1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GRADOVIR 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of GRADOVIR contains dolutegravir sodium equivalent to 50 mg dolutegravir.

Contains sugar: Mannitol (E421) 134,28 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

GRADOVIR is a round, orange, bevelled edged, biconvex, film-coated tablet, marked F33 on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

GRADOVIR is indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral medicines in adults aged 18 years and older.

4.2. Posology and method of administration

Posology

GRADOVIR therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Adults:

Treatment-naïve:

For patients initiating antiretroviral therapy for the first time (treatment-naïve) the recommended dose of GRADOVIR is 50 mg once daily.

Treatment-experienced, and integrase inhibitor naïve:

For patients who are treatment experienced and have not previously been treated with an integrase inhibitor, the recommended dose of GRADOVIR is 50 mg once daily.

Integrase inhibitor resistant:

For patients with integrase inhibitor resistance, the recommended dose of GRADOVIR is 50 mg twice daily.

Medicine interactions:

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given to patients taking GRADOVIR.

There is evidence that the concentration of isoniazid is increased by dolutegravir, as contained in GRADOVIR.

Special populations

Children

GRADOVIR should not be used in children.

Elderly population

There are limited data available on the use of GRADOVIR in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2).

Renal impairment

No dosage adjustment is required in patients with mild, moderate or severe (CrCl < 30 ml/min, not on dialysis) renal impairment. No data are available in subjects receiving dialysis, although differences in pharmacokinetics are not expected in this population (see section 5.2).

Treatment with GRADOVIR resulted in an early small increase of mean serum creatinine levels by 10 % to 14 % which remained stable over time and is not considered clinically relevant (see section 4.8).

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh grade A). GRADOVIR is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

Method of administration

GRADOVIR is taken orally with or without food.

4.3. Contraindications

GRADOVIR is contraindicated in:

- Patients with hypersensitivity to dolutegravir or to any excipients in GRADOVIR (see section 6.1).
- Combination with dofetilide and pilsicainide (see section 4.5).
- Moderate and severe hepatic impairment.
- Metformin is contraindicated in patients taking GRADOVIR (see section 4.5).
- Lactation (see section 4.6)
- Women who plan to become pregnant, during peri/preconception period and in the first trimester of pregnancy (see section 4.6).
- Women of child-bearing age not using highly effective contraception (see section 4.6).

4.4. Special warnings and precautions for use

Hypersensitivity

Hypersensitivity reactions have been reported with integrase inhibitors, including GRADOVIR and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury. Discontinue GRADOVIR and other suspect medicines immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with GRADOVIR or other suspect medicines after the onset of hypersensitivity may result in a life-threatening reaction.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune reconstitution syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are tuberculosis, cytomegalovirus retinitis, generalised and/or focal atypical mycobacterial infections and *Pneumocystis jiroveci (P. carinii)* pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-

immune disorders (such as Graves' disease, polymyositis and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of GRADOVIR therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B coinfected patients (see section 4.8).

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Hepatic impairment

The unbound fraction of dolutegravir, as contained in GRADOVIR, in the blood is doubled in patients with moderate hepatic impairment. GRADOVIR is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

Interactions

Caution should be given to co-administering medicines (prescription and non-prescription) that may change the exposure of GRADOVIR or medicines that may have their exposure changed by GRADOVIR (see sections 4.3 and 4.5).

The co-administration of GRADOVIR with etravirine (ETR) is not recommended unless the patient is also receiving concomitant atazanavir + ritonavir (ATV + RTV), lopinavir + ritonavir (LPV + RTV) or darunavir + ritonavir (DRV + RTV) (see section 4.5).

The recommended dose of GRADOVIR is 50 mg twice daily when co-administered with efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin (see section 4.5).

GRADOVIR should not be co-administered with polyvalent cation-containing antacids. GRADOVIR is recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.5).

Metformin concentrations may be increased by GRADOVIR. Metformin is contraindicated in patients taking GRADOVIR (see section 4.3).

Co-infection with hepatitis B or C

In Phase III studies, patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of GRADOVIR therapy, particularly in those whose anti-hepatitis B therapy was withdrawn.

Opportunistic infections

Patients receiving GRADOVIR or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by medical practitioners experienced in the treatment of these associated HIV diseases.

GRADOVIR should not be used in children.

Transmission of infection

Patients should be advised that current antiretroviral therapy, including GRADOVIR, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Integrase class resistance of particular concern

The decision to use GRADOVIR in the presence of integrase class resistance should take into account that the activity of dolutegravir, as contained in GRADOVIR, is considerably compromised for viral strains harbouring Q148+≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I (see section 5.1). To what extent GRADOVIR provides added efficacy in the presence of such integrase class resistance is uncertain (see section 5.2).

Lamivudine and dolutegravir

The two-drug regimen of dolutegravir 50 mg once daily and lamivudine 300 mg once daily was explored in two large randomised and blinded studies. This regimen is only suitable for the treatment of HIV-1 infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine.

Excipients:

Contains mannitol and may have a laxative effect.

4.5. Interaction with other medicines and other forms of interaction

Effect of GRADOVIR on the pharmacokinetics of other medicines:

In vitro, GRADOVIR demonstrated no direct, or weak inhibition (IC50 > 50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, OATP1B1, OATP1B3, OCT1 or MRP2. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4.

In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, GRADOVIR is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or transporters (e.g., reverse transcriptase and protease inhibitors, opioid analgesics, antidepressants, statins, azole antifungals (such as fluconazole, itraconazole, clotrimazole), proton pump inhibitors (such as esomeprazole, lansoprazole, omeprazole), anti-erectile dysfunction medicines (such as sildenafil, tadalafil, vardenafil), aciclovir, valaciclovir, sitagliptin, adefovir).

In medicine interaction studies, GRADOVIR did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinyl estradiol.

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2). Based on this observation, GRADOVIR may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin) (see Table 2: Medicine interactions – Other medicines).

Effect of other medicines on the pharmacokinetics of GRADOVIR

GRADOVIR is eliminated mainly through metabolism by UGT1A1. GRADOVIR is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore, medicines that induce those enzymes may theoretically decrease dolutegravir plasma concentration and reduce the therapeutic effect of GRADOVIR.

Co-administration of GRADOVIR and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 2).

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and require GRADOVIR dose adjustment to 50 mg twice daily. Etravirine also reduced plasma concentrations, but the effect of etravirine was mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir. Therefore, no GRADOVIR dose adjustment is necessary when co-administered with etravirine and either lopinavir/ritonavir, darunavir/ritonavir, or atazanavir/ritonavir. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment of GRADOVIR. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see Table 1: Medicine interactions – HIV-1 Antiviral medicines).

A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, daclatasvir, telaprevir, prednisone, rifabutin, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no GRADOVIR dose adjustment is required when co-administered with these medicines.

Table 1: Medicine interactions - HIV-1 Antiviral medicines

Concomitant medicine class: Medicine name	**Effect on concentration of GRADOVIR or concomitant medicine**	**Clinical comment**
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	Dolutegravir ↓ AUC ↓ 71 % C_{max} ↓ 52 % Cτ ↓ 88 % ETR ↔	Etravirine decreased dolutegravir plasma concentration, which may result in loss of virologic response and possible resistance to dolutegravir. GRADOVIR should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir.
Non-nucleoside Reverse Transcriptase	Dolutegravir ↓ AUC ↓ 57 % C_{max} ↓ 39 % Cτ ↓ 75 %	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of

Inhibitor: Efavirenz (EFV)	EFV ↔	GRADOVIR is 50 mg twice daily when co-administered with efavirenz. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of GRADOVIR is 50 mg twice daily when co-administered with nevirapine. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 49 % Cτ ↑ 180 % ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 33 % Cτ ↑ 121 % ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % Cτ ↓ 76 % TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of GRADOVIR is 50 mg twice daily when co-administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients.
Protease Inhibitor: Fosamprenavir/ ritonavir (FPV + RTV)	Dolutegravir ↓ AUC ↓ 35 % C_{max} ↓ 24 % Cτ ↓ 49 % FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients. Alternative combinations that do not include fosamprenavir/ritonavir should be used where possible in INI resistant patients.
Protease Inhibitor: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir (LPV + RTV)	DTG ↔ AUC ↔ C_{max} ↔ Cτ ↔ LPV ↔ RTV ↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor:	Dolutegravir ↓ AUC ↓ 32 % C_{max} ↓ 11 %	Darunavir/ritonavir did not change dolutegravir plasma concentration to a

Darunavir/ritonavir (DRV/RTV)	Cτ ↓ 38 % DRV ↔ RTV ↔	clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDV)	Dolutegravir ↔ TDV ↔	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC ↑ 10 % C_{max} ↑ 7 % Cτ ↑ 28 % LPV ↔ RTV ↔ ETR ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir + Etravirine (DRV/RTV + ETR)	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % Cτ ↓ 36 % DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

Table 2: Medicine interactions - Other medicines

Concomitant medicine class: Medicine name	**Effect on concentration of GRADOVIR or concomitant medicine**	**Clinical comment**
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or pilsicainide co-administration with GRADOVIR is contra-indicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort	Dolutegravir↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.
Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir ↔	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
Antacids containing polyvalent cations (e.g., Mg, Al or Ca)	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % C_{24} ↓ 74 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. GRADOVIR is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C_{24} ↓ 39 %	GRADOVIR is recommended to be administered 2 hours before or 6 hours after taking products containing calcium, or alternatively, administer with food.
Iron supplements	Dolutegravir ↓ AUC ↓ 54 %	

	C_{max} ↓ 57 % C_{24} ↓ 56 %	
Multivitamin	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C_{24} ↓ 32% (Complex binding to polyvalent ions)	
Metformin	Metformin ↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contraindicated in patients taking GRADOVIR (see section 4.3)
Isoniazid		There is evidence that the concentration of isoniazid is increased by dolutegravir, as contained in GRADOVIR.
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % $C\tau$ ↓ 72 %	Rifampicin decreased dolutegravir plasma concentration. A supplementary dose of dolutegravir should be given to patients taking GRADOVIR with rifampicin. The recommended dose of GRADOVIR is 50 mg twice daily when co-administered with rifampicin. Alternatives to rifampicin should be used where possible for INI resistant patients.
Oral contraceptives (Ethinyl estradiol (EE) and Norgestromin (NGMN))	Effect of dolutegravir: EE ↔ AUC ↑ 3 % C_{max} ↓ 1 % $C\tau$ ↑ 2 % Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11 % $C\tau$ ↓ 7 %	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with GRADOVIR.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % $C\tau$ ↓ 1 %	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment is necessary of either medicine.

Abbreviations: ↑ = increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration, $C\tau$ = concentration at the end of dosing interval, C_{24} = plasma concentration 24 hours after administration.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir, as in GRADOVIR, (see below), including consideration of using effective contraceptive measures.

Perform pregnancy testing before initiation of GRADOVIR in women of childbearing potential to exclude inadvertent (unintentional) use of GRADOVIR during the first trimester of pregnancy.

If a woman plans pregnancy, the benefits and the risks of starting or continuing treatment with dolutegravir, as in GRADOVIR, versus using another antiretroviral regimen should be discussed with her.

Pregnancy

GRADOVIR is contraindicated in mothers who plan to become pregnant, during peri/preconception period and in the first trimester of pregnancy (see section 4.3).
Use of dolutegravir, as in GRADOVIR, during pregnancy was associated with a small increase in the prevalence of neural tube defects (0,19 %) compared to non-dolutegravir regimens (0,11 %). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

If a pregnancy is confirmed in the first trimester while on dolutegravir, as in GRADOVIR, the benefits and risks of continuing dolutegravir, as in GRADOVIR, versus switching to another antiretroviral regimen should be discussed with the patient, taking the gestational age and the critical time period of neural tube defect development into account.

Dolutegravir, as in GRADOVIR, may be used during the second and third trimester of pregnancy when the expected benefit outweighs the potential risk to the foetus. Dolutegravir, as in GRADOVIR is shown to cross the placenta in humans, leading to significant exposure to the foetus, but the implications of such exposure are not yet known.

Breastfeeding

Mothers taking GRADOVIR should not breastfeed their babies.

HIV infected women should not breastfeed their baby in order to avoid transmission of HIV to the baby or follow appropriate guidelines.

Dolutegravir, as in GRADOVIR is excreted in human breast milk, and there is significant exposure to the neonate/infants due to slow elimination; the half-life of dolutegravir in the newborn was 33 hr compared to 14 hr in the adults. There is insufficient information on the effects of dolutegravir in neonates/infants.

Fertility

There are no data on the effects of dolutegravir, as in GRADOVIR on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility.

4.7. Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with GRADOVIR.

The clinical status of the patient and the adverse event profile of GRADOVIR should be borne in mind when considering the patient's ability to drive or operate machinery.

GRADOVIR may affect the ability to drive and use machines. Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that GRADOVIR does not adversely affect their ability to do so safely (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

The most severe adverse reaction, seen in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see section 4.4). The most commonly seen treatment emergent adverse reactions were nausea, diarrhoea and headache.

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent
Immune system disorders		Hypersensitivity, Immune Reconstitution Syndrome (see section 4.4)
Psychiatric disorders	Insomnia Depression, anxiety	Suicidal ideation, suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)
Nervous system disorders	Headache, dizziness, abnormal dreams	
Gastrointestinal disorders	Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain	Abdominal pain, abdominal discomfort
Hepatobiliary disorders		Hepatitis Acute hepatic failure
Skin and subcutaneous tissue disorders	Rash, pruritus	
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia
General disorders and administrative site conditions	Fatigue	
Investigations	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations, Creatine phosphokinase (CPK) elevations	

The safety profile was similar across the treatment naïve, treatment experienced (and integrase naïve) and integrase resistant patient populations.

c) Description of selected adverse reactions

Changes in laboratory chemistries

Increases in serum creatinine occurred within the first week of treatment with GRADOVIR and remained stable through 48 weeks. In treatment naïve patients a mean change from baseline of 9,96 µmol/l (range: 53 µmol/l to 54,8 µmol/l) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment experienced patients. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (see section 5.1).

Small increases in total bilirubin (without clinical jaundice) were observed on GRADOVIR and raltegravir (but not efavirenz) arms. These changes are not considered clinically relevant as they likely reflect competition between GRADOVIR and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see section 5.2).

Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with GRADOVIR therapy.

Co-infection with Hepatitis B or C

In Phase III studies patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see section 4.4).

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (cART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Paediatric population

Based on limited available data in children and adolescents (6 to less than 18 years of age and weighing at least 15 kg), there were no additional types of adverse reactions beyond those observed in the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.7 Overdose

Symptoms

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Treatment

Management should be as clinically indicated or as recommended by the national poisons centre, where available.

There is no specific treatment for an overdose of GRADOVIR. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As GRADOVIR is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.2.8 Antimicrobial (Chemotherapeutic) Medicines. Antiviral agents

Pharmacotherapeutic group: Antivirals for systemic use, other antiviral

ATC code: J05AX12

Mechanism of action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. *In vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex (t½ 71 hours).

Resistance *in vitro*

Isolation from wild type HIV-1: Viruses highly resistant to dolutegravir were not observed during HIV-1 passage. During wild type HIV-1 passage in the presence of dolutegravir integrase substitutions observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,1 and G193E with FC = 3,2 for strain NL432. Additional passage of wildtype subtype B, C, and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T.

Anti-HIV activity against resistant strains: Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent potency against 2

nonnucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant and 2 PI-resistant HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wildtype strain.

Integrase inhibitor-resistant HIV-1 strains: Dolutegravir showed anti-HIV activity (susceptibility) with FC < 5 against 27 of 28 integrase inhibitor-resistant mutant viruses with single substitutions including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, and N155H.

Integrase inhibitor-resistant HIV-2 strains: Site directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with raltegravir who showed virologic failure. Overall the HIV-2 FCs observed were similar to HIV-1 FCs observed for similar pathway mutations.

Clinical isolates from raltegravir treatment virologic failure patients: 705 raltegravir resistant clinical isolates were analysed for susceptibility to dolutegravir using the Monogram Biosciences PhenoSense assay. Dolutegravir has a < 10 FC against 93,9 % of the 705 clinical isolates.

Resistance *in vivo*: integrase inhibitor naïve patients:

No integrase inhibitor (INI) resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment-naïve studies.

Resistance *in vivo*: integrase inhibitor resistant patients

Data states that dolutegravir (plus optimised background therapy) in 26 subjects with pre-existing INI resistance resulted in patients with virologic failure on dolutegravir (plus optimised background therapy).

Of these, 25 had paired baseline and PDVF resistance data for analysis and 13/25 (52 %) had treatment emergent mutations.

Eleven of the thirteen subjects with virus exhibiting treatment emergent mutations harboured Q148 pathway virus present at baseline or historically.

Effects on renal function

A small decrease of 10 % to 14 % in mean serum creatinine clearance (CrCl) was observed with dolutegravir within the first week of treatment. Dolutegravir had no significant effect on glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). Data suggest that the increases in creatinine observed are due to the non-pathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

5.2 Pharmacokinetic properties

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is between low to moderate. In Phase 1 studies in healthy subjects, between-subject CVb % for AUC and C_{max} ranged from ~ 20 % to 40 % and $C\tau$ from 30 % to 65 % across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw %) is lower than between-subject variability.

Absorption

Dolutegravir is absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for the tablet formulation. The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, dolutegravir exhibited non-linear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 mg to 100 mg; however increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg.

Dolutegravir may be administered with or without food. Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate and high fat meals increased dolutegravir AUC (0 to ∞) by 34 %, 41 %, and 66

%, increased C_{max} by 46 %, 52 %, and 67 %, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant.
The absolute bioavailability of dolutegravir has not been established.

Distribution

Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins based on *in vitro* data. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is estimated at 12,5 ℓ. Binding of dolutegravir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0,441 to 0,535 indicating minimal association of radioactivity with blood cellular components. Free fraction of dolutegravir in plasma is estimated at approximately 0,2 % to 1,1 % in healthy subjects, approximately 0,4 % to 0,5 % in subjects with moderate hepatic impairment, and 0,8 % to 1,0 % in subjects with severe renal impairment and 0,5 % in HIV-1 infected patients.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC50); CSF:plasma concentration ratio of dolutegravir ranged from 0,11 % to 0,66 %. Dolutegravir concentrations in CSF exceeded the IC50, supporting the median reduction from baseline in CSF HIV-1 RNA of 2,1 log after 2 weeks of therapy (see section 5.1).

Biotransformation

Dolutegravir is primarily metabolised via UGT1A1 with a minor CYP3A component (9,7 % of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine is low (< 1 % of the dose). 53 % of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of

this is due to unabsorbed medicine or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. 31 % of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18,9 % of total dose), N-dealkylation metabolite (3,6 % of total dose) and a metabolite formed by oxidation at the benzylic carbon (3,0 % of total dose).

Elimination

Dolutegravir has a terminal half-life of ~ 14 hours and an apparent clearance (CL/F) of 0,56 L/hr.

Special populations

Adolescents

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to < 18 years of age) showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure comparable to that observed in adults who received dolutegravir 50 mg once daily.

Due to lack of clinical data, dolutegravir, as in GRADOVIR, is not recommended for use in patients under 18 years of age (see section 4.2).

Table 3: **Adolescent pharmacokinetic parameters**

Age/weight	**Dolutegravir Dose**	**Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (CV %)**		
		$AUC_{(0-24)}$ µg.hr/mL	C_{max} µg/mL	C_{24} µg/mL
12 to <18 years ≥ 40 kg [a]	50 mg once daily [a]	46 (43)	3,49 (38)	0,90 (59)

[a] One subject weighing 37 kg received 35 mg once daily.

Elderly

There is no clinically relevant effect of age on dolutegravir exposure.

Pharmacokinetic data for dolutegravir in subjects of > 65 years old are limited.

Renal impairment

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr < 30 ml/min) and matching healthy subjects were observed, AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40 %, 23 %, and 43 %, respectively, compared with those in matched healthy subjects. No dosage adjustment is necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment

Dolutegravir is primarily metabolised and eliminated by the liver. No dosage adjustment is necessary for patients with mild hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in metabolising enzymes

There is no evidence that common polymorphisms in metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent.

Co-infection with hepatitis B or C

Hepatitis C virus co-infection has no clinically relevant effect on the exposure to dolutegravir. There are limited data on subjects with hepatitis B co-infection.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421), microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate.

Tablet coating: Macrogol, Sunset yellow FCF (E110), polyvinyl alcohol, talc, titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

28 or 30 tablets packed in a white, high density polyethylene bottle with white polypropylene cap with heat seal liner. The bottle may be packed in an outer cardboard carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

52/20.2.8/1005.004

9. DATE OF FIRST AUTHORISATION

02 April 2020

10. DATE OF REVISION OF TEXT

17 January 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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