solution for infusion using an appropriately sized syringe per Table 2. Discard any unused portion remaining in the DESREM vial.
- Transfer the required volume of reconstituted DESREM powder for concentrate for solution for infusion to the selected infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared solution is stable for 4 hours at room temperature (20 °C to 25 °C) or 24 hours in the refrigerator (2 °C to 8 °C) (including any time before dilution into intravenous infusion fluids).
- After infusion is complete, flush with at least 30 ml of sodium chloride 9 mg/ml.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

MYLAN (PTY) LTD

4 Brewery street

Isando

Gauteng

Republic of South Africa

8 REGISTRATION NUMBER

DESREM: TBA

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date on the registration certificate of the medicine.

10 DATE OF REVISION OF THE TEXT