SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the Medicinal Product

Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg

2. Qualitative and Quantitative Composition

Each film coated tablet contains:

Dolutegravir Sodium equivalent to Dolutegravir 10 mg

For Excipients see point 6.1

3. Pharmaceutical Form

Film Coated Dispersible Tablet

4. Clinical Particulars

4.1 Therapeutic indications

Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mgare indicated in combination with other antiretroviral agentsfor the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults (treatment-naïve or -experienced) and in paediatric patients (treatment-naïve or -experienced but integrase strand transfer inhibitor[INSTI]-naïve) aged at least 4 weeks and weighing at least 3 kg.

This product is intended for use in children. Nonetheless, safety information is provided with respect to adult health issues, to allow full access to all relevant information.

4.2 Posology and method of administration

Recommended Dosage in Paediatric Patients Weighing 3 to 14 kg

The recommended weight-based dosage of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg in paediatricpatients weighing 3 to 14 kg(4 weeks and older, treatment-naïve or treatment-experienced but naïve to INSTI treatment) is described in below Table 1. Do not use Dolutegravir tablets in patients weighing 3 to 14 kg.

Table 1: Recommended Dosage of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg in Paediatric Patients 4 Weeks and Older Weighing 3 to 14 kg

Body Weight	**Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg**	
	Daily Dose[a]	**Number of 10mg tablets**
3 kg to less than 6 kg	5mg once daily	0.5
6 kg to less than 10 kg	15mg once daily	1.5
10 kg to less than 14 kg	20mg once daily	2

[a]If certain UGT1A or CYP3A inducers are coadministered, then administer Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg twice daily.

- **Recommended Dosage in Paediatric Patients Weighing 14 kg or Greater**For **paediatric patients weighing 14 kg or greater** (4 weeks and older, treatment-naïve or treatment-experienced but naïve to INSTI treatment) administer either:
    - Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg (preferred in paediatric patients weighing less than 20 kg), or
    - Dolutegravir tablets for oral use

Table 2: Recommended Dosage of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg inPaediatric PatientsWeighing 14 kg or Greater

Body Weight	**Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg**	
	Daily Dose[a]	**Number of 10mg tablets**
14 kg to less than 20 kg	25mg once daily	2.5
20 kg and greater	30mg once daily	3

aIf certain UGT1A or CYP3A inducers are coadministered, then administer Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg twice daily.

Administer Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg with or without food.

Mode of administration

Instruct patients (or instruct caregivers):

The Dolutegravir sodium Dispersible Tablet should be dispersed in approximately 5 ml (if using 0.5 or 1.5 dispersible tablets)or 10ml (if using 2, 2.5 or 3 dispersible tablets)water in the cup; swirl the mixture so that no lumps remain. After full dispersion, administer the mixture within 30 minutes of mixing.

4.3 Contraindications

Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mgare contraindicated in patients:

- With previous hypersensitivity reaction to Dolutegravir.
- Receivingdofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events.

4.4 Special warnings and precautions for use

Hypersensitivity Reactions

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjectsreceiving Dolutegravir in Phase 3 clinical trials. Discontinue Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mgand other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but notlimited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mgare contraindicated in patients who have experienced a previous hypersensitivity reaction to Dolutegravir.

Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a Dolutegravir-containing regimen. Patients' withunderlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg. In some cases, the elevationsin transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly inthe setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liverbiochemistries, hepatitis, and acute liver failure have been reported in patients receiving a Dolutegravir-containingregimen without pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with FDC of Abacavir, Dolutegravir, and lamivudine. Monitoring forhepatotoxicity is recommended.

Embryo-Fetal Toxicity

An observational study showed an association between Dolutegravir and an increased risk of neural tube defectswhen Dolutegravir was administered at the time of conception and in early pregnancy. As there is limitedunderstanding of reported types of neural tube defects associated with Dolutegravir use and because the date ofconception may not be determined with precision, an alternative treatment to Dolutegravir should be considered atthe time of conception through the first trimester of pregnancy.

Perform pregnancy testing before initiation of Dolutegravir in adolescents of childbearing potential to exclude useof Dolutegravir during the first trimester of pregnancy. Initiation of

Dolutegravir is not recommended in adolescents actively trying to become pregnant unless there is no suitablealternative.

Counsel adolescents of childbearing potential to consistently use effective contraception.

In adolescents of childbearing potential currently on Dolutegravir who are actively trying to become pregnant, or ifpregnancy is confirmed in the first trimester, assess the risks and benefits of continuing Dolutegravir versusswitching to another antiretroviral regimen and consider switching to an alternative regimen.

Dolutegravir may be considered during the second and third trimesters of pregnancy if the expected benefitjustifies the potential risk to the pregnant woman and the fetus.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg and other drugs may result in known orpotentially significant drug interactions, some of which may lead to:

- Loss of therapeutic effect of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg and possible development ofresistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

For concomitant drugs for which the interaction can be mitigated, please see Table 3 for steps to prevent ormanage these possible and known significant drug interactions, including dosing recommendations. Consider thepotential for drug interactions prior to and during therapy with Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg;review concomitant medications during therapy with Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg; and monitorfor the adverse reactions associated with the concomitant drugs.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy,including Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residualopportunistic infections (such as *Mycobacterium avium*infection, cytomegalovirus, *Pneumocystis jirovecii*pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also beenreported to occur in the setting of immune reconstitution; however, the time to onset is more variable and canoccur many months after initiation of treatment.

Different Formulations Are Not Interchangeable

Dolutegravir tablets and Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg are not bioequivalent and are notinterchangeable on a milligram-per-milligram basis. If a paediatric patientswitches from one formulation to the other, the dose must be adjusted for the new dosage formulation. Incorrect dosing of a given formulation may result in under dosing and loss oftherapeutic effect and possible development of resistance or possible clinically significant adverse reactions fromgreater exposure of Dolutegravir.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, Dolutegravir inhibited the renal organic cation transporters, OCT2 (IC50 = 1.93 microM) and multidrugand toxin extrusion transporter (MATE)1 (IC50 = 6.34 microM). In vivo, Dolutegravir inhibits tubular secretion ofcreatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugseliminated via OCT2 or MATE1 (dofetilide, Dalfampridine, and metformin).

In vitro, Dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC50 = 2.12microM) and OAT3 (IC50 = 1.97 microM). However, in vivo, Dolutegravir did not alter the plasma concentrationsof tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, Dolutegravir did not inhibit (IC50 greater than 50 microM) the following: cytochrome CYP1A2, CYP2A6,CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-glycoprotein (P-gp), breastcancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. In vitro, Dolutegravir did notindu1ce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of drug interaction trials,Dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes ortransporters.

Effect of Other Agents on the Pharmacokinetics of Dolutegravir

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrateof UGT1A3, UGT1A9, BCRP, and P-gp in vitro. Drugs that induce those enzymes and transporters maydecreaseDolutegravir plasma concentration and reduce the therapeutic effect of Dolutegravir.

Coadministration of Dolutegravir and other drugs that inhibit these enzymes may increase Dolutegravirplasma concentration.Etravirine significantly reduced plasma concentrations of Dolutegravir, but the effect of etravirine was mitigated bycoadministration of Lopinavir /ritonavir or darunavir/ritonavir and is expected to be mitigated byatazanavir/ritonavir. In vitro, Dolutegravir was not a substrate of OATP1B1 or OATP1B3.

Established and Other Potentially Significant Drug Interactions

Table 3 provides clinical recommendations as a result of drug interactions with Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg. These recommendations are based on either drug interaction trials or predicted interactions due to theexpected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 3:

Concomitant Drug Class: Drug Name	**Effects on Concentration of Dolutegravir and/ or Concomitant Drug**	**Clinical Comment**
HIV -1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirinea	□ Dolutegravir	Use of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mgwith etravirine without Co-administration of atazanavir/ritonavir,darunavir/ritonavir, or lopinavir/ritonavir is notrecommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz	□Dolutegravir	Adjust dose of Dolutegravir to twice daily fortreatment-naïve and treatment-experienced, INSTI-naïve adult patients. In paediatric patients, increase the weight-baseddose of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg to twice daily.Use alternative combinations that do notinclude metabolic inducers where possible forINSTI-experienced patients with certain INSTI-associated resistance substitutions orclinically suspected INSTI resistance.[a]
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	□Dolutegravir	Avoid coadministration with Nevirapine because there are insufficient data to makedosing recommendations.

Protease inhibitors: Fosamprenavir/ritonavira Tipranavir/ritonavira	Dolutegravir	Adjust dose of Dolutegravir to twice daily fortreatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-baseddose of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mgto twice daily.Use alternative combinations that do notinclude metabolic inducers where possible forINSTI-experienced patients with certain INSTI-associated resistance substitutions orclinically suspected INSTI resistance.[a]
Other Agents		
Dofetilide	Dofetilide	Coadministration is contraindicated withDolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg
Carbamazepine[a]	Dolutegravir	Adjust dose of Dolutegravir to twice daily intreatment-naïve or treatment-experienced,INSTI-naïve adult patients.In paediatric patients, increase the weight-baseddose of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg to twice daily.Use alternative treatment that does not includecarbamazepine where possible for INSTI-experiencedpatients with certain INSTIassociatedresistance substitutions or clinicallysuspected INSTI resistance.[a]
OxcarbazepinePhenytoin Phenobarbital St. John's wort (*Hypericumperforatum*)	Dolutegravir	Avoid coadministration with Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg becausethere are insufficient data to make dosingrecommendations

Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacidsaor laxatives Sucralfate Buffered medications	Dolutegravir	Administer Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg 2 hours before or 6 hours after taking medications containing polyvalentcations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron	Dolutegravir	When taken with food, Dolutegravir andsupplements or multivitamins containingcalcium or iron can be taken at the same time.Under fasting conditions, Dolutegravir dispersible tablets should be taken2 hours before or 6 hours after takingsupplements containing calcium or iron.
Potassium channel blocker: Dalfampridine	Dalfampridine	Elevated levels of Dalfampridine increase therisk of seizures. The potential benefits oftaking Dalfampridine concurrently with Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mgshould be considered against the risk ofseizures in these patients.
Metformin	Metformin	Refer to the prescribing information formetformin for assessing the benefit and risk of concomitant use of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mgand metformin.
Rifampin	Dolutegravir	Adjust dose of Dolutegravir to twice daily fortreatment-naïve and treatment-experienced,INSTI-naïve adult patients. In paediatric patients, increase the weight-baseddose of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mgto twice

		daily.Use alternatives to rifampin where possible for INSTI-experienced patients with certainINSTI-associated resistance substitutions or Clinically suspected INSTI resistance. [a]

[a] The lower Dolutegravir exposures observed in INSTI-experienced patients (with certain INSTI-associatedresistance substitutions or clinically suspected INSTI resistance upon coadministrationwith certain inducers may result in loss of therapeutic effect and development of resistance to Dolutegravir or othercoadministered antiretroviral agents.

Drugs without Clinically Significant Interactions with Dolutegravir

Based on drug interaction trial results, the following drugs can be coadministered with Dolutegravir without a doseadjustment: atazanavir/ritonavir, darunavir/ritonavir, daclatasvir, elbasvir/grazoprevir, methadone, midazolam,omeprazole, oral contraceptives containing norgestimate and ethinylestradiol, prednisone, rifabutin, rilpivirine,sofosbuvir/velpatasvir, and tenofovir.

4.6 Pregnancy and Lactation

Risk Summary

Data from a birth outcome surveillance study has identified an increased risk of neural tube defects whenDolutegravir is administered at the time of conception compared with non-Dolutegravir-containing antiretroviralregimens. As defects related to closure of the neural tube occur from conception through the first 6 weeks ofgestation, embryos exposed to Dolutegravir from the time of conception through the first 6 weeks of gestation areat potential risk. In addition, 2 of the 5 birth defects (encephalocele and iniencephaly), which have been observedwith Dolutegravir use, although often termed neural tube defects, may occur post-neural tube closure, the timeperiod of which may be later than 6 weeks of gestation, but within the first trimester. Due to the limitedunderstanding of the types of reported neural tube defects associated with Dolutegravir use and because the date ofconception may not be determined with precision, an alternative treatment to Dolutegravir should be considered atthe time of conception through the first trimester of pregnancy. Initiation of Dolutegravir is not recommended in

adolescents actively trying to become pregnant unless there is no suitable alternative.

In adolescents of childbearing potential currently on Dolutegravir who are actively trying to become pregnant, orif pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing Dolutegravir versusswitching to another antiretroviral regimen and consider switching to an alternative regimen. Advise pregnantadolescents of the potential risk to the embryo exposed to Dolutegravir from the time of conception through thefirst trimester of pregnancy. A benefit-risk assessment should consider factors such as feasibility of switching,tolerability, ability to maintain viral suppression, and risk of transmission to the infant against the risk of neuraltube defects.

There are insufficient human data on the use of Dolutegravir during pregnancy to definitively assess a drugassociatedrisk for birth defects and miscarriage.

The background risk for major birth defects for the indicated population is unknown.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with Dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of Dolutegravir.

Lactation

Risk Summary

It is recommended that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

It is not known whether Dolutegravir is present in human breast milk, affects human milk production, or haseffects on the breastfed infant. When administered to lactating rats, Dolutegravir was present in milk.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (inHIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instructmothers not to breastfeed if they are receiving Dolutegravir.

Females and Males of Reproductive Potential

Pregnancy Testing

Perform pregnancy testing in adolescents and adults of childbearing potential before initiation of Dolutegravir.

Contraception

In adolescents and adults of childbearing potential currently on Dolutegravir who are actively trying to becomepregnant, or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing Dolutegravirversus switching to another antiretroviral regimen and consider switching to an alternative regimen.Counsel adolescents and adults of childbearing potential who are taking Dolutegravir to consistently use effectivecontraception.

Pediatric Use

Safety and effectiveness of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg have not been established in paediatricpatients aged less than 4 weeks or weighing less than 3 kg or in any paediatric patients who are INSTI-experiencedwith documented or clinically suspected resistance to other INSTIs (e.g., raltegravir, elvitegravir).

Geriatric Use

Clinical trials of Dolutegravir did not include sufficient numbers of subjects aged 65 and older to determinewhether they respond differently from younger subjects. In general, caution should be exercised in theadministration of Dolutegravir in elderly patients reflecting the greater frequency of decreased hepatic, renal, orcardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment andmatching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderatehepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) onthe pharmacokinetics of Dolutegravir has not been studied. Therefore, Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mgare not recommended for use in patients with severe hepatic impairment.

Renal Impairment

Dolutegravir plasma concentrations were decreased in subjects with severe renal impairment compared with thosein matched healthy controls. However, no dosage adjustment is necessary for treatment-naïve or treatmentexperiencedand INSTI-naïve patients with mild, moderate, or severe renal impairment or for INSTI-experiencedpatients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with mildor moderate renal impairment. Caution is warranted for INSTI-experienced patients (with certain INSTI-associatedresistance substitutions or clinically suspected INSTI resistance with severe renalimpairment, as the decrease in Dolutegravir concentrations may result in loss of therapeutic effect and developmentof resistance to Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg or other coadministered antiretroviral agents. There is inadequate information to recommend appropriate dosing of Dolutegravirin patients requiring dialysis.

4.7 Effects on ability to drive and use machines

Patients should be informed that Dolutegravir can cause dizziness. The patient's clinical status and Dolutegravir's side effects should be considered for evaluating the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The adverse reactions considered at least possibly related to Dolutegravir are listed by body system, organ class and absolute frequency. Frequencies are defined as 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), very rare (<1/10,000).

Table 4: Adverse Reactions

Immune system disorders	Uncommon	Hypersensitivity
	Uncommon	Immune Reconstitution Syndrome **
Psychiatric disorders	Common	Insomnia
	Common	Abnormal dreams
	Common	Depression
	Common	Anxiety
	Uncommon	Suicidal ideation*, suicide attempt* *particularly in patients with a pre-existing history of depression or psychiatric illness.
Nervous system disorders	Very common	Headache
	Common	Dizziness
Gastrointestinal disorders	Very common	Nausea
	Very common	Diarrhoea
	Common	Vomiting
	Common	Flatulence
	Common	Upper abdominal pain
	Common	Abdominal pain
	Common	Abdominal discomfort
Hepatobiliary disorders	Uncommon	Hepatitis
	Rare	Acute hepatic failure
Skin and subcutaneous tissue disorders	Common	Rash
	Common	Pruritus
Musculoskeletal and	Uncommon	Arthralgia

connective tissue disorders	Uncommon	Myalgia, Myosis
Renal and Urinary disorders	Uncommon	Renal impairment
General disorders and administration site conditions	Common	Fatigue
Investigations	Common	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations
	Common	Creatine phosphokinase (CPK) elevations

**see below under Description of selected adverse reactions.

Description of selected adverse reactions

Changes in laboratory biochemistries

Increases in serum creatinine occurred within the first week of treatment with Dolutegravir and remained stable through 48 weeks. A mean change from baseline of 9.96 µmol/L was observed after 48 weeks of treatment. Creatinine increases were comparable by various background regimens. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.

Co-infection with Hepatitis B or C

In Phase III studies patients with hepatitis B and/or C co-infection were permitted to enroll 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.

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.

Paediatric population

The safety and pharmacokinetics of Dolutegravir tablets and Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg for oral suspension in HIV-1–infected pediatric subjects aged at least 4 weeks and weighing at least 3 kg was evaluated.Overall, the safety data in these paediatric studies were similar to those seen in adults, and there was no clinically significant difference in Dolutegravir exposure.

Post Marketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post-marketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity.

Investigations

Weight increased

Musculoskeletal

Arthralgia, myalgia

Psychiatric

Anxiety.

4.9 Overdose

There is no known specific treatment for overdose with Dolutegravir tablets. Ifoverdose occurs, the patient should be monitored, and standard supportive treatment applied as required. AsDolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Mechanism of Action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step ofretroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transferbiochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC50 values of 2.7nM and 12.6 nM.

Antiviral Activity in Cell Culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC50 values of0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC50value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates.

Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in eachgroup of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC50 values ranging from 0.02 nM to 2.14 nMfor HIV-1. Dolutegravir EC50 values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to0.61 nM.

Antiviral Activity in Combination with Other Antiviral Agents

The antiviral activity of Dolutegravir was not antagonistic when combined with the INSTI, raltegravir; nonnucleosidereverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the NRTIs, abacavir or stavudine;the protease inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusioninhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reversetranscriptase inhibitor, adefovir, or inhibited by the antiviral, ribavirin.

Resistance

Cell Culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in differentpassages and conferred decreased susceptibility to Dolutegravir of up to 4-fold. Passage of mutant virusescontaining the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferreddecreased susceptibility to Dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutionsincluded T97A, E138K, G140S, and M154I.Passage of mutant viruses containing both G140S and Q148Hselected for L74M, E92Q, and N155H.

Pharmacodynamics

Effects on Electrocardiogram

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrationsof placebo, Dolutegravir 250-mg suspension (exposures approximately 3– fold of the 50-mg once-daily dose atsteady state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placeboadjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for Dolutegravir was2.4 msec (1-sided 95% upper CI:4.9msec).Dolutegravir did not prolong the QTc interval over 24 hours postdose.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of Dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose.With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with averageaccumulation ratios for AUC, C_{max}, and C24 h ranging from 1.2 to 1.5.

Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Dolutegraviris a P-gp substrate in vitro. The absolute bioavailability of Dolutegravir has not been established.

Effect of Food: Dolutegravir tablets may be taken with or without food. Food increasedthe extent of absorption and slowed the rate of absorption of Dolutegravir following a 50-mg dose of Dolutegravir.

Low-, moderate-, and high-fat meals increased Dolutegravir AUC(0-t) by 33%, 41%, and 66%; increased C_{max} by46%, 52%, and 67%; and prolonged $T_{max}$to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

Distribution

Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on in vivo data andbinding is independent of plasma concentration of Dolutegravir. The apparent volume of distribution (Vd/F)following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

Cerebrospinal Fluid (CSF): In 12 treatment-naïve subjects on Dolutegravir 50 mg daily plusabacavir/lamivudine, the median Dolutegravir concentration in CSF was 13.2 ng per mL (range:3.74 ng per mL to 18.3 ng per mL) 2 to 6 hours postdose after 16 weeks of treatment. The clinical relevance of thisfinding has not been established.

Elimination

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L per hourbased on population pharmacokinetic analyses.

Metabolism*:* Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A.

Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects withUGT1A1 (n = 7) genotypes conferring poor Dolutegravir metabolism had a 32% lower clearance of Dolutegravirand 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n= 41).

Excretion: After a single oral dose of [14C] Dolutegravir, 53% of the total oral dose was excreted unchanged infeces. Thirty-one percent of the total oral dose was excreted in urine, represented by an ether glucuronide ofDolutegravir (18.9% of total dose), a

metabolite formed by oxidation at the benzylic carbon (3.0% of total dose),and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was low (lessthan 1% of the dose).

5.3 Preclinical safety data

Carcinogenesis

Two-year carcinogenicity studies in mice and rats were conducted with Dolutegravir. Mice were administereddoses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significantincreases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting inDolutegravir AUC exposures approximately 14 times higher than those in humans at the maximum recommendeddose. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested,resulting in Dolutegravir AUC exposures 10 times and 15 times higher in males and females, respectively, thanthose in humans at the maximum recommended dose.

Mutagenesis

Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivorodent micronucleus assay.

Impairment of Fertility

In a study conducted in rats, there were no effects on mating or fertility with Dolutegravir up to 1,000 mg per kgper day. This dose is associated with an exposure that is approximately 24 times higher than the exposure inhumans at the maximum recommended dose.

6. Pharmaceutical Particulars

6.1 List of Excipients

Mannitol, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Silicified Microcrystalline Cellulose, Crospovidone, Calcium Sulphate Dihydrate, Strawberry Cream Flavor, Sucralose, Sodium Stearyl Fumarate, Opadry Pink (Hypromellose, Titanium dioxide, Macrogol and Iron oxide red).

6.2 Incompatibilities

None

6.3 Shelf life

24 months from the manufacturing date.

Never use after the expiry date clearly indicated on the outer packaging.

6.4 Special precautions for storage

Store below 30℃, Store in the original package to protect from moisture.

Keep the bottle tightly closed.

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

Do not use this medicine after the expiry date which is stated after EXP on the carton and bottle.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg will be packed in

Container Pack: 90's Tablet with Silica Gel

90 tablets packed in 60cc white, round HDPE container with 33 mm neck finish with 33 mm Closure, child resistant with pulp and white printed heat seal liner with 1g Silica gel sachet (2x1gm) along with pack insert.

Container Pack: 90's Tablet without Silica Gel

90 tablets packed in 60cc white, round HDPE container with 33 mm neck finish with 33 mm Closure, child resistant with pulp and white printed heat seal liner along with pack insert.

6.6 Special Precaution for disposal

None

7. Supplier

Macleods Pharmaceuticals Ltd.

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Andheri (East), Mumbai- 400 059,

India

Phone: +91-22-66762800

Fax: +91-22-2821 6599

E-mail: exports@macleodsphara.com

8. Who Reference Number (Prequalification Programme)

9. Date of first Prequalification/ last renewal

10. Date of Revision of the Text:

References:

1. https://www.medicines.org.uk/emc/product/5248/smpc
2. Label of RLD of Dolutegravir Sodium Tablet for Oral Suspension (Dispersible Tablets) 10mg 5mg, ViiV