**Product Information as approved by the CHMP on 25 June 2020, pending endorsement by the European Commission**

# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Veklury 100 mg concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of remdesivir.
Each mL of concentrate contains 5 mg of remdesivir.

Excipients with known effect

Each vial contains 6 g betadex sulfobutyl ether sodium

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).
Clear, colorless to yellow, aqueous-based concentrated solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (see section 5.1).

### 4.2 Posology and method of administration

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

Posology

The recommended dosage of remdesivir in patients 12 years of age and older and weighing at least 40 kg is:
- Day 1 – single loading dose of remdesivir 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 remdesivir 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. Remdesivir 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 remdesivir in children under the age of 12 years and weighing <40 kg have not yet been established. No data are available.

Method of administration

For intravenous use.

Remdesivir is for administration by intravenous infusion after further dilution.

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

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

**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 |

## 4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in 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 remdesivir. 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 remdesivir 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 remdesivir and should be monitored while receiving it as clinically appropriate. No clinical studies with remdesivir have been conducted in patients with hepatic impairment. Remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk.

- Remdesivir should not be initiated in patients with Alanine Aminotransferase (ALT) ≥5 times the upper limit of normal at baseline
- Remdesivir 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 (see section 5.3). 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 remdesivir and while receiving it as clinically appropriate. Remdesivir should not be used in patients with eGFR <30 mL/min.

Excipients

Remdesivir contains betadex sulfobutyl ether sodium, which is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function. Therefore remdesivir should not be used in patients with eGFR <30 mL/min (see section 4.2 and 5.2).

Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine

Coadministration of remdesivir 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)

## 4.5 Interaction with other medicinal products 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 medicinal products on remdesivir*

*In vitro*, remdesivir is a substrate for esterases in plasma and tissue, drug 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 remdesivir 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 remdesivir 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

remdesivir as remdesivir has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19.

*Effects of remdesivir on other medicinal products*

*In vitro*, remdesivir is an inhibitor of CYP3A4, OATP1B1 and OATP1B3. The clinical relevance of these *in vitro* drug interactions has not been established. Remdesivir may transiently increase plasma concentrations of medicinal products that are substrates of CYP3A or OATP 1B1/1B3. No data is available, however it can be suggested that medicinal products that are substrates of CYP3A4 or substrates of OATP 1B1/1B3 should be administered at least 2 hours after remdesivir. Remdesivir induced CYP1A2 and potentially CYP3A *in vitro.* Co-administration of remdesivir with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy.

Dexamethasone is a substrate of CYP3A4 and although remdesivir inhibits CYP3A4, due to remdesivir's rapid clearance after I.V administration, remdesivir is unlikely to have a significant effect on dexamethasone exposure.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of remdesivir in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Remdesivir should not be used during pregnancy unless the clinical condition of the women requires treatment with it.

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

Breast-feeding

It is unknown whether remdesivir 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 drug in breast-feeding infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Remdesivir therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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 (see section 5.3). The relevance for humans is unknown.

## 4.7 Effects on ability to drive and use machines

Remdesivir is predicted to have no or negligible influence on these abilities.

## 4.8 Undesirable effects

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%).

Tabulated summary of adverse reactions

The adverse reactions in Table 2 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

**Table 2: Tabulated list of adverse reactions**

| **Frequency** | **Adverse reaction** |
|---|---|
| *Immune system disorders* | |
| Rare | hypersensitivity |
| *Nervous system disorders* | |
| Common | headache |
| *Gastrointestinal disorders* | |
| Common | nausea |
| *Hepatobiliary disorders* | |
| Very common | transaminases increased |
| *Skin and subcutaneous tissue disorders* | |
| Common | rash |
| *Injury, poisoning and procedural complications* | |
| Rare | infusion-related reaction |

Description of selected adverse reactions

*Transaminases Increased*
In healthy volunteer studies, increases in ALT, aspartate aminotransferase (AST) or both in subjects who received remdesivir were grade 1 (10%) or grade 2 (4%). In a randomised, double-blind, placebo-controlled clinical study of patients with COVID-19 (NIAID ACTT-1), the incidence of grade ≥3 non-serious adverse events of increased aminotransferase levels including ALT, AST, or both was 4% in patients receiving remdesivir compared with 6% in receiving placebo. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5773) in hospitalised patients with severe COVID-19 receiving remdesivir for 5 (n=200) or 10 days (n=197), any grade (≥1.25 × upper limit of normal (ULN)) laboratory abnormalities of increased AST and increased ALT occurred in 40% and 42% of patients, respectively, receiving remdesivir. Grade ≥3 (≥5.0 × ULN) laboratory abnormalities of increased AST and increased ALT both occurred in 7% of patients receiving remdesivir. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5774) in hospitalised patients with moderate COVID-19 receiving remdesivir for 5 (n=191) or 10 days (n=193) compared to standard of care (n=200), any grade laboratory abnormalities of increased AST and increased ALT occurred in 32% and 33% of patients, respectively, receiving remdesivir, and 33% and 39% of patients, respectively, receiving standard of care. Grade ≥3 laboratory abnormalities of increased AST and increased ALT occurred in 2% and 3% of patients, respectively, receiving remdesivir and 6% and 7%, respectively, receiving standard of care.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

Treatment of overdose with remdesivir 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 remdesivir.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, other antivirals, ATC code: not yet assigned

Mechanism of action

Remdesivir is an adenosine nucleotide prodrug that is metabolized within host cells 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.

Antiviral activity

Remdesivir exhibited *in vitro* activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial 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 were 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 $EC_{50}$ 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.

Clinical efficacy and safety

*Clinical trials in patients with COVID-19*

NIAID ACTT-1 Study (CO-US-540-5776)
A randomised, double-blind, placebo-controlled clinical trial evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for up to 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalised adult patients with COVID-19 with evidence of lower respiratory tract involvement. The trial enrolled 1,063 hospitalised patients: 120 (11.3%) patients with mild/moderate disease (defined by SpO2 >94% and respiratory rate <24 breaths/min without supplemental oxygen) and 943 (88.7%) patients with severe disease (defined by SpO2 ≤94% on room air, or respiratory rate ≥24 breaths/min and requiring supplemental oxygen or ventilatory support). Patients were randomised 1:1, stratified by disease severity at enrolment, to receive remdesivir (n=541) or placebo (n=522), plus standard of care.

The baseline mean age was 59 years and 36% of patients were aged 65 or older. Sixty-four percent were male, 53% were White, 21% were Black, 13% were Asian. The most common comorbidities

were hypertension (49.6%), obesity (37.0%), type 2 diabetes mellitus (29.7%), and coronary artery disease (11.6%).

Approximately 33% (180/541) of the patients received a 10-day treatment course with remdesivir.

The primary clinical endpoint was time to recovery within 28 days after randomisation, defined as either discharged from hospital (with or without limitations of activity and with or without home oxygen requirements) or hospitalised but not requiring supplemental oxygen and no longer requiring ongoing medical care. In an analysis performed after all patients had been followed up for 14 days, the median time to recovery in the overall population was 11 days in the remdesivir group compared to 15 days in the placebo group (recovery rate ratio 1.32; [95% CI 1.12 to 1.55], p<0.001). The outcome differed relevantly between the two strata. In the severe disease stratum time to recovery was 12 days in the remdesivir group and 18 days in the placebo group (recovery rate ratio 1.37 [95% CI: 1.15 to 1.63]; Table 3). For the mild/moderate disease stratum, time to recovery was not different between the two groups (5 days for both, remdesivir and placebo).

**Table 3: Recovery outcomes in the severe disease stratum from NIAID ACTT-1**

| | Remdesivir (N=476) | Placebo (N=464) |
|---|---|---|
| **Days to recovery** | | |
| Number of recoveries | 282 | 227 |
| Median (95 %CI) | 12 (10; 14) | 18 (15; 21) |
| Recovery rate ratio (95% CI)[a] | 1.37 (1.15; 1.63) | |

[a] Recovery rate ratio calculated from the stratified Cox model. Recovery rate ratios >1 indicate benefit for remdesivir

There was no difference in efficacy in patients randomized during the first 10 days after onset of symptoms as compared to those with symptoms for more than 10 days.
The clinical benefit of remdesivir was most apparent in patients receiving oxygen, however, not on ventilation, at Day 1 (rate recovery ratio 1.47 [95% CI 1.17–1.84]). For patients who were receiving mechanical ventilation or ECMO on Day 1 no difference in recovery rate was observed between the treatment groups (0.95 [95% CI 0.64 to 1.42]).

QT
Current non-clinical and clinical data do not suggest a risk of QT prolongation, but QT prolongation has not been fully evaluated in humans.

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with remdesivir in one or more subsets of the paediatric population (see section 4.2 and 5.2 for information on paediatric use).

## 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 88% bound to human plasma proteins. Protein binding of GS-441524 was low (2% bound) in human plasma. After a single 150 mg dose of [$^{14}$C]-remdesivir in healthy subjects, the blood to plasma ratio of $^{14}$C-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 [$^{14}$C]-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.

Other special populations

*Gender, race and age*
Pharmacokinetic differences for gender, race, and age have not been evaluated.

*Paediatric patients*
The pharmacokinetics in paediatric patients 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. Veklury 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.

Interactions
The potential of interaction of remdesivir as a victim was not studied with regards to the inhibition of the hydrolytic pathway (esterase). The risk of clinically relevant interaction is unknown.

Remdesivir inhibited CYP3A4 *in vitro* (see section 4.5). At physiologically relevant concentrations (steady-state), remdesivir or its metabolites GS-441524 and GS-704277 did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 *in vitro.* Remdesivir may however transiently inhibit CYP2B6, 2C8, 2C9

and 2D6 on the first day of administration. The clinical relevance of this inhibition was not studied. The potential for time-dependent inhibition of CYP450 enzymes by remdesivir was not studied.

Remdesivir induced CYP1A2 and potentially CYP3A4, but not CYP2B6 *in vitro* (see section 4.5).

*In vitro* data indicates no clinically relevant inhibition of UGT1A1, 1A3, 1A4, 1A6, 1A9 or 2B7 by remdesivir or its metabolites GS-441524 and GS-704277.

Remdesivir inhibited OATP1B1 and OATP1B3 *in vitro* (see section 4.5). No data is available for OAT1, OAT3 or OCT2 inhibition by remdesivir.

At physiologically relevant concentrations, remdesivir and its metabolites did not inhibit PgP and BCRP *in vitro.*

## 5.3 Preclinical safety data

*Toxicology*
Following intravenous administration (slow bolus) of remdesivir to rhesus monkeys and rats, severe renal toxicity occurred after short treatment durations. In male rhesus monkeys at dosage levels of 5, 10, and 20 mg/kg/day for 7 days resulted, at all dose levels, in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts, and an unscheduled death of one animal at the 20 mg/kg/day dose level. In rats, dosage levels of >3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction. Systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) were 0.1 times (monkeys at 5 mg/kg/day) and 0.3 times (rat at 3 mg/kg/day) the exposure in humans at the RHD. An unidentified major metabolite (M27) was shown to be present in human plasma (see section 5.2). The exposure of M27 in rhesus monkeys and rats is unknown. Animal studies may therefore not be informative of potential risks associated with this metabolite.

*Carcinogenesis*
Long-term animal studies to evaluate the carcinogenic potential of remdesivir have not been performed.

*Mutagenesis*
Remdesivir was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and *in vivo* rat micronucleus assays.

*Reproductive toxicity*
In female rats, decreases in corpora lutea, numbers of implantation sites, and viable embryos, were seen when remdesivir was administered intravenously daily at a systemically toxic dose (10 mg/kg/day) 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD. There were no effects on female reproductive performance (mating, fertility, and conception) at this dose level.

In rats and rabbits, remdesivir demonstrated no adverse effect on embryofoetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were up to 4 times the exposure in humans at the recommended human dose (RHD).

In rats, there were no adverse effects on pre- and post-natal development at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were similar to the exposure in humans at the recommended human dose (RHD).

It is unknown if the active nucleoside analog triphosphate GS-443902 and the unidentified major human metabolite M27 are formed in rats and rabbits. The reproductive toxicity studies may therefore not be informative of potential risks associated with these metabolites.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Betadex Sulfobutyl Ether Sodium
Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)
Water for injections

### 6.2 Incompatibilities

This medicinal product must not be mixed or administered simultaneously with other medicinal products in the same dedicated line except those mentioned in section 6.6.

### 6.3 Shelf life

Unopened vials
1 year

Diluted solution for infusion
Store diluted remdesivir solution for infusion up to 4 hours below 25°C or 24 hours in a refrigerator or (2°C – 8°C).

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

For storage conditions after dilution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

Type I clear glass vial, an elastomeric closure, and an aluminium overseal with a flip-off cap.

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. Remdesivir 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.

Remdesivir must be 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 remdesivir solution for infusion

*Dilution*
Care should be taken to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, 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.

Remove the required number of single-use vial(s) from storage. For each vial:
- Allow to warm to room temperature (20°C to 25°C).
- Inspect the vial to ensure the container closure is free from defects and the concentrate for solution for infusion is free of particulate matter.

- Using Table 4, determine the volume of sodium chloride 9 mg/mL (0.9%) to withdraw from the infusion bag.

**Table 4: Recommended dilution instructions – remdesivir concentrate for solution for infusion**

| Remdesivir 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 remdesivir |
|---|---|---|---|
| 200 mg (2 vials) | 250 mL | 40 mL | 2 × 20 mL |
| 100 mg (1 vial) | | 20 mL | 20 mL |

- Withdraw and discard the required volume of sodium chloride 9 mg/ml from the bag per Table 4 using an appropriately sized syringe and needle.
- Withdraw the required volume of remdesivir concentrate for solution for infusion from the remdesivir vial using an appropriately sized syringe per Table 4.
  - Pull the syringe plunger rod back to fill the syringe with approximately 10 mL of air.
  - Inject the air into the remdesivir injection vial above the level of the solution.
  - Invert the vial and withdraw the required volume of remdesivir concentrate for solution for infusion into the syringe. The last 5 mL of solution requires more force to withdraw.
- Discard any unused solution remaining in the remdesivir vial.
- Transfer the required volume of remdesivir concentrate for solution for infusion to the infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared diluted infusion solution is stable for 4 hours at room temperature (20°C to 25°C) or 24 hours in the refrigerator at 2°C to 8°C.

After infusion is complete, flush with at least 30 mL of sodium chloride 9 mg/ml.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1459/001

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

Date of first authorisation: {DD month YYYY}

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Veklury 100 mg powder for concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of remdesivir. After reconstitution, each vial contains 5 mg/mL of remdesivir solution.

Excipients with known effect

Each vial contains 3 g betadex sulfobutyl ether sodium

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).
White to off-white to yellow powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (see section 5.1).

### 4.2 Posology and method of administration

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

Posology

The recommended dosage of remdesivir in patients 12 years of age and older and weighing at least 40 kg is:
- Day 1 – single loading dose of remdesivir 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 remdesivir 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. Remdesivir 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 remdesivir in children under the age of 12 years and weighing <40 kg have not yet been established. No data are available.

Method of administration

For intravenous use.

Remdesivir is for administration by intravenous infusion after reconstitution and further dilution.

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

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

**Table 1: Recommended rate of infusion – for reconstituted and diluted remdesivir powder for 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 the active substance(s) or to any of the excipients listed in 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 remdesivir. 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 remdesivir 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 remdesivir and should be monitored while receiving it as clinically appropriate. No clinical studies with remdesivir have been conducted in patients with hepatic impairment. Remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk.

- Remdesivir should not be initiated in patients with Alanine Aminotransferase (ALT) ≥5 times the upper limit of normal at baseline
- Remdesivir 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 (see section 5.3). 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 remdesivir and while receiving it as clinically appropriate. Remdesivir should not be used in patients with eGFR <30 mL/min.

Excipients

Remdesivir contains betadex sulfobutyl ether sodium, which is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function. Therefore remdesivir should not be used in patients with eGFR <30 mL/min (see section 4.2 and 5.2).

Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine

Coadministration of remdesivir 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)

## 4.5 Interaction with other medicinal products 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 medicinal products on remdesivir*

*In vitro*, remdesivir is a substrate for esterases in plasma and tissue, drug 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 remdesivir 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 remdesivir 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

remdesivir as remdesivir has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19.

*Effects of remdesivir on other medicinal products*

*In vitro*, remdesivir is an inhibitor of CYP3A4, OATP1B1 and OATP1B3. The clinical relevance of these *in vitro* drug interactions has not been established. Remdesivir may transiently increase plasma concentrations of medicinal products that are substrates of CYP3A or OATP 1B1/1B3. No data is available, however it can be suggested that medicinal products that are substrates of CYP3A4 or substrates of OATP 1B1/1B3 should be administered at least 2 hours after remdesivir. Remdesivir induced CYP1A2 and potentially CYP3A *in vitro.* Co-administration of remdesivir with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy.

Dexamethasone is a substrate of CYP3A4 and although remdesivir inhibits CYP3A4, due to remdesivir's rapid clearance after I.V administration, remdesivir is unlikely to have a significant effect on dexamethasone exposure.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of remdesivir in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Remdesivir should not be used during pregnancy unless the clinical condition of the women requires treatment with it.

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

Breast-feeding

It is unknown whether remdesivir 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 drug in breast-feeding infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from remdesivir therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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 (see section 5.3). The relevance for humans is unknown.

## 4.7 Effects on ability to drive and use machines

Remdesivir is predicted to have no or negligible influence on these abilities.

## 4.8 Undesirable effects

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%).

Tabulated summary of adverse reactions

The adverse reactions in Table 2 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

**Table 2: Tabulated list of adverse reactions**

| **Frequency** | **Adverse reaction** |
|---|---|
| *Immune system disorders* | |
| Rare | hypersensitivity |
| *Nervous system disorders* | |
| Common | headache |
| *Gastrointestinal disorders* | |
| Common | nausea |
| *Hepatobiliary disorders* | |
| Very common | transaminases increased |
| *Skin and subcutaneous tissue disorders* | |
| Common | rash |
| *Injury, poisoning and procedural complications* | |
| Rare | infusion-related reaction |

Description of selected adverse reactions

*Transaminases Increased*
In healthy volunteer studies, increases in ALT, aspartate aminotransferase (AST) or both in subjects who received remdesivir were grade 1 (10%) or grade 2 (4%). In a randomised, double-blind, placebo-controlled clinical study of patients with COVID-19 (NIAID ACTT-1), the incidence of grade ≥3 non-serious adverse events of increased aminotransferase levels including ALT, AST, or both was 4% in patients receiving remdesivir compared with 6% in receiving placebo. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5773) in hospitalised patients with severe COVID-19 receiving remdesivir for 5 (n=200) or 10 days (n=197), any grade (≥1.25 × upper limit of normal (ULN)) laboratory abnormalities of increased AST and increased ALT occurred in 40% and 42% of patients, respectively, receiving remdesivir. Grade ≥3 (≥5.0 × ULN) laboratory abnormalities of increased AST and increased ALT both occurred in 7% of patients receiving remdesivir. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5774) in hospitalised patients with moderate COVID-19 receiving remdesivir for 5 (n=191) or 10 days (n=193) compared to standard of care (n=200), any grade laboratory abnormalities of increased AST and increased ALT occurred in 32% and 33% of patients, respectively, receiving remdesivir, and 33% and 39% of patients, respectively, receiving standard of care. Grade ≥3 laboratory abnormalities of increased AST and increased ALT occurred in 2% and 3% of patients, respectively, receiving remdesivir and 6% and 7%, respectively, receiving standard of care.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

Treatment of overdose with remdesivir 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 remdesivir.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, other antivirals, ATC code: not yet assigned

Mechanism of action

Remdesivir is an adenosine nucleotide prodrug that is metabolized within host cells 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.

Antiviral activity

Remdesivir exhibited *in vitro* activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial 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 were 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 $EC_{50}$ 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.

Clinical efficacy and safety

*Clinical trials in patients with COVID-19*

NIAID ACTT-1 Study (CO-US-540-5776)
A randomised, double-blind, placebo-controlled clinical trial evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for up to 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalised adult patients with COVID-19 with evidence of lower respiratory tract involvement. The trial enrolled 1,063 hospitalised patients: 120 (11.3%) patients with mild/moderate disease (defined by SpO2 >94% and respiratory rate <24 breaths/min without supplemental oxygen) and 943 (88.7%) patients with severe disease (defined by SpO2 ≤94% on room air, or respiratory rate ≥24 breaths/min and requiring supplemental oxygen or ventilatory support). Patients were randomised 1:1, stratified by disease severity at enrolment, to receive remdesivir (n=541) or placebo (n=522), plus standard of care.

The baseline mean age was 59 years and 36% of patients were aged 65 or older. Sixty-four percent were male, 53% were White, 21% were Black, 13% were Asian. The most common comorbidities

were hypertension (49.6%), obesity (37.0%), type 2 diabetes mellitus (29.7%), and coronary artery disease (11.6%).

Approximately 33% (180/541) of the patients received a 10-day treatment course with remdesivir.

The primary clinical endpoint was time to recovery within 28 days after randomisation, defined as either discharged from hospital (with or without limitations of activity and with or without home oxygen requirements) or hospitalised but not requiring supplemental oxygen and no longer requiring ongoing medical care. In an analysis performed after all patients had been followed up for 14 days, the median time to recovery in the overall population was 11 days in the remdesivir group compared to 15 days in the placebo group (recovery rate ratio 1.32; [95% CI 1.12 to 1.55], p<0.001). The outcome differed relevantly between the two strata. In the severe disease stratum time to recovery was 12 days in the remdesivir group and 18 days in the placebo group (recovery rate ratio 1.37 [95% CI: 1.15 to 1.63]; Table 3). For the mild/moderate disease stratum, time to recovery was not different between the two groups (5 days for both, remdesivir and placebo).

**Table 3: Recovery outcomes in the severe disease stratum from NIAID ACTT-1**

| | Remdesivir (N=476) | Placebo (N=464) |
|---|---|---|
| **Days to recovery** | | |
| Number of recoveries | 282 | 227 |
| Median (95 %CI) | 12 (10; 14) | 18 (15; 21) |
| Recovery rate ratio (95% CI)[a] | 1.37 (1.15; 1.63) | |

[a] Recovery rate ratio calculated from the stratified Cox model. Recovery rate ratios >1 indicate benefit for remdesivir

There was no difference in efficacy in patients randomized during the first 10 days after onset of symptoms as compared to those with symptoms for more than 10 days.
The clinical benefit of remdesivir was most apparent in patients receiving oxygen, however, not on ventilation, at Day 1 (rate recovery ratio 1.47 [95% CI 1.17–1.84]). For patients who were receiving mechanical ventilation or ECMO on Day 1 no difference in recovery rate was observed between the treatment groups (0.95 [95% CI 0.64 to 1.42]).

QT
Current non-clinical and clinical data do not suggest a risk of QT prolongation, but QT prolongation has not been fully evaluated in humans.

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with remdesivir in one or more subsets of the paediatric population (see section 4.2 and 5.2 for information on paediatric use).

## 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 88% bound to human plasma proteins. Protein binding of GS-441524 was low (2% bound) in human plasma. After a single 150 mg dose of [$^{14}$C]-remdesivir in healthy subjects, the blood to plasma ratio of $^{14}$C-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 [$^{14}$C]-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.

Other special populations

*Gender, race and age*
Pharmacokinetic differences for gender, race, and age have not been evaluated.

*Paediatric patients*
The pharmacokinetics in paediatric patients 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. Veklury 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.

Interactions
The potential of interaction of remdesivir as a victim was not studied with regards to the inhibition of the hydrolytic pathway (esterase). The risk of clinically relevant interaction is unknown.

Remdesivir inhibited CYP3A4 *in vitro* (see section 4.5). At physiologically relevant concentrations (steady-state), remdesivir or its metabolites GS-441524 and GS-704277 did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 *in vitro.* Remdesivir may however transiently inhibit CYP2B6, 2C8, 2C9

and 2D6 on the first day of administration. The clinical relevance of this inhibition was not studied. The potential for time-dependent inhibition of CYP450 enzymes by remdesivir was not studied.

Remdesivir induced CYP1A2 and potentially CYP3A4, but not CYP2B6 *in vitro* (see section 4.5).

*In vitro* data indicates no clinically relevant inhibition of UGT1A1, 1A3, 1A4, 1A6, 1A9 or 2B7 by remdesivir or its metabolites GS-441524 and GS-704277.

Remdesivir inhibited OATP1B1 and OATP1B3 *in vitro* (see section 4.5). No data is available for OAT1, OAT3 or OCT2 inhibition by remdesivir.

At physiologically relevant concentrations, remdesivir and its metabolites did not inhibit PgP and BCRP *in vitro.*

## 5.3 Preclinical safety data

*Toxicology*
Following intravenous administration (slow bolus) of remdesivir to rhesus monkeys and rats, severe renal toxicity occurred after short treatment durations. In male rhesus monkeys at dosage levels of 5, 10, and 20 mg/kg/day for 7 days resulted, at all dose levels, in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts, and an unscheduled death of one animal at the 20 mg/kg/day dose level.In rats, dosage levels of >3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction. Systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) were 0.1 times (monkeys at 5 mg/kg/day) and 0.3 times (rat at 3 mg/kg/day) the exposure in humans at the RHD. An unidentified major metabolite (M27) was shown to be present in human plasma (see section 5.2). The exposure of M27 in rhesus monkeys and rats is unknown. Animal studies may therefore not be informative of potential risks associated with this metabolite.

*Carcinogenesis*
Long-term animal studies to evaluate the carcinogenic potential of remdesivir have not been performed.

*Mutagenesis*
Remdesivir was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and *in vivo* rat micronucleus assays.

*Reproductive toxicity*
In female rats, decreases in corpora lutea, numbers of implantation sites, and viable embryos, were seen when remdesivir was administered intravenously daily at a systemically toxic dose (10 mg/kg/day) 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD. There were no effects on female reproductive performance (mating, fertility, and conception) at this dose level.

In rats and rabbits, remdesivir demonstrated no adverse effect on embryofoetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were up to 4 times the exposure in humans at the recommended human dose (RHD).

In rats, there were no adverse effects on pre- and post-natal development at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were similar to the exposure in humans at the recommended human dose (RHD).

It is unknown if the active nucleoside analog triphosphate GS-443902 and the unidentified major human metabolite M27 are formed in rats and rabbits. The reproductive toxicity studies may therefore not be informative of potential risks associated with these metabolites.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Betadex Sulfobutyl Ether Sodium
Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)

### 6.2 Incompatibilities

This medicinal product must not be mixed or administered simultaneously with other medicinal products in the same dedicated line except those mentioned in section 6.6.

### 6.3 Shelf life

Unopened vials
3 years

Reconstituted and diluted solution for infusion
Store diluted remdesivir solution for infusion up to 4 hours at below 25°C or 24 hours in a refrigerator (2°C – 8°C).

### 6.4 Special precautions for storage

No special precautions for storage.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

Type I clear glass vial, an elastomeric closure, and an aluminium overseal with a flip-off cap.

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. Remdesivir 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.

Remdesivir 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 remdesivir solution for infusion

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

- Aseptically reconstitute remdesivir 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 product, 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 4, determine the volume of sodium chloride 9 mg/mL (0.9%) solution for injection to withdraw from the infusion bag.

**Table 4: Recommended dilution instructions – Reconstituted remdesivir powder for concentrate for solution for infusion**

| Remdesivir 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 remdesivir |
|---|---|---|---|
| 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 4.
- Withdraw the required volume of reconstituted remdesivir powder for concentrate for solution for infusion using an appropriately sized syringe per Table 4. Discard any unused portion remaining in the remdesivir vial.
- Transfer the required volume of reconstituted remdesivir 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.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1459/002

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

Date of first authorisation: {DD month YYYY}

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

| Description | Due date |
|---|---|
| In order to improve the impurity control strategy, lower the risk of contamination and assure comprehensive control throughout the lifecycle of the product, the MAH should, as agreed, re-define the starting materials of active substance synthesis, update all dossier documentation accordingly and implement the re-defined starting materials. The corresponding variation application must be submitted no later than by August 2020. | June 2021 |
| In order to ensure batch to batch consistency the MAH should expand description of the active substance synthesis with more details regarding yields, process conditions, unambiguously specifying when each process stage is applicable, materials used and their specifications, and defining the batch size. Further, process parameter ranges should be further justified or tightened. | August 2020 |
| In order to further substantiate the control strategy for the active substance the MAH should further elaborate the impurities discussion with regard to the formation of potential impurities in the current and redefined starting materials, the representativeness of the active substance used in the toxicological programme versus the commercial product, the contamination of the active substance by elemental impurities, and the proposed justification regarding the suitability and adequateness of the proposed controls. | August 2020 |
| In order to improve the control strategy for the active substance the MAH should revise the active substance specification by including the parameter "microbial limits", by revising the proposed limits for assay, impurities, residual solvents, and water in line with batch data and/ or relevant guidelines and Ph. Eur. as applicable, and confirm that the analytical method can control unspecified impurities GS-832698 and GS-832699. | August 2020 |
| In order to ensure batch to batch consistency of the Powder for Concentrate for Solution for Infusion the MAH should expand the description of the manufacture of the finished product with more details, by providing the actual process validation report, by justifying the level of betadex sulfobutyl ether sodium, by clearly defining the batch size in line with process validation studies and per manufacturing site, by defining process parameters and acceptance criteria and by introducing additional in-process controls. | August 2020 |
| In order to confirm the appropriateness of aseptic processing of sterile bulk product for the Powder for Concentrate for Solution for Infusion the MAH should submit the media fill results. | August 2020 |
| In order to improve the control strategy for the Powder for Concentrate for Solution for Infusion product the MAH should revise the excipient and finished product specifications by revising the limits for assay, impurities and water content in line with batch and stability data, relevant Ph.Eur. requirements and guidelines, as applicable. | August 2020 |
| In order to further substantiate the recommendations for reconstitution and storage of the Powder for Concentrate for Solution for Infusion product the MAH should submit in-use stability data for reconstituted Powder for Concentrate for Solution for Infusion diluted to 100ml with 0.9% saline solution. Moreover, a justification for the different dilution regimens for Powder for Concentrate for Solution for Infusion (dilute to 100ml or 250ml) and Concentrate for Solution for Infusion (dilute to 250ml) should be provided. The potential for handling errors should be considered. | August 2020 |

| | |
|---|---|
| In order to ensure batch to batch consistency of the Concentrate for Solution for Infusion the MAH should expand the description of the manufacture of the finished product with more details by providing the actual process validation report, by justifying the level of betadex sulfobutyl ether sodium, by clearly defining the batch size in line with process validation studies and per manufacturing site, by defining process parameters and acceptance criteria, by introducing additional in-process controls and by providing additional batch data. | August 2020 |
| In order to confirm the appropriateness of aseptic processing of sterile bulk product for Concentrate for Solution for Infusion the MAH should submit the media fill results. | August 2020 |
| In order to improve the control strategy for the Concentrate for Solution for Infusion product the MAH should revise the excipient and finished product specifications by revising the limits for assay, impurities and endotoxins in line with batch and stability data, relevant Ph. Eur. requirements and guidelines, as applicable. | August 2020 |
| In order to confirm the efficacy and safety of remdesivir, the MAH should submit the final clinical study report (CSR) of Study CO-US-540-5776 (NIAID-ACTT1). | December 2020 |
| In order to confirm the efficacy and safety of remdesivir in patients on IMV/ECMO, the MAH should submit the published final D28 mortality data by ordinal scale categories of Study CO-US-540-5776 (NIAID-ACTT1). In addition, the MAH should discuss potential imbalance in the use of corticosteroids and effect modification in Study CO-US-540-5776. | August 2020 |
| In order to confirm the efficacy and safety of remdesivir, the MAH should submit the final CSR for Part A (Day 28) of Study GS-US-540-5773. | December 2020 |
| In order to confirm the efficacy and safety of remdesivir, the MAH should submit the final CSR for Part A (Day 28) of Study GS-US-540-5774. | December 2020 |
| In order to confirm the safety profile of remdesivir, the MAH should submit in Module 2.7.4 an analysis of all available safety data from clinical trials CO-US-540-5776, GS-US-540-5773, GS-US-540-5774 and CO-US-540-5758 when completed, including case narratives, detailed information about adverse reaction and exposure data as well as an analysis of occurrence and aggravation of AEs, SAEs and ADRs are associated with increasing exposure. | December 2020 |

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**VIAL CARTON (CONCENTRATE FOR SOLUTION FOR INFUSION)**

## 1. NAME OF THE MEDICINAL PRODUCT

Veklury 100 mg concentrate for solution for infusion
remdesivir

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg remdesivir (5 mg/mL).

## 3. LIST OF EXCIPIENTS

It also contains betadex sulfobutyl ether sodium, water for injections, hydrochloric acid and sodium hydroxide, see leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after dilution.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1459/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

QR code to be included www.veklury.eu

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL (CONCENTRATE FOR SOLUTION FOR INFUSION)**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Veklury 100 mg sterile concentrate
remdesivir
For IV use after dilution.

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mL
(5 mg/mL)

## 6. OTHER

Store in a refrigerator.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**VIAL CARTON (POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION)**

## 1. NAME OF THE MEDICINAL PRODUCT

Veklury 100 mg powder for concentrate for solution for infusion
remdesivir

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg remdesivir (5 mg/mL after reconstitution).

## 3. LIST OF EXCIPIENTS

It also contains betadex sulfobutyl ether sodium, hydrochloric acid and sodium hydroxide, see leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1459/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

QR code to be included www.veklury.eu

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL (POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION)**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Veklury 100 mg powder for concentrate
remdesivir
For IV use after reconstitution and dilution.

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mg/mL after reconstitution

## 6. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Veklury 100 mg concentrate for solution for infusion**
remdesivir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you are given this medicine, because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Veklury is and what it is used for

The active substance in is remdesivir. It is an antiviral medicine used for treating COVID-19.

COVID-19 is caused by a virus called a coronavirus. Veklury stops the virus multiplying in cells and this stops the virus multiplying in the body. This can help your body to overcome the virus infection, and may help you get better faster.

Veklury will be given to people with COVID-19. It is suitable for adults and adolescents (aged 12 and over who weigh 40 kg or more). It will only be given to patients who have pneumonia, and need extra oxygen to help them breathe.

## 2. What you need to know before you are given Veklury

**You will not usually be given Veklury:**
- **if you are allergic** to remdesivir, or any of the other ingredients of this medicine (listed in section 6)

➔ **Talk to your doctor or nurse as soon as possible,** if this applies to you.

**Warnings and precautions**
Talk to your doctor or nurse before starting on Veklury:
- **if you have liver problems.** Some people developed increased liver enzymes when given Veklury. Your doctor will do blood tests before starting treatment to check whether you can be given it safely.
- **if you have kidney problems.** Some people with severe kidney problems may not be given this medicine. Your doctor will do blood tests to check whether you can be given it safely.

**Reactions following the infusion**
Veklury can cause allergic reactions or reactions following the infusion. Symptoms can include:

- Changes to blood pressure or heart rate.
- Low oxygen level in blood
- High temperature
- Shortness of breath, wheezing
- Swelling of the face, lips, tongue or throat (angioedema)
- Rash
- Feeling sick (nausea)
- Sweating
- Shivering.

➔ **Tell your doctor** if you get any of these signs or symptoms.

**Blood tests before and during treatment**
If you are prescribed Veklury, you will be given blood tests before treatment starts. Patients being treated with Veklury will have blood tests during their treatment as determined by their health care provider. These tests are to check for kidney or liver problems. Veklury will be stopped if your kidney or liver show signs of damage during treatment. See *Possible side effects,* below.

**Children and adolescents**
Veklury is not to be given to children under 12 years who weigh less than 40 kg. Not enough is known for it to be given to these children.

**Other medicines and Veklury**
**Tell your doctor or nurse** about any other medicines you are taking, or have recently taken.

Do not take chloroquine or hydroxychloroquine at the same time as remdesivir.

Certain medicines e.g. midazolam or pitavastatin should be taken at least 2 hours after Veklury as Veklury can affect the way they work.

Veklury may affect the way certain medicines (e.g. theophylline or midazolam) work.

**➔ Tell your doctor if you are taking any of these medicines**

Veklury can be used with dexamethasone.

It is not yet known if Veklury affects other medicines, or is affected by them. Your healthcare team will monitor you for signs of medicines affecting each other.

**Pregnancy and breast-feeding**
**Tell your doctor or nurse if you are pregnant,** or if you might be. There is not enough information to be sure that Veklury is safe for use in pregnancy. Veklury will only be given if the potential benefits of treatment outweigh the potential risks to the mother and the unborn child. You must use effective contraception while having remdesivir treatment.

**Tell your doctor or nurse if you are breast-feeding.** It is not yet known whether Veklury or the COVID-19 virus pass into human breast milk, or what the effects might be on the baby or milk production. Your doctor will help you decide whether to continue breast-feeding or to start treatment with Veklury. You will need to consider the potential benefits of treatment for you, compared with the health benefits and risks of breast-feeding for your baby.

**Driving and using machines**
Veklury is not expected to have any effect on your ability to drive.

**Veklury contains a cyclodextrin**
This medicine contains 6 g betadex sulfobutyl ether sodium in each 100 mg dose of Veklury (12 g in the starting dose). This ingredient is a *cyclodextrin emulsifier* that helps the medicine to disperse in the body.

## 3. How Veklury is given to you

Veklury will be given to you by a nurse or doctor, as a drip into a vein (an *intravenous infusion*) lasting 30 to 120 minutes, once a day. You will be closely monitored during your treatment.

**The recommended dose** is:
- a single starting dose of 200 mg on day 1
- then daily doses of 100 mg starting on day 2.

You will be given Veklury every day **for at least 5 days.** Your doctor may extend the treatment up to a total of 10 days.

See the *Instructions for healthcare professionals* which give details on how the Veklury infusion is given.

**If you are given more or less Veklury than you should be**
As Veklury is only given to you by a healthcare provider, it is unlikely that you will be given too much or too little. If you have been given an extra dose, or missed one, **tell your nurse or doctor straight away.**

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Very common side effects**
(these may affect more than 1 in 10 patients)
- Blood tests may show an increase in liver enzymes, called *transaminases.*

**Common side effects**
(these may affect up to 1 in 10 patients)
- Headache
- Feeling sick (nausea)
- Rash

**Rare side effects**
(these may affect up to 1 in 1000 patients)
- Allergic reactions or reactions following the infusion. Symptoms can include:
  - Changes to blood pressure or heart rate
  - Low oxygen level in blood
  - High temperature
  - Shortness of breath, wheezing
  - Swelling of the face, lips, tongue or throat (angioedema)
  - Rash
  - Feeling sick (nausea)
  - Sweating
  - Shivering

**Reporting of side effects**
If you notice any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Veklury

- **Before use,** store unopened Veklury concentrated solution in a refrigerator until the day it is needed. Before diluting it, allow the concentrated solution to come up to room temperature.
- **Once diluted,** Veklury should be used immediately. If necessary, bags of diluted solution can be stored for up to 4 hours below 25°C, or for up to 24 hours in a refrigerator. Do not allow more than 24 hours between dilution and administration.

Keep this medicine out of the sight and reach of children.

Do not use this medicine if you see particles in the vial, or if the solution does not appear colorless to yellow.

## 6. Contents of the pack and other information

**What Veklury contains**
- **The active substance** is remdesivir. Each vial contains 100 mg.
- **The other ingredients** are: betadex sulfobutyl ether sodium, hydrochloric acid, sodium hydroxide and water for injections.

**What Veklury looks like and contents of the pack**
Veklury 100 mg concentrate for solution for infusion is a clear, colourless to yellow, aqueous-based concentrated solution, to be diluted into sodium chloride solution prior to administration by intravenous infusion. It is supplied in a single-use clear glass vial.

Veklury is available in cartons containing 1 vial.

**Marketing Authorisation Holder and Manufacturer**
Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**Česká republika**
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**Lietuva**
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**Ireland**
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**Nederland**
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**Österreich**
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**Slovenská republika**
Gilead Sciences Slovakia s.r.o.
Tel: + 421 232 121 210

**Suomi/Finland**
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Puh/Tel: + 46 (0) 8 5057 1849

**Sverige**
Gilead Sciences Sweden AB
Tel: + 46 (0) 8 5057 1849

**United Kingdom**
Gilead Sciences Ltd.
Tel: + 44 (0) 8000 113 700

**This leaflet was last revised in .**

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

**Other sources of information**

Scan the code below with a mobile device to get **this information in different languages.**

QR code to be included www.veklury.eu

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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The following information is intended for healthcare professionals only.
Please refer to the Summary of Product Characteristics for further information.

**Instructions for healthcare professionals**

**Veklury 100 mg concentrate for solution for infusion**
**remdesivir**

Each single-use vial contains 100 mg of remdesivir (5 mg/mL) as a clear, colorless to yellow, aqueous-based concentrate for dilution.

**Summary of treatment**

Veklury is for adults and adolescents (aged 12 years and older and weighing 40 kg or more) with pneumonia, who require supplemental oxygen.

Veklury should be administered by intravenous infusion in a total volume of 250 mL 0.9% sodium chloride over 30 to 120 minutes.

**The recommended dosage** is:
- a single loading dose of 200 mg on day 1
- once daily maintenance doses of 100 mg starting on day 2.

**The recommended course** of treatment is:
- one infusion **every day for at least 5 days.** Treatment can be extended to a total of up to 10 days.

The concentrated solution must be diluted with sodium chloride solution 9 mg/mL (0.9%) under aseptic conditions. Administer the diluted solution immediately.

All patients must have their liver function and renal function checked before starting treatment and as clinically appropriate during treatment. Serum chemistries, hematology, ALT, AST, bilirubin and alkaline phosphatase must be checked as clinically appropriate.

Monitor the patient for side effects during and after the infusion. See below for details on reporting of side effects.

**Dilute the concentrate with sodium chloride solution**

Veklury concentrated solution must be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection under aseptic conditions.

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

- Allow to warm to room temperature (20°C to 25°C).
- Inspect the vial to ensure the container closure is free from defects and the concentrate for solution for infusion is free of particulate matter.
- Using Table 1, determine the volume of sodium chloride 9 mg/mL (0.9%) to withdraw from the infusion bag.

**Table 1: Dilution instructions**

| Dose | Size of infusion bag to be used | How much sodium chloride solution to withdraw and discard from infusion bag | Volume of concentrated Veklury |
|---|---|---|---|
| 200 mg (2 vials) | 250 mL | **40 mL** | 2 × 20 mL |
| 100 mg (1 vial) | 250 mL | **20 mL** | 20 mL |

- Withdraw and discard the required volume of sodium chloride solution from the infusion bag using an appropriately sized syringe and needle. See Table 1.
- Pull the syringe plunger rod back to fill the syringe with approximately 10 mL of air.
- Inject the air into the Veklury vial above the level of the solution.
- Invert the vial and withdraw the required volume of Veklury from the vial into the syringe. See Table 1. The last 5 mL requires more force to withdraw.
- Transfer the concentrated solution to the infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- Administer the diluted solution immediately, or as soon as possible after preparation. The diluted solution is stable for 4 hours at room temperature (20°C to 25°C) or 24 hours in a fridge (2°C to 8°C), from the time the solution is diluted.
- Discard any unused portion remaining in the Veklury vial.

**Administer the infusion**

- Administer the diluted solution over 30 to 120 minutes at the rate described in Table 2.
- After infusion is complete, flush with at least 30 mL of 9 mg/mL (0.9%) sodium chloride solution.
- The diluted solution should not be administered simultaneously with any other medication in the same intravenous line. The compatibility of Veklury with IV solutions and medications other than sodium chloride is not known.

**Table 2: Rate of 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 |

**Monitor and report side effects**

- Monitor the patient for side effects during and after the infusion.
- Report side effects via the national reporting system listed in Appendix V.

**Store Veklury safely**

- **Before use,** store Veklury vials in a fridge (2°C to 8°C) until they are required. Do not use after expiry date, marked on the vials/cartons after the letters EXP.

- Veklury concentrate is a clear, colorless to yellow, aqueous-based concentrated solution.
- **Before dilution,** allow Veklury vials to warm up to room temperature (20°C to 25°C).
- **Once diluted,** Veklury should be administered immediately. If necessary, bags of diluted solution can be stored for up to 4 hours at room temperature (20°C to 25°C), or for up to 24 hours in a fridge (2°C to 8°C). Do not leave more than 24 hours between dilution and administration.

Do not reuse or save unused Veklury concentrated solution or diluted solution.

**Information in other languages**

- Scan the code below with a mobile device to get the information in different languages.

QR code to be included www.veklury.eu

This leaflet was last revised in .

**Package leaflet: Information for the patient**

**Veklury 100 mg powder for concentrate for solution for infusion**
remdesivir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you are given this medicine, because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Veklury is and what it is used for

The active substance in is remdesivir. It is an antiviral medicine used for treating COVID-19.

COVID-19 is caused by a virus called a coronavirus. Veklury stops the virus multiplying in cells and this stops the virus multiplying in the body. This can help your body to overcome the virus infection, and may help you get better faster.

Veklury will be given to people with COVID-19. It is suitable for adults and adolescents (aged 12 and over who weigh 40 kg or more). It will only be given to patients who have pneumonia, and need extra oxygen to help them breathe.

## 2. What you need to know before you are given Veklury

**You will not usually be given Veklury:**
- **if you are allergic** to remdesivir, or any of the other ingredients of this medicine (listed in section 6)

➔ **Talk to your doctor or nurse as soon as possible,** if this applies to you.

**Warnings and precautions**
Talk to your doctor or nurse before starting on Veklury:
- **if you have liver problems.** Some people developed increased liver enzymes when given Veklury. Your doctor will do blood tests before starting treatment to check whether you can be given it safely.
- **if you have kidney problems.** Some people with severe kidney problems may not be given this medicine. Your doctor will do blood tests to check whether you can be given it safely.

**Reactions following the infusion**
Veklury can cause allergic reactions or reactions following the infusion. Symptoms can include:

- Changes to blood pressure or heart rate.
- Low oxygen level in blood
- High temperature
- Shortness of breath, wheezing
- Swelling of the face, lips, tongue or throat (angioedema)
- Rash
- Feeling sick (nausea)
- Sweating
- Shivering.

➔ **Tell your doctor** if you get any of these signs or symptoms

**Blood tests before and during treatment**
If you are prescribed Veklury, you will be given blood tests before treatment starts. Patients being treated with Veklury will have blood tests during their treatment as determined by their health care provider. These tests are to check for kidney or liver problems. Veklury will be stopped if your kidney or liver show signs of damage during treatment. See *Possible side effects,* below.

**Children and adolescents**
Veklury is not to be given to children under 12 years who weigh less than 40 kg. Not enough is known for it to be given to these children.

**Other medicines and Veklury**
**Tell your doctor or nurse** about any other medicines you are taking, or have recently taken.

Do not take chloroquine or hydroxychloroquine at the same time as remdesivir.

Certain medicines e.g. midazolam or pitavastatin should be taken at least 2 hours after Veklury as Veklury can affect the way they work.

Veklury may affect the way certain medicines (e.g. theophylline or midazolam) work.

➔ **Tell your doctor if you are taking any of these medicines**

Veklury can be used with dexamethasone.

It is not yet known if Veklury affects other medicines, or is affected by them. Your healthcare team will monitor you for signs of medicines affecting each other.

**Pregnancy and breast-feeding**
**Tell your doctor or nurse if you are pregnant,** or if you might be. There is not enough information to be sure that Veklury is safe for use in pregnancy. Veklury will only be given if the potential benefits of treatment outweigh the potential risks to the mother and the unborn child. You must use effective contraception while having remdesivir treatment.

**Tell your doctor or nurse if you are breast-feeding.** It is not yet known whether Veklury or the COVID-19 virus pass into human breast milk, or what the effects might be on the baby or milk production. Your doctor will help you decide whether to continue breast-feeding or to start treatment with Veklury. You will need to consider the potential benefits of treatment for you, compared with the health benefits and risks of breast-feeding for your baby.

**Driving and using machines**
Veklury is not expected to have any effect on your ability to drive.

**Veklury contains a cyclodextrin**
This medicine contains 3 g betadex sulfobutyl ether sodium in each 100 mg dose of Veklury (6 g in the starting dose). This ingredient is a *cyclodextrin emulsifier* that helps the medicine to disperse in the body.

## 3. How Veklury is given to you

Veklury will be given to you by a nurse or doctor, as a drip into a vein (an *intravenous infusion*) lasting 30 to 120 minutes, once a day. You will be closely monitored during your treatment.

**The recommended dose** is:
- a single starting dose of 200 mg on day 1
- then daily doses of 100 mg starting on day 2.

You will be given Veklury every day **for at least 5 days.** Your doctor may extend the treatment up to a total of 10 days.

See the *Instructions for healthcare professionals* which give details on how the Veklury infusion is given.

**If you are given more or less Veklury than you should be**
As Veklury is only given to you by a healthcare provider, it is unlikely that you will be given too much or too little. If you have been given an extra dose, or missed one, **tell your nurse or doctor straight away.**

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Very common side effects**
(these may affect more than 1 in 10 patients)
- Blood tests may show an increase in liver enzymes, called *transaminases.*

**Common side effects**
(these may affect up to 1 in 10 patients)
- Headache
- Feeling sick (nausea)
- Rash

**Rare side effects**
(these may affect up to 1 in 1000 patients)
- Allergic reactions or reactions following the infusion. Symptoms can include:
  - Changes to blood pressure or heart rate
  - Low oxygen level in blood
  - High temperature
  - Shortness of breath, wheezing
  - Swelling of the face, lips, tongue or throat (angioedema)
  - Rash
  - Feeling sick (nausea)
  - Sweating
  - Shivering

**Reporting of side effects**
If you notice any side effects, **talk to your doctor or nurse.** This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Veklury

- **Before use,** this medicinal product does not require any special storage conditions.
- **Once reconstituted,** Veklury should be diluted immediately.
- **Once diluted,** Veklury should be used immediately. If necessary, bags of diluted solution can be stored for up to 4 hours below 25°C, or for up to 24 hours in a refrigerator. Do not allow more than 24 hours between dilution and administration.

Keep this medicine out of the sight and reach of children.

## 6. Contents of the pack and other information

**What Veklury contains**
- **The active substance** is remdesivir. Each vial contains 100 mg.
- **The other ingredients** are: betadex sulfobutyl ether sodium, hydrochloric acid and sodium hydroxide.

**What Veklury looks like and contents of the pack**
Veklury 100 mg powder for concentrate for solution for infusion is a white, off-white to yellow powder, to be reconstituted and then diluted into sodium chloride solution prior to administration by intravenous infusion. It is supplied in a single-use clear glass vial.

Veklury is available in cartons containing 1 vial.

**Marketing Authorisation Holder and Manufacturer**
Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last revised in .**

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

**Other sources of information**

Scan the code below with a mobile device to get **this information in different languages.**

QR code to be included www.veklury.eu

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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The following information is intended for healthcare professionals only.
Please refer to the Summary of Product Characteristics for further information.

**Instructions for healthcare professionals**

**Veklury 100 mg powder for concentrate for solution for infusion**
remdesivir

Each single-use vial contains 100 mg of remdesivir as a white to off-white to yellow powder for reconstitution and dilution.

**Summary of treatment**

Veklury is for adults and adolescents (aged 12 years and older and weighing 40 kg or more) with pneumonia, who require supplemental oxygen.

Veklury should be administered by intravenous infusion in a total volume of 100 mL or 250 mL 0.9% sodium chloride over 30 to 120 minutes.

**The recommended dosage** is:
- a single loading dose of 200 mg on day 1
- once daily maintenance doses of 100 mg starting on day 2.

**The recommended course** of treatment is:
- one infusion **every day for at least 5 days.** Treatment can be extended to a total of up to 10 days.

The powder must be reconstituted with water for injections, and then diluted with sodium chloride solution 9 mg/mL (0.9%) under aseptic conditions. Administer the diluted solution immediately.

All patients must have their liver function and renal function checked before starting treatment and as clinically appropriate during treatment. Serum chemistries, hematology, ALT, AST, bilirubin and alkaline phosphatase must be checked as clinically appropriate.

Monitor the patient for side effects during and after the infusion. See below for details on reporting of side effects.

**Reconstitute the powder**

For each single-use vial, the powder must be reconstituted and then diluted under aseptic conditions.
- Add 19 mL of sterile water for injections to the vial, using a suitably sized syringe and needle for each vial. This produces a solution of 5 mg/mL of remdesivir.
  - Discard the vial if a vacuum does not pull the sterile water 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.

- The solution should only be used if it is clear and free from particles.
- Dilute immediately after reconstitution.

**Dilute the concentrate with sodium chloride solution**

Reconstituted Veklury must be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection under aseptic conditions.

Using Table 1, decide how much sodium chloride solution 9 mg/mL (0.9%) to withdraw from the infusion bag.

**Table 1: Dilution instructions**

| Dose | Size of infusion bag to be used | How much sodium chloride solution to withdraw and discard from infusion bag | Volume of reconstituted Veklury |
|---|---|---|---|
| 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 infusion should only be used for patients with severe fluid restrictions.

- Withdraw and discard the required volume of sodium chloride solution from the infusion bag using an appropriately sized syringe and needle. See Table 1.
- Withdraw the required volume of reconstituted Veklury from the vial using an appropriately sized syringe. See Table 1.
- Transfer the reconstituted Veklury to the infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- Administer the diluted solution immediately, or as soon as possible after preparation. The diluted solution is stable for 4 hours at room temperature (20°C to 25°C) or 24 hours in a fridge (2°C to 8°C), from the time the powder is reconstituted.

**Administer the infusion**

- Administer the diluted solution over 30 to 120 minutes at the rate described in Table 2.
- After infusion is complete, flush with at least 30 mL of 9 mg/mL (0.9%) sodium chloride solution.
- The diluted solution should not be administered simultaneously with any other medicines in the same intravenous line. The compatibility of Veklury with IV solutions and medications other than sodium chloride is not known.

**Table 2: Rate of 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 |

**Monitor and report side effects**

- Monitor the patient for side effects during and after the infusion.
- Report side effects via the national reporting system listed in Appendix V.

**Store Veklury safely**

- **Before use,** this medicinal product does not require any special storage conditions. Do not use after expiry date, marked on the vials/cartons after the letters EXP.
- Veklury powder appears white to off-white to yellow. The color does not affect product stability.
- **Once reconstituted,** Veklury should be diluted immediately.
- **Once diluted,** Veklury should be administered immediately. If necessary, bags of diluted solution can be stored for up to 4 hours at room temperature (20°C to 25°C), or for up to 24 hours in a fridge (2°C to 8°C). Do not leave more than 24 hours between dilution and administration.

Do not reuse or save unused Veklury powder, reconstituted solution or diluted solution.

**Information in other languages**

- Scan the code below with a mobile device to get the information in different languages.

QR code to be included www.veklury.eu

This leaflet was last revised in .

# ANNEX IV

# CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

**Conclusions presented by the European Medicines Agency on:**

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.