WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA678 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Pink, round, film-coated tablets. They are biconvex (rounded on top and bottom) with bevelled edges. The tablets have 'M' debossed (stamped into) one side and 'DT5' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA678 trade name] is indicated, in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in patients weighing at least 20 kg.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

[HA678 trade name] may also be used as part of a regimen for post-exposure prophylaxis to HIV. For use of antiretroviral agents for post-exposure prophylaxis the most recent official guidelines, e.g. those by WHO, should be consulted.

4.2 Posology and method of administration

Treatment with [HA678 trade name] should be initiated by a health care provider experienced in the management of HIV infection.

Posology

Treatment of HIV infection

Adults

The dose in adults with HIV infection not resistant to integrase inhibitors is 1 tablet of [HA678 trade name] once daily.

The dose should be 1 tablet of [HA678 trade name] twice daily if:

- dolutegravir is used with medicines that reduce dolutegravir exposure such as efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin (see section 4.5)
- the patient's HIV infection is known or suspected to be resistant to integrase inhibitors.

When HIV genotype testing is available and for patients whose treatment options are limited (fewer than 2 active antiretrovirals) due to advanced multi-class resistance, a higher dose of dolutegravir may be considered. Such resistance may include Q148 with two or more secondary mutations from G140A/C/S, E138A/K/T, L74I.

The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern. In these patients, dolutegravir should not be given with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin; see section 4.5).

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† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Children and adolescents

The dose in children and adolescents weighing at least 20 kg with HIV infection not resistant to integrase inhibitors is 1 tablet of [HA678 trade name] once daily.

There is insufficient information to recommend a dose of dolutegravir in children and adolescents with HIV infection resistant to integrase inhibitors.

The dose should be 1 tablet of [HA678 trade name] twice daily if dolutegravir is used with rifampicin (for treatment of tuberculosis) in children weighing 20 kg to less than 35 kg. The twice-daily dosing of [HA678 trade name] should continue for two weeks after the final rifampicin dose.

[HA678 trade name] is not suitable for patients weighing less than 20 kg. Other formulations with a lower strength should be used.

Post-exposure prophylaxis (PEP)

The recommended dose of [HA678 trade name] as part of a regimen for PEP in adults, adolescents and children weighing at least 20 kg is the same as for treatment of HIV infection.

PEP should start as early as possible after exposure, ideally within 72 hours of exposure, and is given for a total of 28 days.

Dosing in special populations

Elderly

Based on limited data, there is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2).

Renal impairment

No dose adjustment is needed for patients with renal impairment. The use of dolutegravir has not been studied in patients on dialysis but the dose is not expected to be different for these patients.

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available in patients with severe hepatic impairment (Child-Pugh grade C); therefore, dolutegravir should be used with caution in these patients.

Missed dose

If the patient misses a dose of dolutegravir, the patient should take it as soon as possible, provided that the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and just take the next dose at the usual time. The patient should not take a double dose.

Method of administration

Oral use.

Dolutegravir can be taken with food or between meals. If the HIV strain is resistant to integrase inhibitors, dolutegravir should preferably be taken with food to increase absorption (particularly in patients with Q148 mutations).

4.3 Contraindications

Hypersensitivity to dolutegravir or to any of the excipients listed in section 6.1.

Dolutegravir must not be administered concurrently with medicines with narrow therapeutic windows that are substrates of organic cation transporter 2 (OCT2), including dofetilide and fampridine (also known as dalfampridine; see section 4.5).

4.4 Special warnings and precautions for use

HIV resistant to integrase inhibitors

The decision to use dolutegravir in the presence of HIV resistance to integrase inhibitors should take into account that it is considerably less active against viral strains with Q148 with two or more secondary mutations from G140A/C/S, E138A/K/T, L74I. Dolutegravir's contribution to efficacy is uncertain when it is used to treat HIV with this type of resistance to integrase inhibitors. A two-drug regimen of dolutegravir and lamivudine once daily is only suitable for the treatment of HIV infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine.

Hypersensitivity reactions

Dolutegravir and other suspect substances should be discontinued immediately if hypersensitivity reactions develop (including severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, and angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with dolutegravir or other suspect substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Immune reactivation syndrome

Immune reactivation syndrome has been reported in patients treated with combination antiretroviral therapy. During early stages of treatment, patients whose immune system responds to antiretroviral therapy may develop an inflammatory response to slow-developing or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus retinitis, *Pneumocystis jirovecii* pneumonia, or tuberculosis). These reactions may require further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, autoimmune hepatitis, polymyositis, and Guillain-Barré syndrome) have also been reported in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after starting antiretroviral treatment.

Raised liver enzymes, consistent with immune reactivation syndrome, occurred in some patients who also had hepatitis B or C at the start of dolutegravir therapy. Monitoring of liver function is recommended in patients with hepatitis B or C. Particular care should be taken in initiating or maintaining hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy.

Opportunistic infections

Health care providers should tell patients with impaired immunity that opportunistic infections or other complications of HIV infection may still develop while receiving antiretroviral medicines. This risk reduces as the immune system recovers.

Osteonecrosis

Osteonecrosis has been reported particularly in patients with advanced HIV disease or following long-term combination antiretroviral therapy. Its aetiology can be multifactorial and include corticosteroid use, excessive alcohol consumption, severe immunosuppression, and being overweight. Patients should be advised to speak to their health care provider if they have joint aches and pain, joint stiffness or difficulty in movement.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy, including with regimens that incorporate dolutegravir. Such changes may in part be linked to disease control and lifestyle. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. Blood lipids and glucose should be monitored as clinically appropriate and in line with HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents on dolutegravir

Medicines that lower plasma concentration of dolutegravir should be avoided in the presence of HIV-1 resistant to integrase inhibitors. These medicines include magnesium- or aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents such as etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St John's wort and certain antiepileptic medicines (see table, below).

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, and the transporters P-gp and BCRP; therefore, medicines that induce the function of these proteins may decrease dolutegravir plasma concentration and reduce its therapeutic effect. Conversely, giving dolutegravir with other medicines that inhibit their function may increase dolutegravir plasma concentration (see table, below).

Effects of dolutegravir on other agents

In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on in vivo and in vitro data, dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of major enzymes or transporters such as CYP3A4, CYP2C9 and P-gp (see section 5.2).

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1). In vivo, a 10–14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE1 transport) was observed in patients. In vivo, dolutegravir may increase plasma concentrations of medicines whose excretion depends on OCT2 and/or MATE1 (e.g. fampridine [also known as dalfampridine], metformin) (see the table below).

In vitro, dolutegravir inhibited the renal uptake transporters, organic anion transporters OAT1 and OAT3. Based on the lack of effect on the in vivo pharmacokinetics of the OAT substrate tenofovir, in vivo inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been studied in vivo. Dolutegravir may increase plasma concentrations of medicines whose excretion depends on OAT3.

Interaction table

Interactions between dolutegravir and co-administered medicinal products are listed in the following table. The pharmacokinetic data reflect studies in adults (increase is indicated as ↑, decrease as ↓, no change as ↔, area under the concentration versus time curve as AUC, maximum observed concentration as C_{max}, concentration at end of dosing interval as C_{τ}).

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Antimicrobials		
Antiretrovirals		
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71%; C_{max} ↓ 52%; C_{τ} ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine decreased plasma dolutegravir concentration. The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. When used with etravirine for infection resistant to integrase inhibitors, dolutegravir should be co-administered with atazanavir/ritonavir, or darunavir/ritonavir, or lopinavir/ritonavir (see below in table).
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11%; C_{max} ↑ 7%; C_{τ} ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25%; C_{max} ↓ 12%; C_{τ} ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓ 57%; C_{max} ↓ 39%; C_{τ} ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with efavirenz. For infection resistant to integrase inhibitors, alternative combinations that do not include efavirenz should be considered.
Nevirapine	Dolutegravir ↓ (Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with nevirapine. For infection resistant to integrase inhibitors, alternative combinations that do not include nevirapine should be considered.
Rilpivirine	Dolutegravir ↔ AUC ↑ 12%; C_{max} ↑ 13%; C_{τ} ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside reverse transcriptase inhibitors (NRTI)		
Tenofovir disoproxil	Dolutegravir ↔ AUC ↑ 1%; C_{max} ↓ 3%; C_{τ} ↓8% Tenofovir ↔	No dose adjustment is necessary.
Protease inhibitors (PIs)		
Atazanavir	Dolutegravir ↑ AUC ↑ 91%; C_{max} ↑ 50%; C_{τ} ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. The dose of dolutegravir should not exceed 50 mg twice daily in combination with atazanavir because data are not available.
Atazanavir/ritonavir	Dolutegravir ↑ AUC ↑ 62%; C_{max} ↑ 34%; C_{τ} ↑ 121% Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. The dose of dolutegravir should not exceed 50 mg twice daily in combination with atazanavir because data are not available.
Tipranavir/ritonavir	Dolutegravir ↓ AUC ↓ 59%; C_{max} ↓ 47%; C_{τ} ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with tipranavir/ritonavir. For infection resistant to integrase inhibitors, alternative combinations that do not include tipranavir/ritonavir should be considered.
Fosamprenavir/ ritonavir	Dolutegravir ↓ AUC ↓ 35%; C_{max} ↓ 24%; Cτ ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. For infection resistant to integrase inhibitors, alternative combinations that do not include fosamprenavir/ritonavir should be considered.

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22%; C_{max} ↓ 11%; $C_{24hours}$ ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Lopinavir/ritonavir	Dolutegravir ↔ AUC ↓ 4%; C_{max} ↔ 0%; $C_{24hours}$ ↓ 6%	No dose adjustment is necessary.
Antivirals against hepatitis C		
Daclatasvir	Dolutegravir ↔ AUC ↑ 33%; Cmax ↑ 29%; Cτ ↑ 45% Daclatasvir ↔	No dose adjustment is necessary.
Elbasvir/grazoprevir Glecaprevir/pibrentasvir Ledipasvir/sofosbuvir Ombitasvir/paritaprevir Ombitasvir/paritaprevir/dasabuvir Sofosbuvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/voxilaprevir	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary.
Antibiotics		
Rifampicin	Dolutegravir ↓ AUC ↓ 54%; C_{max} ↓ 43%; C_{τ} ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with rifampicin. In paediatric patients the weight-based once daily dose should be given twice daily. For infection resistant to integrase inhibitors, co-administration of dolutegravir and rifampicin should be avoided.
Rifabutin	Dolutegravir ↔ AUC ↓ 5%; C_{max} ↑ 16%; C_{τ} ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Antifungals		
Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
Antacids and supplements		
Magnesium- or aluminium-containing antacid	Dolutegravir ↓ AUC ↓ 74%; C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium- or aluminium-containing antacid should be taken well separated in time from dolutegravir (minimum 2 hours after or 6 hours before).

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Calcium supplements (fasted intake)	Dolutegravir ↓ AUC ↓ 39%; C_{max} ↓ 37%; $C_{24hours}$ ↓ 39% (Complex binding to polyvalent ions)	When taken with food, dolutegravir and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. When dolutegravir is taken in the fasted state, calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before). The stated reduction in dolutegravir exposure were observed with the intake of doluegravir and these supplements during fasted conditions. In fed state, the changes in exposure following intake together with calcium or iron supplements were modified by the food effect, resulting in an exposure similar to that obtained with dolutegravir administered in the fasted state.
Iron supplements (fasted intake)	Dolutegravir ↓ AUC ↓ 54%; C_{max} ↓ 57%; $C_{24hours}$ ↓ 56% (Complex binding to polyvalent ions)	
Multivitamins (containing calcium, iron and magnesium) (fasted intake)	Dolutegravir ↓ AUC ↓ 33%; C_{max} ↓ 35% $C_{24hours}$ ↓ 32% (Complex binding to polyvalent ions)	
Antiarrhythmics		
Dofetilide	Dofetilide ↑ (Not studied, potential increase via inhibition of OCT2 transporter)	Dolutegravir and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration.
Antidiabetics		
Metformin	Co-administered with dolutegravir 50 mg once daily: Metformin ↑ AUC ↑ 79%; C_{max} ↑ 66% Co-administered with dolutegravir 50 mg twice daily: Metformin ↑ AUC ↑ 145%; C_{max} ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when given with dolutegravir, because the risk of lactic acidosis is increased in patients with moderate renal impairment due to increased metformin concentration.
Antiepileptics		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49%; C_{max} ↓ 33%; C_{τ} ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when given with carbamazepine. In paediatric patients the weight-based once-daily dose should be given twice daily. Alternatives to carbamazepine should be used in patients with infection resistant to integrase inhibitors.
Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a reduction in exposure similar to carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with these enzyme inducers. Alternatives to these medicines that are not enzyme inducers should be used in patients with infection resistant to integrase inhibitors.

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Contraceptives		
Ethinylestradiol and norelgestromin	Dolutegravir ↔ Ethinylestradiol ↔ AUC ↑ 3%; C_{max} ↓ 1% Norelgestromin ↔ AUC ↓ 2%; C_{max} ↓ 11%	Dolutegravir had no pharmacodynamic effect on luteinizing hormone, follicle stimulating hormone and progesterone. No dose adjustment of oral contraceptives is necessary when given with dolutegravir.
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11%; C_{max} ↑ 6%; C_{τ} ↑ 17%	No dose adjustment is necessary.
Drug abuse		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓ 2%; C_{max} ↔ 0%; C_{τ} ↓ 1%	No dose adjustment is necessary.
Herbal products		
St John's wort	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a reduction in exposure similar to carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with St John's wort. Alternatives to St John's wort should be used in patients with infection resistant to integrase inhibitors.
Multiple sclerosis medicines		
Fampridine (also known as dalfampridine)	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Fampridine co-administration with dolutegravir is contraindicated.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential

There has been concern about the potential risk of neural tube defects with dolutegravir (see below).

Dolutegravir-based regimens can be recommended for HIV treatment in women of childbearing potential, as the overall benefits are considered likely to outweigh the risks. Use of effective contraceptive measures, and pregnancy testing before beginning treatment, may be considered. Health care providers should discuss any concerns, and the benefits and risks of available treatment options, with women who are planning to become pregnant.

Pregnancy

Dolutegravir may be used for the treatment of HIV in pregnancy.

There has been concern about the possibility of a small increased risk of neural tube defects with dolutegravir taken in the periconceptional period (see *Human and animal data on pregnancy*, below). However, it is unclear that the risks with dolutegravir-based regimens are genuinely greater than for alternative options, and the benefits of effective HIV treatment with dolutegravir are considered likely to outweigh the risks.

More than 1000 outcomes in women who took dolutegravir in the second and third trimester of pregnancy do not indicate increased risk of fetal or neonatal toxicity.

Breast-feeding

Dolutegravir is excreted in human milk in small amounts (a median dolutegravir breast milk to maternal plasma ratio of 0.033 has been shown). There is insufficient information on the effects of dolutegravir in neonates/infants.

Current recommendations on HIV and breast-feeding (including those from the WHO) should be consulted before advising patients about breast-feeding. Preferred options may depend on local circumstances.

Fertility

There are no data on dolutegravir's effects on male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility.

Human and animal data on pregnancy

Two large birth outcome surveillance studies (more than 14 000 pregnancy outcomes) in Botswana (Tsepamo) and Eswatini, and other sources, do not indicate an increased risk for neural tube defects after dolutegravir exposure.

The incidence of neural tube defects in the general population ranges from 0.5–1 case per 1000 live births (0.05–0.1%).

Data from the Tsepamo study show no significant difference in the prevalence of neural tube defects (0.11%) in infants whose mothers were taking dolutegravir at conception (more than 9400 exposures) compared to those taking non-dolutegravir containing antiretroviral regimens at conception (0.11%) or compared to women without HIV (0.07%).

Data from an Eswatini study show the same prevalence of neural tube defects (0.08%) in infants whose mothers were taking dolutegravir at conception (more than 4,800 exposures), as infants of women without HIV (0.08%).

Data from the Antiretroviral Pregnancy Registry (APR) of more than 1000 pregnancies with first trimester dolutegravir treatment, do not indicate an increased risk of major birth defects with dolutegravir, lamivudine or abacavir compared to the background rate or women with HIV.

In animal reproductive toxicology studies with dolutegravir, no adverse development outcomes, including neural tube defects, were identified.

Dolutegravir crosses the placenta in animals (see section 5.3). In pregnant women living with HIV, the median fetal umbilical cord concentration of dolutegravir was approximately 1.3-fold greater compared with the maternal peripheral plasma concentration.

4.7 Effects on ability to drive and use machines

Patients should be informed that dolutegravir can cause dizziness. The patient's clinical status as well as dolutegravir's side effects should be considered when evaluating the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

Data from clinical trials were used to estimate the frequency of adverse events linked to dolutegravir treatment. The most severe adverse reactions are hypersensitivity reactions that include rash and severe liver effects. The most common adverse reactions of dolutegravir are nausea (13%), diarrhoea (18%) and headache (13%).

Tabulated list of adverse reactions

Adverse reactions considered related to dolutegravir are listed below by body system or organ. Frequencies are defined as follows: very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000

to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Blood and lymphatic system disorders

Not known	sideroblastic anaemia

Immune system disorders

Uncommon	hypersensitivity (see section 4.4), immune reactivation syndrome (see section 4.4 and also described below)

Metabolism and nutrition disorders

Common	weight gain

Psychiatric disorders

Common	insomnia, abnormal dreams, depression, anxiety
Uncommon	panic attack, suicidal ideation or suicide attempt (particularly in patients with history of depression or psychiatric illness; deaths from suicide have occurred)

Nervous system disorders

Very common	headache
Common	dizziness

Gastrointestinal disorders

Very common	nausea, diarrhoea
Common	vomiting, flatulence, upper abdominal pain, abdominal pain, abdominal discomfort

Hepatobiliary disorders

Common	raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
Uncommon	hepatitis
Rare	acute hepatic failure, increased bilirubin (in combination with increased transaminases)

Skin and subcutaneous tissue disorders

Common	rash, pruritus

Musculoskeletal and connective tissue disorders

Uncommon	arthralgia, myalgia

General disorders

Common	fatigue

Investigations

Common	raised creatine kinase

Description of selected adverse reactions

Changes in serum creatinine

Serum creatinine can increase in the first week of treatment with dolutegravir and then remain stable. A mean change from baseline of 10 µmol/L occurred after 48 weeks of treatment. Creatinine increases were comparable between various background regimens. These changes are not considered clinically relevant since they do not reflect a change in glomerular filtration rate.

Co-infection with hepatitis B or C

In clinical studies, the side effects profile in patients also infected with hepatitis B or C or both was similar to that in patients without hepatitis, provided that the baseline liver function tests did not exceed 5 times the

upper limit of normal. However, the rates of AST and ALT abnormalities were higher in patients with hepatitis B or C co-infection. Liver enzyme elevations consistent with immune reactivation syndrome occurred in some patients with hepatitis B or C co-infection at the start of dolutegravir therapy, particularly in those whose hepatitis B therapy was stopped.

Immune reactivation syndrome

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

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.

Paediatric population

The limited data available for children and adolescents suggest no additional adverse reactions beyond those that occur in adults.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Experience of dolutegravir overdosage is limited. Single doses of up to 250 mg in healthy subjects revealed no specific symptoms or signs, apart from those listed as adverse reactions.

There is no specific treatment for dolutegravir overdose. In an overdose, the patient should be treated supportively with appropriate monitoring as necessary, and with advice from a national poisons centre where available. Dialysis is unlikely to remove dolutegravir to any significant extent because it is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Antivirals for systemic use, integrase inhibitors, ATC code: J05AJ03.

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.

Pharmacodynamic effects

Antiviral activity in cell culture

The IC_{50} for dolutegravir for clinical isolates showed no major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC_{50} was 0.2 nM (range 0.02–2.14 nM). The mean IC_{50} for three HIV-2 isolates was 0.18 nM (range 0.09–0.61 nM).

Antiviral activity in combination with other antiviral agents

No antagonistic effects were seen in vitro with dolutegravir and other antiretrovirals tested: stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc and raltegravir. In addition, no antagonistic effects were seen for dolutegravir and adefovir. Ribavirin had no apparent effect on dolutegravir activity.

Effect of human serum

In 100% human serum, the mean protein fold shift was 75-fold, resulting in protein adjusted IC_{90} of 0.064 µg/mL.

Resistance in vitro

Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q and T66I) do not affect the in vitro susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase inhibitor associated mutations (for raltegravir/elvitegravir) are added to most of these primary mutations in experiments with site-directed mutants, dolutegravir susceptibility is still unchanged (FC < 2 vs wild-type virus). However, for Q148-mutations in combination with certain secondary mutations, the FC (fold-change as compared to wild-type virus) is 5–10 times or higher. The effect of the Q148-mutations (H/R/K) was verified in passage experiments with site-directed mutants. In serial passage, starting with mutants harbouring mutation Q148H (FC 1), a variety of secondary mutations were seen with a consequent increase of FC to values > 10.

A clinically relevant phenotypic cut-off value (FC vs wild type virus) has not been determined; genotypic resistance was a better predictor for outcome.

In an analysis for susceptibility to dolutegravir in raltegravir-resistant isolates (from raltegravir-experienced patients), dolutegravir had a less than or equal to 10 FC against 94% of the 705 clinical isolates. The E92Q mutation has been selected in patients with pre-existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

Resistance in vivo

The most common clinically significant dolutegravir-resistance mutations are T66K, E92Q, G118R, E138K/A/T, G140S/A/G Q148H/R/K, N155H, R263K. The Q148H/R/K mutations reduce integrase strand transfer inhibitor (INSTI) susceptibility or virological response, while the other mutations listed contribute to reduced susceptibility in combination with other INSTI-resistance mutations.

Throughout the studies in previously untreated patients no cases of treatment-emergent primary resistance to the integrase inhibitors or to nucleoside reverse transcriptase occurred in patients treated with dolutegravir.

In treatment-experienced patients without prior exposure to integrase inhibitors statistically fewer subjects failed therapy with treatment-emergent integrase resistance on dolutegravir (4/354, 1%) than on raltegravir (17/361, 5%) (p = 0.003). Of these four, two subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, one subject had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and one subject had pre-existing integrase mutations and is assumed to have been integrase-experienced or infected with integrase-resistant virus by transmission. The R263K mutation was also selected in vitro.

In the presence of integrase class-resistance (VIKING-3 study) the following mutations were selected in 32 patients with protocol defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimised background agents): L74L/M (n = 1), E92Q (n = 2), T97A (n = 9), E138K/A/T (n = 8), G140S (n = 2), Y143H (n=1), S147G (n = 1), Q148H/K/R (n = 4), and N155H (n = 1) and E157E/Q (n = 1). Treatment emergent integrase resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic). Five further subjects experienced PDVF between weeks 24 and 48, and 2 of these 5 had treatment-emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74I (n = 1), N155H (n = 2). Treatment-emergent mutations observed in another study in 30 subjects with primary genotypic resistance to integrase inhibitors at screening given dolutegravir plus optimised background therapy were consistent with those in the VIKING-3 study.

In paediatric patients with prior failed therapies, but naïve to the integrase class, the integrase inhibitor substitution G118R was observed in 5/159 patients treated with dolutegravir, given in combination with an investigator selected background regimen. Of these five, 4 participants had additional integrase associated substitutions as follows: L74M, E138E/K, E92E/Q and T66I. Four of the 5 participants with emergent G118R had phenotypic data available. Dolutegravir FC (fold change as compared to wildtype virus) for these four participants ranged from 6 to 25-fold.

For more detailed information reference is made to the current Stanford University HIV Drug Resistance Database.

Effects on electrocardiogram

No relevant effects were seen on the QTc interval, with doses 3-fold higher than the clinical dose.

Clinical efficacy and safety

The efficacy of dolutegravir has been shown in combination with various antiretroviral background regimens in previously untreated adult patients, patients treated previously with regimens that excluded integrase inhibitors and patients in whom an integrase inhibitor had failed (patients with HIV-1 resistant to integrase inhibitors, who were dosed with dolutegravir 50 mg twice daily). Virologic response rates (HIV-RNA < 50 copies/mL) at week 48 ranged according to the population studied from 90% to 69% (response was, however, lower in the presence of the Q148 mutation at baseline, especially if there were also 2 or more secondary mutations).

In a study in HIV-1 infected infants, children and adolescents aged ≥ 4 weeks to < 18 years, mostly treatment-experienced, dosed once daily with dolutegravir film-coated tablets or dispersible tablets in combination regimens, 65.2% of the patients achieved virologic response (HIV-RNA < 50 copies/mL) at week 48. In participants experiencing virologic failure, 5/36 acquired integrase inhibitor substitution G118R, mostly with additional integrase associated substitutions. Dolutegravir FC (fold change as compared to wildtype virus) for participants with phenotypic data available ranged from 6 to 25-fold.

5.2 Pharmacokinetic properties

The absorption characteristics of [HA678 trade name] after one dolutegravir (as sodium) 50 mg tablet was administered to healthy volunteers in the fasted state are as follows:

Characteristic	**Arithmetic mean ± standard deviation**
Maximum concentration (C_{max}) ng/mL	2324 ± 648
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.h/mL	45667 ± 15354
Time to attain maximum concentration (T_{max}) hour	2.50 ± 1.51

Pharmacokinetics of dolutegravir

	Dolutegravir
General	
	PK similar for healthy and HIV-infected subjects. Low to moderate PK variability
Absorption	
Absolute bioavailability	Not known
Oral bioavailability	At least 32%. The relative bioavailability of dispersible tablets is approximately 1.6-fold higher than film-coated tablets.

<table>
<tr><td>Food effect</td><td>
<table>
<tr><td></td><td>AUC $_{(0-\infty)}$</td><td>C_{max}</td><td>T_{max}</td></tr>
<tr><td>Low fat</td><td>33%↑</td><td>46%↑</td><td>3 h</td></tr>
<tr><td>Moderate fat:</td><td>41%↑</td><td>52%↑</td><td>4 h</td></tr>
<tr><td>High fat:</td><td>66%↑</td><td>67%↑</td><td>5 h</td></tr>
</table>
Increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, it is recommended that patients infected with HIV resistant to integrase inhibitors take dolutegravir with food.</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Volume of distribution (mean)</td><td>17 to 20 L</td></tr>
<tr><td>Plasma protein binding in vitro</td><td>> 99%, increase in unbound fraction with low serum albumin (as in moderate hepatic impairment)</td></tr>
<tr><td>Tissue distribution</td><td>CSF: mean 18 ng/mL
(comparable to unbound plasma concentration, and > IC_{50})
Vaginal, cervical tissue, cervicovaginal fluid: 6–10%
Semen: 7%
Rectal tissue: 17%
(each of corresponding plasma levels at steady state)</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td></td><td>Hepatic metabolism:
glucuronidation via UGT1A1
minor pathway CYP3A</td></tr>
<tr><td colspan="2">Elimination</td></tr>
<tr><td>Elimination half life</td><td>14 h</td></tr>
<tr><td>Mean systemic clearance (Cl/F)</td><td>≈1 L/h</td></tr>
<tr><td>% of dose excreted in urine</td><td>32% in total;
< 1% unchanged, 19% as ether glucuronide
Other metabolites: N-dealkylation metabolite and metabolite formed by oxidation at the benzylic carbon</td></tr>
<tr><td>% of dose excreted in faeces</td><td>53% is excreted unchanged in the faeces</td></tr>
<tr><td>Pharmacokinetic linearity</td><td>Depending on dose and formulation. For film-coated tablets: dose-proportional increases from 25 to 50 mg</td></tr>
<tr><td colspan="2">Drug interactions (in vitro)</td></tr>
<tr><td>Transporters</td><td>Inhibition of OCT2, MATE-1, OAT3 and OAT1 (clinical relevance of the latter unlikely).
No relevant inhibition of P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4.
No substrate of human OATP 1B1, OATP 1B3 or OCT 1.</td></tr>
<tr><td>Metabolising enzymes</td><td>No relevant inhibition of (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7
No induction of CYP1A2, CYP2B6 or CYP3A4</td></tr>
</table>

Pharmacokinetic/pharmacodynamic relationship

A dose-ranging trial involving dolutegravir monotherapy found rapid and dose-dependent antiviral activity, with mean decline in HIV-1 RNA of 2.5 log10 at day 11 for 50 mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

Modelling of pooled data from clinical studies in integrase-inhibitor-resistant patients suggest that increasing the dose from 50 mg twice daily to 100 mg twice daily may increase the effectiveness of dolutegravir in patients with integrase-inhibitor-resistance and limited treatment options due to advanced multi-class resistance. The proportion of responders (HIV-1 RNA < 50 copies/mL) at week 24 was predicted to increase around 4–18% in the subjects with Q148 with two or more secondary mutations from G140A/C/S, E138A/K/T, L74I. Although these simulated results have not been confirmed in clinical trials, this high dose may be considered in the presence of the Q148 with two or more secondary mutations from G140A/C/S, E138A/K/T, L74I in patients with limited treatment options due to advanced multi-class resistance. There are no clinical data on the safety or efficacy of the 100 mg twice daily dose. Co-treatment with atazanavir increases the exposure of dolutegravir markedly and should not be used in combination with this high dose, since safety with the resulting dolutegravir exposure has not been established.

Special populations

Children

The pharmacokinetics of dolutegravir given once daily as film-coated and dispersible tablets in HIV-1 infected infants, children and adolescents aged ≥ 4 weeks to < 18 years were evaluated in two studies. Steady state simulated plasma exposure at once daily weight band doses is summarised in the below table.

Weight band (kg)	**Dolutegravir dosage form[a]**	**Once daily dose (mg)**	**PK parameter Geometric mean (90% CI)**		
			C_{max} (µg/mL)	**AUC_{0-24h} (µg*h/mL)**	**C_{24h} (ng/mL)**
3 to <6	DT	5	4.02 (2.12, 7.96)	49.4 (21.6, 115)	1070 (247, 3830)
6 to <10[b]	DT	10	5.90 (3.23, 10.9)	67.4 (30.4, 151)	1240 (257, 4580)
6 to <10[c]	DT	15	6.67 (3.75, 12.1)	68.4 (30.6, 154)	964 (158, 4150)
10 to <14	DT	20	6.61 (3.80, 11.5)	63.1 (28.9, 136)	719 (102, 3340)
14 to <20	DT	25	7.17 (4.10, 12.6)	69.5 (32.1, 151)	824 (122, 3780)
	FCT	40	6.96 (3.83, 12.5)	72.6 (33.7, 156)	972 (150, 4260)
20 to <25	DT	30	7.37 (4.24, 12.9)	72.0 (33.3, 156)	881 (137, 3960)
	FCT	50	7.43 (4.13, 13.3)	78.6 (36.8, 171)	1080 (178, 4690)
25 to <30	FCT	50	6.74 (3.73, 12.1)	71.4 (33.2, 154)	997 (162, 4250)
30 to <35	FCT	50	6.20 (3.45, 11.1)	66.6 (30.5, 141)	944 (154, 4020)
≥35	FCT	50	4.93 (2.66, 9.08)	54.0 (24.4, 118)	814 (142, 3310)
Target: Geometric Mean				**46 (37-134)**	**995 (697-2260)**

DT=dispersible tablet
FCT=film-coated tablet

a. The bioavailability of dolutegravir DT is ~1.6-fold dolutegravir FCT.
b. < 6 months of age
c. ≥ 6 months of age

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.

Pharmacokinetic data for dolutegravir in subjects aged over 65 years are limited.

Renal impairment

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. Pharmacokinetics of dolutegravir were studied in adults with severe renal impairment (creatinine clearance less than 30 mL/minute) and matched healthy controls. The exposure to dolutegravir was decreased by about 40% in subjects with severe renal impairment. The mechanism for the decrease is unknown. No dosage adjustment is considered necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis.

Hepatic impairment

Dolutegravir is primarily metabolised and eliminated by the liver. When a single dose of dolutegravir 50 mg was given to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 matched healthy adult controls, the total dolutegravir concentration in plasma was similar. However, there was a 1.5- to 2-fold increase in unbound dolutegravir in moderate hepatic impairment compared to healthy controls. No dosage adjustment is considered necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in drug metabolising enzymes

Common polymorphisms in drug metabolising enzymes have not been found to alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics, subjects with UGT1A1 genotypes had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1.

Gender

Analyses of pooled pharmacokinetic data from trials in adults revealed no clinically relevant effect of gender on the exposure of dolutegravir.

Race

Population analyses using pooled pharmacokinetic data from trials in adults revealed no clinically relevant effect of race on the exposure of dolutegravir.

Co-infection with hepatitis B or C

Pharmacokinetic analysis indicated that hepatitis C co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited data on subjects with hepatitis B co-infection.

5.3 Preclinical safety data

Dolutegravir was not mutagenic or clastogenic in bacteria and cultured mammalian cells, and an in vivo rodent micronucleus assay. Dolutegravir was not carcinogenic in long-term studies in the mouse and rat.

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg daily (around 25 times normal human clinical exposure based on AUC). Oral administration of dolutegravir to pregnant rats at similar doses from days 6 to 17 of gestation did not cause maternal toxicity, developmental toxicity or teratogenicity.

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits, maternal toxicity (decreased food consumption, reduced urine or faeces, suppressed bodyweight gain) was observed at 1000 mg/kg.

In a juvenile toxicity study in rats, there were two pre-weaning deaths at dolutegravir dose of 75 mg/kg daily. Over the pre-weaning period, mean bodyweight gain decreased, and the decrease persisted throughout the study for females during the post-weaning period. The systemic exposure at this dose (based on AUC) to dolutegravir was about 17 to 20-fold higher than in humans at the recommended paediatric exposure. No new target organs were identified in juveniles compared to adults. In the rat prenatal and postnatal development study, bodyweight decreased in the developing offspring during lactation at a maternally toxic dose (about 27 times human exposure at the maximum recommended dose).

The primary effect of high doses of dolutegravir and prolonged daily treatment (up to 26 weeks in rats and up to 38 weeks in monkeys) was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures about 21 and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal intolerance is considered to be due to local effects of the active substance, comparison based on bodyweight or on body surface area is appropriate for this toxicity. Gastrointestinal intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50 kg human), and 5 times the human mg/m^2 equivalent dose for a clinical dose of 50 mg twice daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Mannitol
Povidone
Sodium starch glycolate
Microcrystalline cellulose
Sodium stearyl fumarate

Film coat: Polyvinyl alcohol
Macrogol/polyethylene glycol
Talc
Titanium dioxide
Red iron oxide
Black iron oxide

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

- *Blisters*

Clear colourless plastic (PVC/ACLAR) on aluminium foil blister cards, each containing 10 tablets. Available in cartons of 1×10 tablets.

- *Bottles*

Round, opaque blue plastic (HDPE) bottle containing 30, 90 or 180 tablets. The bottle has an opaque blue plastic (polypropylene) screw cap.

6.6 Special precautions for disposal and other handling

No special precautions.

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

7. SUPPLIER

Mylan Laboratories Limited,

Plot no. 564/A/22, Road No. 92, Jubilee Hills,

Hyderabad-500096,

Telangana, India.

E-mail: ProductSafety@viatris.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA678

9. DATE OF PREQUALIFICATION

31 October 2018

10. DATE OF REVISION OF THE TEXT

July 2026

References

General reference sources for this SmPC include:

Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization July 2021 (https://www.who.int/publications/i/item/9789240031593, accessed 12 March 2024).

Guideline for HIV post-exposure prophylaxis. Geneva: World Health Organization; 2024 (https://www.who.int/publications/i/item/9789240095137, accessed 17 May 2026)

Update on the transition to dolutegravir-based antiretroviral therapy: report of a WHO meeting, 29–30 March 2022. Geneva: World Health Organization; 2022 (https://iris.who.int/bitstream/handle/10665/360836/9789240053335-eng.pdf, accessed 12 March 2024).

Tivicay 5 mg dispersible tablets and 10, 25 and 50 mg film-coated tablets: summary of product characteristics. European Medicines Agency; 14 November 2025 (https://www.ema.europa.eu/en/documents/product-information/tivicay-epar-product-information_en.pdf, accessed 16 May 2026).

World Health Organization (2026). WHO optimal antiretroviral dosing guidance. Recommendations for dosing medicines for HIV prevention and treatment in paediatric populations. (https://iris.who.int/bitstreams/9b15a65b-7eb9-4669-ac3d-88977f2e7795/download; accessed 4 July 2026)

Further references relevant to sections of the SmPC include:

Section 4.5

University of Liverpool, HIV Drug interactions, available at: http://www.hiv-druginteractions.org

Section 4.6

Drug and Lactation Database (LactMed) Available at: https://www.ncbi.nlm.nih.gov/books/NBK500631/

Reefhuis J. et al. Neural tube defects in pregnancies among women with diagnosed HIV infection – 15 Jurisdictions, 2013-2017. MMWR 2020: Vol 69(1):1-5

Zash R, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo Study, Botswana [conference report] 2022. Available at: https://programme.aids2022.org/PAGMaterial/PPT/3726_4873/AIDS2022_TsepamoUpdate.pdf

Section 5.1

Stanford University. HIV Drug Resistance Database; INSTI resistance notes, available at https://hivdb.stanford.edu/dr-summary/resistance-notes/INSTI/

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products