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

[HA779 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 70.28 mg abacavir sulfate equivalent to 60 mg abacavir, 5.26 mg dolutegravir sodium equivalent to 5 mg dolutegravir and 30 mg lamivudine.

Excipients with potential clinical effect

Each film-coated dispersible tablet contains about 9.5 mg of aspartame.

3. PHARMACEUTICAL FORM

Pink, oval, film- coated, dispersible tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have 'C' debossed (stamped into) on one side and are plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA779 trade name] is indicated for the treatment of HIV infection in infants and children aged from 4 weeks and weighing 6 to 25 kg.

Because [HA779 trade name] contains abacavir, patients must be screened for HLA-B*5701 (a variant form of a gene) and [HA779 trade name] must not be used in patients who carry it (see section 4.4).

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

This medicine is for use in children. However, information from its use in adults is also included to give a fuller picture of the medicine's effects.

4.2 Posology and method of administration

Oral use.

Antiretroviral therapy should be prescribed by a health care provider experienced in the management of HIV infection.

Posology

Infants and children aged over 4 weeks weighing 6 to less than 25 kg

[HA779 trade name] is not intended for patients weighing less than 6 kg. Separate formulations containing required amounts of abacavir, dolutegravir and lamivudine are more suitable.

[HA779 trade name] is taken once daily and the number of tablets depends on body weight as follows:

Child's weight	Number of tablets	Dose in mg
6 to less than 10 kg	3 tablets once daily	abacavir 180 mg + dolutegravir 15 mg + lamivudine 90 mg once daily

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

10 to less than 14 kg	4 tablets once daily	abacavir 240 mg +dolutegravir 20 mg + lamivudine 120 mg once daily
14 to less than 20 kg	5 tablets once daily	abacavir 300 mg + dolutegravir 25 mg + lamivudine 150 mg once daily
20 to less than 25 kg	6 tablets once daily	abacavir 360 mg + dolutegravir 30 mg + lamivudine 180 mg once daily

Patients weighing 25 kg or more

[HA779 trade name] is not intended for patients weighing 25 kg or more. Different formulations containing higher amounts of abacavir, dolutegravir and lamivudine are more suitable.

Dose adjustment

[HA779 trade name] should not be prescribed for patients requiring dosage adjustments. Separate formulations of abacavir, dolutegravir or lamivudine should be used if it is necessary to discontinue or adjust the dose of one of the active substances.

Renal impairment*:*

[HA779 trade name] is not recommended in patients whose creatinine clearance is less than 50 mL/minute; see also section 5.2.

Hepatic impairment

Abacavir is primarily metabolised by the liver. No data are available in patients with moderate or severe hepatic impairment; therefore, [HA779 trade name] is not recommended unless the benefits are considered to outweigh the risks. In patients with mild hepatic impairment close monitoring is required (see sections 4.4 and 5.2).

Missed dose

If the patient misses a dose, the patient should take the missed dose as soon as possible unless the next dose is due within 4 hours. The patient should then take the next regular dose at the usual time.

If the next dose is due within 4 hours, the patient should not take the missed dose and take the normal dose when it is next due. No double dose should be given to make up for a forgotten dose.

Method of administration

[HA779 trade name] can be taken with food or between meals.

Instructions for dispersing [HA779 trade name] tablets

1. Drinking water (about 10 mL per tablet up to a maximum of 50 mL) should be poured into a small, clean cup and the required number of tablets added.
2. The cup should be gently swirled until the tablets disperse completely, and the patient should take the entire mixture immediately.
3. The cup should be rinsed with an additional 10 mL of water, which the patients should drink to ensure the entire dose is taken.

4.3 Contraindications

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

[HA779 trade name] must not be used in patients:

- carrying the variant gene allele HLA-B*5701
- who have already had or are suspected to have had abacavir-associated hypersensitivity reactions (see section 4.8)
- using other medicines with narrow therapeutic window 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

Hypersensitivity reactions

Both abacavir and dolutegravir are associated with serious hypersensitivity reactions and share some common features such as fever and rash with other symptoms indicating multi-organ involvement. Clinically it is not possible to determine if a hypersensitivity reaction with [HA779 trade name] is caused by abacavir or dolutegravir.

Hypersensitivity reactions are more common with abacavir. The risk of such hypersensitivity reactions is high for patients with the HLA-B*5701 gene variant (allele) but they can also occur in patients who do not carry this allele. Screening for HLA-B*5701 is mandatory before prescribing [HA779 trade name] as the medicine is contraindicated in patients with this allele.

Features of hypersensitivity reactions with abacavir and dolutegravir

abacavir	***dolutegravir***
Symptoms of abacavir hypersensitivity reactions usually appear within the first 6 weeks (median time to onset 11 days) of starting abacavir treatment, but they may occur at any time during therapy.	
Almost all abacavir hypersensitivity reactions include fever or rash. Other signs and symptoms of the hypersensitivity reactions are detailed in section 4.8 (under 'Abacavir hypersensitivity'); they include respiratory and gastrointestinal symptoms. Importantly, such symptoms may be mistaken for respiratory disease (pneumonia, bronchitis, pharyngitis) or gastroenteritis.	Hypersensitivity reactions due to dolutegravir include 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. The reactions are sometimes accompanied by organ dysfunction, including severe liver reactions.
The symptoms of hypersensitivity reactions resolve on discontinuing abacavir but worsen with continued therapy. Restarting an abacavir-containing medicine after a hypersensitivity reaction can cause return of symptoms within hours. This recurrence is usually more severe than the previous reaction and may include life-threatening hypotension and death. Rarely, patients who stopped abacavir for reasons other than hypersensitivity reaction have also suffered life-threatening reactions within hours of restarting abacavir. In such patients, abacavir must be restarted in a setting where medical assistance is readily available.	After stopping [HA779 trade name] for suspected dolutegravir hypersensitivity, the patient's clinical status, including liver aminotransferases and bilirubin, should be monitored.

Management of hypersensitivity reactions

- [HA779 trade name] **must be stopped at once** if a hypersensitivity reaction occurs. Delay in stopping [HA779 trade name] after the hypersensitivity reaction may be life threatening.
- After stopping [HA779 trade name] for a suspected hypersensitivity reaction, the patient must **never** be given [HA779 trade name] or any other medicine containing abacavir or dolutegravir.
- To prevent accidental use of abacavir or dolutegravir, patients who have had a hypersensitivity reaction should be instructed to dispose of all remaining [HA779 trade name].

Other warnings and precautions

HIV resistant to integrase inhibitors

The use of [HA779 trade name] is not recommended for patients with integrase inhibitor resistance. This is because the recommended dose of dolutegravir is higher for adults with resistance to integrase inhibitors and there is insufficient information to recommend a dose of dolutegravir in integrase inhibitor resistant adolescents, children and infants.

Mitochondrial dysfunction following exposure in the uterus or after birth

Nucleoside analogues such as abacavir and lamivudine may cause a variable degree of mitochondrial damage. Mitochondrial dysfunction has been reported in HIV-negative infants exposed to nucleoside analogues either in the uterus or after birth; these have predominantly involved regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events have often been transitory. Late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown.

Mitochondrial damage should be considered if any child who has been exposed in the uterus to a nucleoside or nucleotide analogue presents with severe clinical findings of unknown aetiology, particularly neurological defects. These findings do not affect current guidelines on the use of antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Weight changes and metabolic disturbances

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. There is some evidence that antiretroviral treatment affects lipid levels but no strong evidence that it affects weight gain. Lipid disorders should be managed as clinically appropriate.

Pancreatitis

Pancreatitis has been reported, but it is uncertain if abacavir or lamivudine treatment causes it.

If signs, symptoms or laboratory abnormalities for pancreatitis occur then management of pancreatitis would include stopping [HA779 trade name] and the substitution of abacavir or lamivudine with another therapeutic class.

Liver disease

The safety and efficacy of [HA779 trade name] has not been established in patients with significant liver disorder. [HA779 trade name] is not recommended in patients with moderate or severe hepatic impairment.

Patients with liver dysfunction, including chronic active hepatitis, have a higher frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored. If liver disease worsens in such patients, interruption or discontinuation of treatment must be considered.

Patients with chronic hepatitis B or C

Patients with chronic hepatitis B or C who receive combination antiretroviral therapy are at higher risk of severe and potentially fatal hepatic events. Product information for antiviral medicines for treating hepatitis B or C may include further information.

If [HA779 trade name] is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of hepatitis B virus replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

Administration in subjects with moderate renal impairment

Adult patients with a creatinine clearance between 30 and 49 mL/min receiving [HA779 trade name] may experience a 1.6-to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL/min. There are no safety data from randomised, controlled trials comparing [HA779 trade name] to the individual components in adults with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of haematologic toxicities (neutropenia and anaemia), although discontinuations due to neutropenia or anaemia each occurred in <1% of subjects. Other lamivudine-related adverse events (such as gastro-intestinal and hepatic disorders) may occur.

Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive [HA779 trade name] should be monitored for lamivudine-related adverse events, notably haematologic toxicities. If new or worsening neutropenia or anaemia develop, a dose adjustment of lamivudine, as per lamivudine prescribing information, is indicated, which cannot be achieved with [HA779 trade name]. [HA779 trade name] should be discontinued and the individual components should be used to construct the treatment regimen.

Cardiovascular events

Although the available data from clinical and observational studies with abacavir show inconsistent results, several studies suggest an increased risk of cardiovascular events (notably myocardial infarction) in patients treated with abacavir. Therefore, when prescribing {DotWP-ProductName}, action should be taken to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). In addition, alternative treatment options to the abacavir-containing regimen should be considered when treating patients with a high cardiovascular risk.

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.

Osteonecrosis

Osteonecrosis has been reported, particularly in patients with advanced HIV disease or after long-term combination antiretroviral therapy. Its aetiology is considered to be multifactorial and includes corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index. Patients should be advised to speak with their health care provider about joint aches and pain, joint stiffness or movement difficulty.

Opportunistic infections

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

Excipients

[HA779 trade name] contains 9.5 mg aspartame per tablet. Aspartame is a source of phenylalanine. It may be harmful if the patient has phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

[HA779 trade name] contains abacavir, dolutegravir and lamivudine, therefore any interactions identified for these individually may occur with [HA779 trade name]. There are no clinically significant interactions between abacavir, dolutegravir and lamivudine.

[HA779 trade name] should not be taken with other medicines containing lamivudine, abacavir, dolutegravir or with medicines containing emtricitabine.

Abacavir is metabolised by UDP-glucuronosyltransferase (UGT) enzymes and alcohol dehydrogenase; co-administration of inducers or inhibitors of UGT enzymes or with compounds eliminated through alcohol dehydrogenase could alter abacavir exposure.

Abacavir may inhibit CYP1A1 and has a limited potential to inhibit CYP3A4. Abacavir inhibits multidrug and toxin extrusion transporter, MATE1, but the clinical consequences of these interactions are not known.

Dolutegravir is eliminated mainly through metabolism by UGT1A1. It is also a substrate of UGT1A3, UGT1A9, CYP3A4, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP); therefore, medicines that induce these enzymes may decrease dolutegravir plasma concentration and reduce its therapeutic effect. Co-administration of dolutegravir with medicines that inhibit these enzymes may increase dolutegravir plasma concentration.

In laboratory studies, dolutegravir inhibited the renal uptake organic anion transporters, OAT1 and OAT3. However, based on pharmacokinetic studies of the OAT substrate tenofovir, dolutegravir is unlikely to inhibit OAT1 in vivo. Dolutegravir may increase plasma concentrations of medicines whose excretion depends on OAT3 but this has not been studied in vivo.

Dolutegravir can inhibit MATE1 and the organic cation transporter, OCT2; it may increase plasma concentrations of medicines whose excretion is dependent on OCT2 or MATE1.

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).

Active renal secretion of *lamivudine* in the urine is mediated through OCT1, OCT2, MATE1 and MATE2-K; co-administration of lamivudine with these transporters may increase lamivudine exposure. Lamivudine inhibits OCT1 and OCT2 but it is not known if this inhibition has any clinical effect on co-administered medicines that are substrates of these transporters.

Abacavir and *lamivudine* are not significantly metabolised by cytochrome P450 enzymes (such as CYP3A4, CYP2C9 or CYP2D6) nor do they induce this enzyme system. Lamivudine does not inhibit cytochrome P450 enzymes. Abacavir shows limited potential to inhibit CYP3A4-mediated metabolism and has been shown in vitro not to inhibit CYP2C9 or CYP2D6 enzymes. In vitro studies found that abacavir has potential to inhibit CYP1A1. Therefore, there is little potential for interactions with antiretrovirals and other medicines metabolised by major P450 enzymes.

Certain antacids as well as iron and calcium supplements and multivitamins may reduce the absorption of *dolutegravir* (see table, below). [HA779 trade name] should not be co-administered with medicines that reduce the plasma concentration of dolutegravir, unless the patient can also be given dolutegraivr alone, 12 hours after each dose of [HA779 trade name]. Medicines that reduce the plasma concentration of dolutegravir include: etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St. John's wort and certain epilepsy medicines (see table, below).

The list below should not be considered exhaustive but is representative of the classes studied.

Interacting drugs	**Interaction** **Geometric mean change (%)** **(Possible mechanism)**	**Recommendation on co-administration**

Interacting drugs	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation on co-administration
Antiretroviral medicines		
Emtricitabine with lamivudine		Due to similarities, [HA779 trade name] should not be co-administered with other cytidine analogues, such as emtricitabine.
Etravirine without boosted protease inhibitors and dolutegravir	Dolutegravir ↓ AUC ↓ 71%; C_{max} ↓ 52%; C_{τ} ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	The dose of dolutegravir may need to be increased. Therefore, [HA779 trade name] is not suitable for co-administration with etravirine unless the patient can also be given an age-appropriate dose of dolutegravir alone, 12 hours after each dose of [HA779 trade name].
Efavirenz with dolutegravir	Dolutegravir ↓ AUC ↓ 57%; C_{max} ↓ 39%; C_{τ} ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The dose of dolutegravir may need to be increased. Therefore, [HA779 trade name] is not suitable for co-administration with efavirenz unless the patient can also be given an age or weight-appropriate dose of dolutegravir alone, 12 hours after each dose of [HA779 trade name].
Nevirapine with dolutegravir	Dolutegravir ↓ (Not studied, but a reduction in exposure similar to efavirenz is expected, due to induction)	The dose of dolutegravir may need to be increased. Therefore, [HA779 trade name] is not suitable for co-administration with nevirapine unless the patient can also be given an age-weight appropriate dose of dolutegravir alone, 12 hours after each dose of [HA779 trade name].
Tipranavir/ritonavir with dolutegravir	Dolutegravir ↓ AUC ↓ 59%; C_{max} ↓ 47%; C_{τ} ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The dose of dolutegravir may need to be increased. Therefore, [HA779 trade name] is not suitable for co-administration with tipranavir/ritonavir unless the patient can also be given an age-weight appropriate dose of dolutegravir alone, 12 hours after each dose of [HA779 trade name].
Anti-infective medicines		
Trimethoprim/sulfamethoxazole with abacavir	Interaction not studied.	No [HA779 trade name] dose adjustment necessary, unless the

Interacting drugs	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation on co-administration
Trimethoprim/sulfamethoxazole with lamivudine Trimethoprim/sulfamethoxazole 160 mg/800 mg once daily for 5 days Lamivudine300 mg single dose	Lamivudine: AUC ↑ 40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	patient has renal impairment. When co-administration with trimethoprim/sulfamethoxazole is necessary, patients should be monitored clinically. High doses of trimethoprim/sulfamethoxazole for treating *Pneumocystis jirovecii* pneumonia and toxoplasmosis have not been studied and should be avoided.
Flucytosine with lamivudine	Potential for haematological toxicity	Haematological parameters should be monitored, and dose reduction should be considered
Sulfadiazine with lamivudine	Sulfadiazine is associated with renal toxicity and in some cases renal failure. Potential for renal toxicity as lamivudine is mainly excreted by active renal transport.	Renal function should be monitored.
Antimycobacterials		
Rifampicin with dolutegravir	Dolutegravir ↓ AUC ↓ 54%; C_{max} ↓ 43%; C_{τ} ↓72% (induction of UGT1A1 and CYP3A enzymes)	The dose of dolutegravir may need to be increased. Therefore, [HA779 trade name] is not suitable for co-administration with rifampicin unless the patient can also be given an age-weight appropriate dose of dolutegravir alone, 12 hours after each dose of [HA779 trade name]. The extra dose of dolutegravir should continue to be given for 2 weeks after stopping rifampicin. Co-administration should be avoided in the presence of integrase class resistance.
Antacids and supplements		
Magnesium- or aluminium-containing antacid with dolutegravir	Dolutegravir ↓ AUC ↓ 74%; C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium- or aluminium-containing antacid should be taken well separated in time from [HA779 trade name] (minimum 2 hours after or 6 hours before).
Calcium supplements with dolutegravir	Dolutegravir ↓ AUC ↓ 39%; C_{max} ↓ 37%; $C_{24hours}$ ↓ 39% (Complex binding to polyvalent ions)	When taken with food, [HA779 trade name] can be taken at the same time as supplements or multivitamins containing calcium, iron or magnesium. If [HA779 trade name] is taken on an empty stomach, such supplements should be taken at least 2 hours after,
Iron supplements with dolutegravir	Dolutegravir ↓ AUC ↓ 54%; C_{max} ↓ 57%; $C_{24hours}$ ↓ 56% (Complex binding to polyvalent ions)	

Interacting drugs	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation on co-administration
Multivitamins with dolutegravir	Dolutegravir ↓ AUC ↓ 33%; C_{max} ↓ 35% $C_{24hours}$ ↓ 32% (Complex binding to polyvalent ions)	or 6 hours before, the taking [HA779 trade name]. Dolutegravir exposure was reduced when dolutegravir and these supplements were taken on an empty stomach. When [HA779 trade name] together with calcium or iron supplements were taken after a meal, dolutegravir exposure was similar to that obtained with dolutegravir taken on an empty stomach.
Antidiabetics		
Metformin with dolutegravir	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.
Anticonvulsants		
Phenobarbital with lamivudine	Interaction not studied.	
Phenytoin with abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dose adjustment. Monitor phenytoin concentrations.
Phenytoin with lamivudine	Interaction not studied.	
Carbamazepine with dolutegravir	Dolutegravir ↓ AUC ↓ 49%; C_{max} ↓ 33%; C_{τ} ↓ 73%	The dose of dolutegravir may need to be increased. Therefore, [HA779 trade name] is not suitable for co-administration with carbamazepine unless the patient can also be given an age-weight appropriate dose of dolutegravir alone, 12 hours after each dose of [HA779 trade name]. Alternatives to carbamazepine should be used in patients with infection resistant to integrase inhibitors

Interacting drugs	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation on co-administration
Cytotoxics		
Cladribine with lamivudine	Interaction not studied. In vitro, lamivudine inhibits intracellular phosphorylation of cladribine, leading to a risk of reduced cladribine efficacy. Some clinical findings also support a possible interaction between lamivudine and cladribine	Concomitant use of [HA779 trade name] with cladribine is not recommended.
Cisplatin with lamivudine	Cisplatin and lamivudine could potentially compete for OCT2 which could slow their elimination. Also, cisplatin may impair renal function	Renal function should be monitored.
Opioids		
Methadone with abacavir Methadone 40–90 mg once daily for 14 days Abacavir 600 mg single dose, then 600 mg twice daily for 14 days	Abacavir: AUC ↔ C_{max} ↓ 35% Methadone: CL/F ↑ 22%	No [HA779 trade name] dose adjustment necessary. Methadone dose adjustment unlikely to be needed in most patients; occasionally methadone re-titration may be required.
Retinoids		
Retinoid compounds (e.g. isotretinoin) with abacavir	Interaction not studied. Possible interaction given common pathway of elimination via alcohol dehydrogenase.	Insufficient data to recommend dose adjustment.
Retinoid compounds (e.g. isotretinoin) with lamivudine	Interaction not studied.	
Miscellaneous		
Dofetilide with dolutegravir	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.
Ethanol with abacavir Ethanol 700 mg/kg single dose Abacavir 600 mg single dose	Abacavir: AUC ↑41% Ethanol: AUC ↔ (Inhibition of alcohol dehydrogenase)	No dose adjustment necessary.
Ethanol with lamivudine	Interaction not studied.	
Sorbitol with lamivudine Sorbitol solution (3.2 g, 10.2 g, 13.4 g) Lamivudine oral solution 300 mg single dose	Lamivudine: AUC ↓ 14%; 32%; 36% C_{max} ↓ 28%; 52%, 55%.	When possible, avoid chronic co-administration of [HA779 trade name] with medicines containing sorbitol or other osmotic-acting poly-alcohols or monosaccharide alcohols (e.g. lactitol, maltitol, mannitol and xylitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

Interacting drugs	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation on co-administration
St John's wort with dolutegravir	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a reduction in exposure similar to carbamazepine is expected)	Co-administration of [HA779 trade name] should be avoided as St John's wort reduces plasma concentration of dolutegravir.
Riociguat with abacavir	Riociguat ↑ In vitro, abacavir inhibits CYP1A1. Concomitant administration of a single dose of riociguat (0.5 mg) to HIV patients receiving abacavir/dolutegravir/lamivudine (600 mg/50 mg/300 mg once daily) led to about 3-fold higher riociguat AUC compared to historical riociguat AUC in healthy subjects.	Riociguat dose may need to be reduced. Consult the riociguat prescribing information for dosing recommendations.
Clopidrogrel with abacavir	Pharmacodynamic effect of clopidogrel maybe reduced.	An alternative NRTI or antiplatelet agent should be considered.
Fampridine (also known as dalfampridine) with dolutegravir	Fampridine ↑ (inhibition of OCT2 transporter)	Fampridine co-administration with DotWP-ProductName} is contraindicated. Co-administration has the potential to cause seizures due to increased fampridine plasma concentration; co-administration has not been studied.

↓	Decreased	AUC	area under the curve (bioavailability)
↑	Increased	C_{max}	maximum (peak) concentration (in plasma or blood)
↔	No change	C_{τ}	minimum (trough) concentration (in plasma or blood)

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

[HA779 trade name] can be used for the treatment of HIV in pregnancy as the overall benefits are likely to outweigh the risks.

Nevertheless, health care providers should discuss any concerns, and the benefits and risks of treatment options, with women planning to become pregnant. If there any concerns, the woman can be tested for pregnancy before starting treatment and advised to use effective contraceptive measures during treatment.

No increased birth defects have been reported for abacavir or lamivudine in humans. However, placental transfer of abacavir and lamivudine can occur.

More than 1000 outcomes in women who took dolutegravir during pregnancy do not indicate increased risk of fetal or neonatal toxicity (see Human and animal data on pregnancy, below). 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 about 1.3-fold higher than the maternal peripheral plasma concentration.

Mitochondrial dysfunction has been reported in HIV-negative infants exposed to nucleoside analogues in the uterus or after birth (see section 4.4).

Breast-feeding

Abacavir, dolutegravir and lamivudine are present in breast milk.

Current recommendations on HIV and breast-feeding (e.g. those from the WHO) should be followed to advise patients on breast-feeding. Preferred options may vary depending on the local circumstances.

Fertility

There are no data on the effects of [HA779 trade name] on human male or female fertility. Animal studies indicate no effects of abacavir, dolutegravir or lamivudine on male or female fertility (see section 5.3).

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 the 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, more than 1000 pregnancies with first trimester abacavir treatment and more than 1000 pregnancies with first trimester lamivudine 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.

There are no or limited APR data (fewer than 300 first trimester exposures) from the use of dolutegravir + lamivudine + abacavir in pregnant women.

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

4.7 Effects on ability to drive and use machines

[HA779 trade name] can cause dizziness. The patient's clinical status and individual adverse effects (e.g. fatigue) should be considered to determine if the patient can safely perform skilled tasks.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions reported with [HA779 trade name] are consistent with those of abacavir, dolutegravir and lamivudine given separately. The most frequently reported adverse reactions related to dolutegravir and abacavir/lamivudine were nausea (12%), insomnia (7%), dizziness (6%) and headache (6%).

Many of the adverse reactions listed below occur commonly (nausea, vomiting, diarrhoea, fever, lethargy, rash) in patients with hypersensitivity reactions— see 'Abacavir hypersensitivity' and 'Dolutegravir hypersensitivity' below. Therefore, patients with any of these symptoms should be carefully evaluated for hypersensitivity.

Very rarely, cases of erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported where abacavir hypersensitivity could not be ruled out. In such cases medicines containing abacavir should be permanently discontinued.

Tabulated list of adverse reactions

The undesirable effects of [HA779 trade name] are listed below. Frequencies are defined as 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), and very rare (less than 1 in 10 000).

Blood and lymphatic system disorders

Uncommon	neutropenia, anaemia, thrombocytopenia
Very rare	pure red cell aplasia
Not known	sideroblastic anaemia

Immune system disorders

Common	hypersensitivity (see section 4.4)
Uncommon	immune reactivation syndrome (see section 4.4)

Metabolism and nutrition disorders

Common	anorexia
Uncommon	hypertriglyceridaemia, hyperglycaemia
Very rare	lactic acidosis

Psychiatric disorders

Very common	insomnia
Common	abnormal dreams, depression, anxiety, nightmare, sleep disorder
Uncommon	suicidal ideation or suicide attempt (particularly in patients with a history of depression or psychiatric illness), panic attack
Rare	completed suicide (particularly in patients with a history of depression or psychiatric illness)

Nervous system disorders

Very common	headache
Common	dizziness, somnolence, lethargy
Very rare	peripheral neuropathy, paraesthesia

Respiratory, thoracic and mediastinal disorders

Common	cough, nasal symptoms

Gastrointestinal disorders

Very common	nausea, diarrhoea
Common	vomiting, flatulence, abdominal pain, upper abdominal pain, abdominal distension, abdominal discomfort, gastro-oesophageal reflux disease, dyspepsia
Rare	pancreatitis

Hepatobiliary disorders

Common	raised alanine aminotransferase (ALT), raised aspartate aminotransferase (AST)
Uncommon	hepatitis
Rare	acute hepatic failure, raised bilirubin (accompanied by raised transaminases)

Skin and subcutaneous tissue disorders

Common	rash, pruritus, alopecia
Very rare	erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Common	arthralgia, muscle disorders (including myalgia)
Rare	rhabdomyolysis

General disorders and administration site conditions

Very common	fatigue
Common	asthenia, fever, malaise

Investigations

Common	Raised creatine kinase (creatine phosphokinase, CPK), weight increase
Rare	Raised amylase

Description of selected adverse reactions

Abacavir hypersensitivity

See also section 4.4.

The signs and symptoms of abacavir hypersensitivity are listed below. They have been identified from clinical studies and post-marketing surveillance. Those reported in at least 10% of patients with a hypersensitivity reaction are shown in **bold**.

Almost all patients developing hypersensitivity reactions had fever or rash (usually maculopapular or urticarial) as part of the syndrome; however, reactions have occurred without rash or fever. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

Skin	**Rash** (usually maculopapular or urticarial)
Gastrointestinal tract	**Nausea, vomiting, diarrhoea, abdominal pain**, mouth ulceration
Respiratory tract	**Dyspnoea, cough**, sore throat, adult respiratory distress syndrome, respiratory failure
Miscellaneous	**Fever, lethargy, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry	**Headache**, paraesthesia
Haematological	Lymphopenia
Liver	**Elevated liver function tests,** hepatitis, hepatic failure
Musculoskeletal	**Myalgia**, rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology	Elevated creatinine, renal failure

Symptoms related to abacavir hypersensitivity worsen with continued therapy and can be life-threatening and in rare instances, fatal.

Dolutegravir hypersensitivity

See also section 4.4.

Symptoms of dolutegravir hypersensitivity have included rash, constitutional findings and sometimes organ dysfunction, including severe liver reactions.

Changes in serum creatinine

Serum creatinine can increase in the first week of treatment with dolutegravir and then remain stable. In one study, the mean change from baseline was 12.6 μmol/L after 96 weeks of treatment. 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 enzymes elevations consistent with immune reactivation syndrome occurred in some subjects with hepatitis B or C co-infection at the start of dolutegravir therapy, particularly in those whose hepatitis B therapy was stopped.

Children and adolescents

No additional safety issues have been identified in paediatric subjects receiving abacavir, dolutegravir and lamivudine.

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

No specific symptoms or signs have been identified following acute overdose with abacavir, dolutegravir or lamivudine, apart from those listed as undesirable effects. An important feature of toxicity may be mitochondrial damage, which can result in disorders such as lactic acidosis.

If overdose occurs the patient should be monitored for toxicity (see section 4.8) and receive standard supportive treatment as necessary. Since lamivudine is dialysable, continuous haemodialysis may be used to treat an overdose, but this has not been studied. It is not known if abacavir can be removed by peritoneal dialysis or haemodialysis. 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 treatment of HIV infections, combinations,
ATC code: J05AR13

Mechanism of action

Abacavir and lamivudine are nucleoside analogue reverse transcriptase inhibitors (NRTIs). Both are metabolised sequentially by intracellular kinases to the respective 5′-triphosphate (TP) active forms. Carbovir-TP (the active triphosphate form of abacavir) and lamivudine-TP competitively inhibit the reverse transcriptase of HIV. However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Abacavir and lamivudine triphosphates have significantly less affinity for host cell DNA polymerases.

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.

Clinical efficacy

Adults

Several studies in adult HIV patients have compared regimens comprising abacavir, dolutegravir and lamivudine with regimens composed of other antiretroviral medicines.

In the first randomised, double-blind study involving 833 patients the viral load after 48 weeks of treatment was less than 50 copies/mL in 88% of patients who received abacavir, dolutegravir and lamivudine

compared to 81% of patients who received efavirenz, tenofovir disoproxil fumarate and emtricitabine. At 96 weeks of treatment, viral load was less than 50 copies/mL in 80% of patients receiving abacavir, dolutegravir and lamivudine compared to 72% in the other group.

In a second randomised, double-blind study, 822 patients received abacavir and lamivudine with either dolutegravir or raltegravir. After treatment for 48 weeks, viral load was less than 50 copies/mL in 88% of patients receiving the regimen comprising dolutegravir compared to 85% of patients receiving raltegravir. At 96 weeks of treatment, viral load was less than 50 copies/mL in 81% of patients receiving the dolutegravir regimen compared to 76% in the raltegravir group.

In an open-label study, 485 patients received abacavir and lamivudine with either dolutegravir or darunavir/ritonavir. After treatment for 48 weeks, viral load was less than 50 copies/mL in 90% of patients receiving the regimen comprising dolutegravir compared to 83% of patients receiving darunavir/ritonavir. At 96 weeks of treatment, viral load was less than 50 copies/mL in 80% of patients receiving the dolutegravir regimen compared to 68% in the darunavir/ritonavir group.

In a randomised open-label study, involving 499 women who had not previously been treated with antiretrovirals, the viral load after 48 weeks of treatment was less than 50 copies/mL in 82% of women who received abacavir, dolutegravir and lamivudine compared to 71% of women who received atazanavir/ritonavir, tenofovir disoproxil and emtricitabine.

Children

The efficacy of dolutegravir (in combination with other antiretroviral medicines) has been evaluated in infants aged over 4 weeks, children and adolescents aged up to 18 years. After 48 weeks of treatment, viral load was less than 50 copies/mL in 67% (16 out of 24) of the children.

In another study in 331 children and adolescents with HIV infection who weighed at least 25 kg received abacavir and lamivudine with a third antiretroviral. After treatment for 96 weeks, the viral load was less than 80 copies/mL in 69% of patients.

Resistance – abacavir and lamivudine

Clinically significant reduction of susceptibility to abacavir has occurred in patients with uncontrolled viral replication, who were resistant to other nucleoside inhibitors. In clinical trials where abacavir was added to the antiretroviral regimen, patients had M184V/I (74%), T215Y/F (30%), M41L (27%), K70R (18%) and D67N (15%). Variants L74V and Y115F were uncommon (no more than 3%). It was considered that the presence of 3 or more NRTI resistance-associated mutations was associated with reduced response at week 4, or 4 or more mutations at week 24. In addition, the 69 insertion complex or the Q151M mutation, usually found in combination with A62V, V75I, F77L and F116Y, causes a high level of resistance to abacavir.

Resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple thymidine analogue mutations. Cross-resistance to other NRTIs with M184V or M184I mutation alone is limited. Zidovudine, didanosine, stavudine and tenofovir remain active against such HIV-1 variants. M184V with K65R confers cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. M184V with Y115F confers cross-resistance between abacavir and lamivudine.

Isolates resistant to abacavir may also show reduced sensitivity to lamivudine. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the substitutions K65R with or without the M184V/I substitution, and to viruses with L74V plus the M184V/I substitution.

The M184V or M184I variants arise in patients treated with lamivudine-containing antiretroviral therapy and confer high-level resistance to lamivudine. Laboratory data suggest that continuing lamivudine despite the development of M184V might provide residual antiretroviral activity. However, the clinical relevance of these findings has not been established and the patient should preferably be switched to NRTIs that the HIV is susceptible to. Lamivudine may be continued only if no other active NRTI is available.

Resistance: Dolutegravir

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. 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 > 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 up to 10 FC against 94% of the 705 clinical isolates.

In previously untreated patients receiving dolutegravir with 2 nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), no development of resistance to the integrase class, or to the NRTI class was seen (n=876, follow-up of 48-96 weeks).

In patients whose previous antiretroviral treatment had failed but who had not received integrase class antiretrovirals, integrase inhibitor substitutions occurred in 4/354 patients (follow-up 48 weeks) treated with dolutegravir, which was given in combination with an investigator selected background regimen. Of these four, two patients had a unique R263K integrase substitution, with a maximum FC of about 2, one had a polymorphic V151V/I integrase substitution, with maximum FC of about 1, and one had integrase mutations and is assumed to have been exposed to integrase inhibitors or was infected with resistant virus.

5.2 Pharmacokinetic properties

The absorption characteristics of [HA779 trade name] have been determined after administration of one tablet (1) in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value* (±standard deviation)**		
	Abacavir	**Dolutegravir**	**Lamivudine**
Maximum concentration (Cmax) ng/mL	748 ± 266	630 ± 116	378 ± 120
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.h/mL	985 ± 386	11597 ± 3177	1710 ± 471
Time to attain maximum concentration (T_{max}) hour	0.74 ± 0.59	1.37 ± 0.86	1.38 ± 0.71

Pharmacokinetics of abacavir, dolutegravir and lamivudine

	Abacavir	**Dolutegravir**	**Lamivudine**
General	Information not available	PK similar for healthy and HIV-infected subjects. Low to moderate PK variability	Information not available
Absorption			
Absolute bioavailability	83%	Information not available	Information not available
Oral bioavailability	At least 83%	At least 32%	80–85%

<table>
<tr><th></th><th>Abacavir</th><th>Dolutegravir</th><th>Lamivudine</th></tr>
<tr><td>Food effect</td><td>Concomitant food intake did not affect the extent of absorption but increased T_{max} and decreased C_{max}</td><td><table><tr><th></th><th>$AUC_{(0-\infty)}$</th><th>C_{max}</th><th>T_{max}</th></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><td>Not clinically relevant</td></tr>
<tr><td colspan="4">Distribution</td></tr>
<tr><td>Volume of distribution (mean)</td><td>0.8 L/kg</td><td>17–20 L/kg</td><td>1.3 L/kg</td></tr>
<tr><td>Plasma protein binding in vitro</td><td>About 49% (binding to human plasma proteins)</td><td>> 99%, increase in unbound fraction with low serum albumin (as in moderate hepatic impairment)</td><td>< 36%</td></tr>
<tr><td>Tissue distribution</td><td>CSF to plasma AUC ratio: 30–44%</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><td></td></tr>
<tr><td colspan="2">Metabolism</td><td></td><td></td></tr>
<tr><td></td><td>hepatic metabolism followed by glucuronidation to produce 5'-carboxylic acid and 5'-glucuronide</td><td>Hepatic metabolism:
glucuronidation via UGT1A1
minor pathway CYP3A</td><td>Only minor route (< 10%)</td></tr>
<tr><td>Active metabolites</td><td>None</td><td>None</td><td>None</td></tr>
<tr><td colspan="2">Elimination</td><td></td><td></td></tr>
<tr><td>Elimination half life</td><td>1.5 hours after single dose
21 hours for intracellular carbovir triphosphate</td><td>14 hours</td><td>18–19 hours
16–19 hours for intracellular lamivudine triphosphate</td></tr>
<tr><td>Mean systemic clearance (Cl/F)</td><td>Information not available</td><td>About 1 L/hour/kg</td><td>0.32 L/hour/kg.</td></tr>
<tr><td>% of dose excreted in urine</td><td>Approximately 2% excreted unchanged; total 83%</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><td>> 70%
(predominantly cleared unchanged)</td></tr>
</table>

	Abacavir	Dolutegravir	Lamivudine
% of dose excreted in faeces	16%	53% is excreted unchanged in the faeces	Information not available
Pharmacokinetic linearity	Linear pharmacokinetics and dose proportional over the range of 300–1200 mg/day	Depending on dose and formulation. For tablets: dose-proportional increases from 25 to 50 mg	Linear pharmacokinetics
Drug interactions (in vitro)			
Transporters	Information not available	Inhibition of OCT2, MATE-1, OAT3 and OAT1 (latter unlikely to be clinically relevant) 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.	OCT (organic cationic transporters)
Metabolising Enzymes	Alcohol dehydrogenase, UDP-glucuronyltransferase	No relevant inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7 No induction of CYP1A2, CYP2B6 or CYP3A4	–

Special populations

Hepatic impairment

Abacavir is metabolised primarily by the liver. In patients with mild hepatic impairment (Child-Pugh score 5–6) receiving a single 600-mg dose, the mean abacavir AUC increased nearly 2-fold and the mean elimination half-life increased over 1.5-fold. No recommendation on dose adjustments can be made for these patients due to the substantial variability of abacavir exposure.

Lamivudine pharmacokinetics are not significantly affected by moderate to severe 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.

[HA779 trade name] is not recommended in patients with moderate or severe hepatic impairment.

Renal impairment

Abacavir is primarily metabolised by the liver, with about 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function.

Lamivudine plasma concentrations are increased in patients with renal dysfunction due to decreased clearance.

Patients with sustained creatinine clearance of 30 to 49 mL/minute who receive [HA779 trade name] should be monitored for lamivudine-related adverse events, notably haematologic toxicity. If new or worsening

neutropenia or anaemia develop, the dose of lamivudine may need to be reduced. In such a case, [HA779 trade name] should be discontinued and the individual components used at appropriate doses.

In patients with creatinine clearance of 30 to 49 mL/minute, lamivudine exposure (AUC) may be 1.6- to 3.3-fold higher than in patients with creatinine clearance of at least 50 mL/minute. In studies on patients receiving lamivudine and zidovudine, higher lamivudine exposure was associated with higher rates of haematological toxicity but it was rarely necessary to discontinue lamivudine. Other lamivudine-related adverse events (such as gastrointestinal and hepatic disorders) may also occur.

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 about 40% lower in adults with severe renal impairment. The mechanism for the lower exposure is unknown. Dolutegravir has not been studied in patients on dialysis.

[HA779 trade name] is not recommended in patients with a creatinine clearance less than 50 mL/minute because necessary dose adjustments cannot be made.

Children

Abacavir is rapidly and well absorbed from oral formulations administered to children. Paediatric pharmacokinetic studies have demonstrated that once-daily dosing provides equivalent AUC_{24} to twice-daily dosing of the same total daily dose for both oral solution and tablet formulations.

The absolute bioavailability of lamivudine (about 58 to 66%) was lower and more variable in children under 12 years of age. However, paediatric pharmacokinetic studies with tablet formulations have demonstrated that once-daily dosing provides equivalent $AUC_{0\text{-}24h}$ to twice-daily dosing of the same total daily dose.

Studies involving steady-state simulated plasma dolutegravir exposure show that the recommended weight-based doses of [HA779 trade name] achieve effective mean 24-hour AUC and plasma dolutegravir concentrations for children weighing 6 kg to less than 25 kg.

Elderly

No pharmacokinetic data are available for abacavir and lamivudine in patients over 65 years of age.

Population pharmacokinetic analysis of dolutegravir in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure. Pharmacokinetic data for dolutegravir in patients aged over 65 years are limited.

5.3 Preclinical safety data

There are no data available on the effects of the combination of abacavir, dolutegravir and lamivudine in animals, except a negative in vivo rat micronucleus test which tested the effects of the combination of abacavir and lamivudine.

General toxicity

In toxicology studies abacavir increased liver weights in rats and monkeys. The clinical relevance of this is unknown. There is no evidence from clinical studies that abacavir is hepatotoxic. Additionally, autoinduction of abacavir metabolism, or induction of the metabolism of other medicines metabolised in the liver has not been seen in humans.

Mild myocardial degeneration occurred in mice and rats after administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

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.

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reductions in liver weight. Clinically relevant effects were a reduction in red blood cell count and neutropenia.

Mutagenicity and carcinogenicity

Abacavir and lamivudine were not mutagenic in bacterial tests but, like many nucleoside analogues, they inhibit cellular DNA replication in in vitro mammalian tests such as the mouse lymphoma assay. Based on available data, lamivudine should not pose a genotoxic hazard to patients. Abacavir has a weak potential to cause chromosomal damage both in vitro and in vivo at high tested concentrations.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential. Carcinogenicity studies with oral abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in rats in the thyroid gland of males and in the liver, urinary bladder, lymph nodes and the subcutis of females.

Most of these tumours occurred at the highest abacavir dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg in mice. The systemic exposure at the no-effect level in mice and rats was equivalent to 3 and 7 times the human systemic exposure during therapy. While the clinical relevance of these findings is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

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.

The carcinogenic potential of a combination of abacavir, dolutegravir and lamivudine has not been tested.

Reproductive toxicology

Abacavir, dolutegravir and lamivudine crossed the placenta in animal studies.

Abacavir was toxic to the developing embryo and fetus in rats, but not in rabbits. These findings included decreased fetal body weight, fetal oedema, increased skeletal variations or malformations, early intra-uterine deaths and stillbirths. No conclusion can be drawn about the teratogenic potential of abacavir because of this embryo-fetal toxicity.

Dolutegravir did not affect male or female fertility in rats at doses up to 24 times the 50 mg twice daily human clinical exposure based on AUC. Oral administration of dolutegravir to pregnant rats at doses up to 27 times the 50 mg twice daily human clinical exposure based on AUC 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 was 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).

Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryo lethality at systemic exposure similar to the recommended clinical dose. A similar effect was not seen in rats even at very high systemic exposure.

A fertility study in rats has shown that abacavir and lamivudine had no effect on male or female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Microcrystalline cellulose,
Sodium starch glycolate
Povidone
Crospovidone
Strawberry cream flavour
Aspartame
Colloidal silicon dioxide
Iron oxide red
Mannitol
Calcium sulphate dihydrate
Magnesium stearate.

Film coat: Polyvinyl alcohol-partially hydrolysed
Macrogol/polyethylene glycol
Talc
Titanium dioxide
Iron oxide yellow
Iron oxide red.

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

24 months

6.4 Special precautions for storage

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

In-Use Period

90’s HDPE container
Should be used within 30 days, once opened.
When the bottle is first opened the “Discard after date” should be written on the bottle label in the place provided.

180’s HDPE container
Should be used within 60 days, once opened.
When the bottle is first opened the “Discard after date” should be written on the bottle label in the place provided.

6.5 Nature and contents of container

Round, opaque, white plastic (HDPE) bottle containing 30, 90 or 180 tablets. It also contains a desiccant (drying material). The bottle has an aluminium/plastic foil seal printed with “SFYP” in black and a white, childproof plastic (polypropylene) screw cap.

6.6 Special precautions for disposal and other handling

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

7. SUPPLIER

Cipla Limited
Cipla House, Peninsula Business Park,
Ganpatrao, Kadam Marg, Lower Parel,
Mumbai, Maharashtra 400013,
India
Tel: 9122 24826000
Email: globalra@cipla.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA779

9. DATE OF PREQUALIFICATION

16 November 2023

10. DATE OF REVISION OF THE TEXT

January 2026

References

General

Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/9789240031593, accessed July 2025).

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 July 2025).

Triumeq 50 mg/600 mg/300 mg film-coated tablets and 5 mg/60 mg/30 mg dispersible tablets: summary of product characteristics. European Medicines Agency; 10 December 2024 (https://www.ema.europa.eu/en/documents/product-information/triumeq-epar-product-information_en.pdf, accessed July 2025)

Kivexa 600 mg/200 mg film-coated tablets: summary of product characteristics. European Medicines Agency; 27 Novmember 2023 (https://www.ema.europa.eu/en/documents/product-information/kivexa-epar-product-information_en.pdf, accessed July 2025).

Tivicay mg dispersible tablets and 10 mg, 25 mg and 50 mg film-coated tablets: summary of product characteristics. European Medicines Agency; 10 December 2024, https://www.ema.europa.eu/en/documents/product-information/tivicay-epar-product-information_en.pdf, accessed July 2025)

Section 4.5

HIV drug interactions: interactions checker [online database]. Liverpool Drug Interactions Group, University of Liverpool; 2023 (https://hiv-druginteractions.org/checker, accessed July 2025).

Sections 4.6 and 5.3

Drugs and lactation database [online database]. Bethesda: National Institute of Child Health and Human Development; 2023 (https://www.ncbi.nlm.nih.gov/books/NBK500631/ accessed July 2025).

Ikumi NM, Anumba D, Matjila M. Pharmacokinetics and placental transfer of dolutegravir in pregnancy. J Antimicrob Chemother. 2022 Feb 2;77(2):283-289. doi: 10.1093/jac/dkab365. PMID: 34618029.

Zash R, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo Study, Botswana [conference report]; 2022. Available at: https://www.natap.org/2022/IAC/IAC_31.htm

Section 4.9

van Dam PM, van Geffen MW, Havenith TR, Posthouwer D. Intentional overdose of dolutegravir/abacavir/lamivudine (Triumeq) in a 26-year-old man. Antivir Ther. 2018;23:549–552. doi:10.3851/IMP3229.

Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. Lancet 2002;359:733–40. doi:10.1016/S0140-6736(02)07874-1

Section 5.1

Stanford University. HIV Drug Resistance Database; INSTI resistance notes, available at https://hivdb.stanford.edu/dr-summary/resistance-notes/INSTI/, accessed July 2025.

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