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 (term to be revised).
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

1. NAME OF THE MEDICINAL PRODUCT

[HA433 trade name]*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains lamivudine 30 mg, nevirapine 50 mg and zidovudine 60 mg.

Excipients: each tablet contains 21.7 mg lactose monohydrate and 20 mg aspartame.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet

Yellow coloured mottled, round shaped, beveled edged tablets with break-line and debossed with 'M09' on one side and plain on the other.

The break-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA433 trade name] is indicated for the treatment of of Human Immunodeficiency Virus Type 1 (HIV-1) infection in children weighing less than 25 kg.

This combination replaces lamivudine, nevirapine and zidovudine used separately in similar dosages. Treatment must be started with lamivudine, nevirapine and zidovudine separately at least for the first 2 weeks (see section 4.2), until the patient is on the twice daily nevirapine maintenance.

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).

4.2 Posology and method of administration

Oral use.

Treatment with [HA433 trade name] should be supervised by a health care provider experienced in the management of HIV infection.

[HA433 trade name] is not suitable for the first two weeks of treatment when the lead-in dose of nevirapine is lower. It should also not be used if the dose of any component needs adjusting; the components should be given separately in such cases.

[HA433 trade name] is given in the following doses after the lead-in with low-dose nevirapine:

Child's weight	Dose of [HA433 trade name]
3–5.9 kg	1 tablet twice daily
6–9.9 kg	1.5 tablets twice daily
10–13.9 kg	2 tablets twice daily
14–19.9 kg	2.5 tablets twice daily
20–24.9 kg	3 tablets twice daily

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

[HA433 trade name] dispersible tablet is not for children and adolescents weighing over 25 kg, who can take other formulations.

Haematological side effects

If there is a clinically significant fall in haemoglobin or neutrophil count, zidovudine may need to be substituted and the other components of [HA433 trade name] will need to be given separately.

Hepatic impairment

[HA433 trade name] is contraindicated in severe hepatic impairment. In moderate hepatic impairment, the components of [HA433 trade name] may have to be given separately if the dose of zidovudine needs to be reduced.

Renal impairment

If creatinine clearance is less than 50 mL/minute, the components of [HA433 trade name] need to be given separately so that the doses of lamivudine and zidovudine can be adjusted appropriately.

Interruption of treatment

If treatment with [HA433 trade name] is interrupted for longer than 7 days, then the components should be given separately while nevirapine is reintroduced at a smaller dose for 14 days. Treatment with the combination can resume once the patient can take the full dose of nevirapine.

[HA433 trade name] should be taken every 12 hours and it can be taken with food or between meals.

The required number of tablets should be dispersed, using dry hands; the recommended dose should be placed in a drinking container such as a tumbler or a beaker. Drinking water should then be added to the container. The minimum volume of water for dispersing the dose is shown below:

Dose of [HA433 trade name]recommended for the child	**Minimum volume of drinking water to be used**
1 or 1½ tablets	10 mL (about 2 teaspoonfuls)
2 or 2½ tablets	15 mL (about 3 teaspoonfuls)
3 tablets	20 mL (about 4 teaspoonfuls)

The mixture should be swirled or stirred to disperse the tablets completely. The child should drink all the content of the container. The container should then be rinsed with more water and the child should drink this also to ensure that the whole dose is taken. The water and all the mixture should be swallowed within 10 minutes.

4.3 Contraindications

[HA433 trade name] is contraindicated in patients with:

- hypersensitivity to lamivudine, nevirapine, zidovudine or to any of the excipients contained in the formulation
- abnormally low neutrophil counts (less than 0.75×10^9/litre) or abnormally low haemoglobin level (less than 7.5 g/decilitre or 4.7 mmol/litre).
- severe hepatic impairment (Child-Pugh C or ALT or AST values more than 5 times the upper limit of normal [ULN])
- history of severe rash, rash accompanied by symptoms of liver toxicity due to nevirapine

[HA433 trade name] must not be used concomitantly with rifampicin or herbal preparations containing St. John's wort (*Hypericumperforatum*) because they can reduce plasma concentrations of nevirapine and reduced its clinical effects (see section 4.5).

4.4 Special warnings and precautions for use

Dose adjustments
It is recommended that separate preparations of lamivudine, nevirapine and zidovudine be administered when any dosage adjustment is necessary (see section 4.2). In these cases the health care provider should refer to the individual prescribing information of these medicinal products.

Opportunistic infections
Patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of HIV infection.

Transmission of HIV
Treatment with [HA433 trade name] has not been shown to eliminate the risk of transmission of HIV infection by sexual contact or by blood transfer, although the risk may be reduced. Patients should continue to use appropriate precautions to prevent transmission of HIV.

Liver disease
Severe and life-threatening liver toxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine. This has mainly occurred during the initial 6 weeks of therapy but may occur up to 18 weeks after start of nevirapine. Nevirapine-associated liver toxicity is a hypersensitivity reaction, thought to be immune mediated, which may or may not be associated with a cutaneous reaction (rash) and/or constitutional symptoms, including fever, arthralgia, myalgia and general malaise. Factors linked to nevirapine-associated liver toxicity are female sex, higher baseline CD4 counts, higher baseline levels of alanine aminotransferase, hepatitis C co-infection and alcohol abuse. Women with CD4 cell counts >250 cells/mm^3 had a 12-fold higher risk of symptomatic liver toxicity compared to women with CD4 counts <250 cells/mm^3. A 5-fold increased risk was observed in men with CD4 counts > 400 cells/mm^3. This increased risk for toxicity based on CD4 cell count thresholds has not been demonstrated in patients with undetectable viral load (i.e. <50 copies/ml). Unless the benefit outweighs the risk treatment with nevirapine should not be initiated in adult females with CD4 cell counts greater than 250 cells/mm^3 or in adult males with CD4 cell counts greater than 400 cells/mm^3, who are not already on a suppressive antiretroviral regimen with a viral load <50 copies/mL
Monitoring of liver transaminases should be performed if the patient experiences signs or symptoms suggestive of liver toxicity (e.g. anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness).
Patients developing signs or symptoms of liver toxicity and/or hypersensitivity should promptly seek medical evaluation. [HA433 trade name] and any other nevirapine-containing products must be permanently discontinued in any patient experiencing severe liver toxicity (see section 4.3).

Caution should be exercised when administering [HA433 trade name] to any patient with chronic hepatitis B infection. Specifically, lamivudine is a potent inhibitor of hepatitis B virus (HBV) replication. Discontinuation of lamivudine or virologic failure after development of resistance to lamivudine by HBV may cause hepatic deterioration and a hepatitis flare. If [HA433 trade name] is discontinued in a patient with HBV infection, the patient should be periodically monitored, both clinically and by assessment of liver function tests (ALT and bilirubin levels) and markers of HBV replication, for at least four months, and then as clinically indicated.

Patients with chronic hepatitis B and C that are treated with combination antiretroviral therapy, have an increased risk of severe and potentially fatal hepatic adverse events.

Patients with pre-existing liver dysfunction have an increased frequency of liver function abnormalities during combination ART, and should be monitored according to current standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of therapy should be considered (see section 4.3).

Skin reactions

Rash is a common adverse reaction to nevirapine. Cases are usually mild to moderate but severe and life-threatening skin reactions including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred. These have mainly been reported during the initial 6 weeks of therapy, but may occur up to 18 weeks after start of nevirapine. Patients should be warned to report symptoms of a hypersensitivity reaction immediately (e.g. fever, rash, arthralgias or myalgias). Nevirapine must be permanently discontinued in any patient experiencing severe rash or a rash accompanied by systemic symptoms (see section 4.3).

Neither prednisone nor antihistamines decrease the incidence of nevirapine-associated rash.

Factors linked to nevirapine-associated rash are higher baseline CD4 count, higher baseline HIV RNA level, female sex, higher age and higher nevirapine concentration. Furthermore, failure to follow the initial dosing of 200 mg nevirapine daily during the lead-in period and a long delay between the initial symptoms and medical consultation are risk factors for developing serious cutaneous reactions.

Patients with a rash should be assessed for liver toxicity, and nevirapine must be permanently discontinued if the liver transaminases are elevated.

Nevirapine must not be restarted following severe skin reactions.

Discontinuation and reintroduction of nevirapine-containing preparations, such as [HA433 trade name]

Because nevirapine is an inducer of drug-metabolizing hepatic enzymes, administration of full therapeutic doses of nevirapine without a two-week, low-dose escalation phase may result in excess plasma drug levels and potentially increase the risk for toxicity. Therefore, in a patient who has interrupted treatment with [HA433 trade name] for more than two weeks and is to be restarted later, therapy should be reintroduced with separate formulations of lamivudine, nevirapine and zidovudine with a dose escalation period of 200 mg nevirapine once daily for 14 days, then a 200 mg twice-daily regimen. Only when the patient is stable on this triple combination, therapy with [HA433 trade name] may be resumed (see section 4.1).

Due to the long half-life of nevirapine, discontinuation of [HA433 trade name] without immediate institution of another effective antiretroviral therapy, will lead to a period of de facto nevirapine monotherapy. Since nevirapine has a low barrier of resistance, this may lead to high-level nevirapine resistance (see section 5.1). There is no validated strategy for handling this risk. However, covering the slow nevirapine elimination after discontinuation with 2-4 weeks of boosted PI monotherapy, in case a new antiretroviral regimen is not immediately instituted, has been suggested.

Haematological adverse reactions

Anaemia, neutropenia and leucopenia have been reported in patients receiving zidovudine-containing preparations, especially in patients with advanced HIV disease (poor bone marrow reserve) or low serum vitamin B12 levels, and usually after at least 4-6 weeks of therapy.

Therefore, it is recommended to monitor haematological parameters in patients receiving [HA433 trade name], e.g. as follows:

- In advanced HIV disease: at least every two weeks during the first three months of zidovudine therapy, and monthly thereafter.
- In early (non-symptomatic) HIV disease, at a frequency depending on the overall condition of the patient: e.g. every one to three months

Since substitution, dose reduction or interruption of zidovudine therapy may be necessary in patients whose haemoglobin concentrations or neutrophil counts fall to clinically significant levels, separate preparations of lamivudine, nevirapine and (if appropriate) zidovudine should be administered (refer to the Summary of Product Characteristics of zidovudine-only containing products).

Lactic acidosis
Lactic acidosis is a rare but severe, potentially life-threatening complication associated with NRTI use. It may occur after a few to several months of treatment. Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI-related lactic acidosis include female gender and obesity. Patients at increased risk should be closely monitored clinically. Screening for hyperlactataemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have levels > 5 mmol/l and require discontinuation of all NRTIs, including zidovudine/lamivudine. Lactic acid levels > 10 mmol/l usually are a medical emergency.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV- negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia and neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether these neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These considerations, however, do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lipodystrophy
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. A higher risk of lipodystrophy has been associated e.g. with older age of the patient, longer duration of ART and related metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered (see section 4.8).

Immune Reactivation Syndrome
In HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary.

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

Pancreatitis
Treatment with [HA433 trade name] should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur. Patients with a high risk of pancreatitis or those receiving also other products (see section 4.8).

Transmission
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Excipients
[HA433 trade name] contains **aspartame**, which is a source of phenylalanine and may be harmful for people with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

[HA433 trade name] contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Since [HA433 trade name] contains lamivudine, nevirapine and zidovudine, any interactions identified for these individually are relevant to [HA433 trade name].

Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through organic cation transporters; co-administration of lamivudine with OCT inhibitors or nephrotoxic drugs may increase lamivudine exposure.

Nevirapine is an inducer of CYP3A and potentially CYP2B6, with maximal induction occurring within 2-4 weeks of treatment. The plasma concentration of compounds using this metabolic pathway may decrease when co-administered with nevirapine. Careful monitoring of the effectiveness of medicines metabolised by the P450 system is recommended when taken in combination with [HA433 trade name].

Zidovudine is primarily metabolised by UGT enzymes; co-administration of inducers or inhibitors of UGT enzymes could alter zidovudine exposure.

[HA433 trade name] should not be taken with medicines containing:

- atazanavir (in combination with ritonavir) – interaction with nevirapine
- boceprevir – interaction with nevirapine
- cladribine – interaction with lamivudine
- delavirdine – interaction with nevirapine
- efavirenz – interaction with nevirapine
- elvitegravir (in combination with cobicistat) – interaction with nevirapine
- emtricitabine – overlapping resistance and lack of additional antiretroviral effect
- etravirine – interaction with nevirapine
- fosamprenavir (if not co-administered with low dose ritonavir) – interaction with nevirapine
- ketoconazole – interaction with nevirapine
- ombitasvir/paritaprevir/ritonavir – interaction with nevirapine
- rifampicin – interaction with nevirapine
- rilpivirine – interaction with nevirapine

The list below should not be considered exhaustive but is representative of the classes studied. The interaction data are presented as geometric mean value with 90% confidence interval (90% CI) when possible. ND = Not Determined, ↑ = Increased, ↓ = Decreased, ↔ = No effect.

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of** [HA433 trade name]
Antimicrobials		
Antiretrovirals		
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Abacavir	No interaction or interaction not studied	Abacavir and [HA433 trade name]can be co-administered without dose adjustment
Didanosine	No interaction or interaction not studied	Didanosine and [HA433 trade name]can be co-administered without dose adjustment
Emtricitabine	Overlapping resistance and lack of additional antiviral effect	Combination not recommended
Stavudine	Antagonism of anti-HIV activity between stavudine and zidovudine could decrease the efficacy of both drugs	Combination not recommended
Tenofovir	No interaction or interaction not studied	Tenofovir and [HA433 trade name]can be co-administered without dose adjustment
Non-nucleoside reverse transcriptase inhibitors (NNRTI)		
Delavirdine + nevirapine	Interaction has not been studied	Combination of [HA433 trade name] with NNRTIs is not recommended
Efavirenz + nevirapine	Efavirenz AUC ↓ 0.72 (0.66–0.86) Efavirenz C_{min} ↓ 0.68 (0.65–0.81) Efavirenz C_{max} ↓ 0.88 (0.77–1.01)	Combination not recommended because of additive toxicity and no benefit in efficacy over either efavirenz or nevirapine alone.
Etravirine + nevirapine	Concomitant use of etravirine with nevirapine may significantly decrease the plasma concentration of etravirine with loss of therapeutic effect of etravirine	Combination of [HA433 trade name] with NNRTIs is not recommended
Rilpivirine + nevirapine	Interaction has not been studied	Combination of [HA433 trade name] with NNRTIs is not recommended
Protease inhibitors		
Atazanavir/ritonavir 300/100 mg once daily 400/100 mg once daily + nevirapine	<u>Atazanavir/ritonavir 300/100 mg:</u> Atazanavir/ritonavir AUC ↓0.58 (0.48–0.71) Atazanavir/ritonavir C_{min} ↓ 0.28 (0.20–0.40) Atazanavir/ritonavir C_{max} ↓ 0.72 (0.60–0.86) <u>Atazanavir/ritonavir 400/100 mg:</u> Atazanavir/ritonavir AUC ↓0.81 (0.65–1.02) Atazanavir/ritonavir C_{min} ↓ 0.41 (0.27–0.60) Atazanavir/ritonavir C_{max} ↔1.02 (0.85–1.24) (compared to 300/100 mg without nevirapine) Nevirapine AUC ↑ 1.25 (1.17–1.34) Nevirapine C_{min} ↑ 1.32 (1.22–1.43) Nevirapine C_{max} ↑ 1.17 (1.09–1.25)	Combination of atazanavir/ritonavir and [HA433 trade name] is not recommended

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of** [HA433 trade name]
Darunavir/ritonavir 400/100 mg twice daily + nevirapine	Darunavir AUC ↑ 1.24 (0.97–1.57) Darunavir C_{min} ↔ 1.02 (0.79–1.32) Darunavir C_{max} ↑ 1.40 (1.14–1.73) Nevirapine AUC ↑ 1.27 (1.12–1.44) Nevirapine C_{min} ↑ 1.47 (1.20–1.82) Nevirapine C_{max} ↑ 1.18 (1.02–1.37)	Darunavir and [HA433 trade name] can be co-administered without dose adjustment
Fosamprenavir 1.4 g twice daily + nevirapine	Amprenavir AUC ↓ 0.67 (0.55–0.80) Amprenavir C_{min} ↓ 0.65 (0.49–0.85) Amprenavir C_{max} ↓ 0.75 (0.63–0.89) Nevirapine AUC ↑1.29 (1.19–1.40) Nevirapine C_{min} ↑1.34 (1.21–1.49) Nevirapine C_{max} ↑1.25 (1.14–1.37)	Combination of fosamprenavir and [HA433 trade name] is not recommended if fosamprenavir is not co-administered with ritonavir.
Fosamprenavir/ritonavir 700/100 mg twice daily + nevirapine	Amprenavir AUC ↔ 0.89 (0.77–1.03) Amprenavir C_{min} ↓ 0.81 (0.69–0.96) Amprenavir C_{max} ↔ 0.97 (0.85–1.10) Nevirapine AUC ↑ 1.14 (1.05–1.24) Nevirapine C_{min} ↑ 1.22 (1.10–1.35) Nevirapine C_{max} ↑ 1.13 (1.03–1.24)	Fosamprenavir/ritonavir and [HA433 trade name] can be co-administered without dose adjustment
Indinavir 800 mg three times daily + nevirapine	Indinavir AUC ↓ 28% Nevirapine ↔ (CYP3A4 induction)	A higher dose of indinavir or ritonavir-boosted indinavir should be considered if given with [HA433 trade name]
Lopinavir/ritonavir (capsules) 400/100 mg twice daily + nevirapine	Adults: Lopinavir AUC ↓ 0.73 (0.53–0.98) Lopinavir C_{min} ↓ 0.54 (0.28–0.74) Lopinavir C_{max} ↓ 0.81 (0.62–0.95)	An increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) or 500/125 mg (5 tablets with 100/25 mg each) twice daily with food is recommended in combination with nevirapine. Dose adjustment of [HA433 trade name] is not required when co-administered with lopinavir.
Lopinavir/ritonavir (oral solution) 300/75 mg/m^2 twice daily + nevirapine	Children: Lopinavir AUC ↓ 0.78 (0.56–1.09) Lopinavir C_{min} ↓ 0.45 (0.25–0.82) Lopinavir C_{max} ↓ 0.86 (0.64–1.16)	For children, increasing the dose of lopinavir/ritonavir to 300/75 mg/m^2 twice daily with food should be considered when used in combination with nevirapine, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected
Ritonavir 600 mg twice daily + nevirapine	Ritonavir AUC ↔ 0.92 (0.79–1.07) Ritonavir C_{min} ↔ 0.93 (0.76–1.14) Ritonavir C_{max} ↔ 0.93 (0.78–1.07) Nevirapine: co-administration of ritonavir does not lead to clinically relevant change in nevirapine plasma levels.	Ritonavir and [HA433 trade name]can be co-administered without dose adjustment
Saquinavir/ritonavir + nevirapine	Limited data on saquinavir soft gel capsule boosted with ritonavir do not suggest clinically relevant interaction between saquinavir boosted with ritonavir and nevirapine	Saquinavir/ritonavir and [HA433 trade name] can be co-administered without dose adjustment
Tipranavir/ritonavir 500/200 mg twice daily + nevirapine	No specific drug-drug interaction study has been performed. Limited data from a phase IIa study in HIV-infected patients have shown a clinically non-significant 20% decrease of tipranavir C_{min}.	Tipranavir and [HA433 trade name]can be co-administered without dose adjustment

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of** [HA433 trade name]
Entry inhibitors		
Enfuvirtide + nevirapine	Due to the metabolic pathway no clinically significant pharmacokinetic interaction is expected between enfuvirtide and nevirapine.	Enfuvirtide and [HA433 trade name]can be co-administered without dose adjustment
Maraviroc 300 mg once daily + nevirapine	Maraviroc AUC ↔ 1.01 (0.6–1.55) Maraviroc C_{min} ND Maraviroc C_{max} ↔ 1.54 (0.94–2.52) compared to historical controls Nevirapine concentrations not measured, no effect is expected.	Maraviroc and [HA433 trade name]can be co-administered without dose adjustment
Integrase inhibitors		
Elvitegravir/cobicistat + nevirapine	Interaction has not been studied. Cobicistat, a CYP3A-inhibitor significantly inhibits hepatic enzymes as well as other metabolic pathways. Therefore, co-administration would likely result in altered plasma levels of cobicistat and nevirapine	Combination of [HA433 trade name]with elvitegravir in combination with cobicistat is not recommended
Raltegravir 400 mg twice daily + nevirapine	No clinical data available. Due to the metabolic pathway of raltegravir no interaction is expected.	Raltegravir and [HA433 trade name]can be co-administered without dose adjustment
Antivirals for chronic hepatitis B and C		
Adefovir + nevirapine	Weak antagonism of nevirapine by adefovir in vitro has not been confirmed in clinical trials and reduced efficacy is not expected. Adefovir did not affect the common CYP isoforms involved in drug metabolism and is excreted renally. No clinically relevant interaction is expected.	Adefovir and [HA433 trade name] may be co-administered without dose adjustment
Boceprevir + nevirapine	Boceprevir is partly metabolised by CYP3A4/5. Giving boceprevir with medicines that induce or inhibit CYP3A4/5 could increase or decrease exposure. Plasma trough concentrations of boceprevir fell when administered with an NNRTI with a similar metabolic pathway as nevirapine. The clinical outcome of this reduction of boceprevir trough concentrations has not been directly assessed.	Combination of boceprevir and [HA433 trade name] not recommended
Daclatasvir + nevirapine	Interaction between nevirapine and daclatasvir has not been studied but daclatasvir concentrations are expected to fall due to induction of CYP3A4 by nevirapine.	Combination of [HA433 trade name] and daclatasvir not recommended
Elbasvir/grazoprevir + nevirapine	Interaction between elbasvir/grazoprevir and nevirapine has not been studied but elbasvir/grazoprevir concentrations are expected to fall because of induction of CYP3A4, CYP2B6 and BCRP by nevirapine; this may lead to reduced therapeutic effect	Combination of [HA433 trade name] and elbasvir/grazoprevir not recommended
Entecavir + nevirapine	Entecavir is not a substrate, inducer or an inhibitor of CYP enzymes. No clinically relevant drug-drug interaction is expected.	Entecavir and [HA433 trade name] may be co-administered without dose adjustment

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of** [HA433 trade name]
Glecaprevir/pibren-tasvir + nevirapine	Co-administration of nevirapine and glecaprevir/pibrentasvir has not been studied but glecaprevir/pibrentasvir concentrations may fall due to induction of CYP3A4 by nevirapine.	Combination of [HA433 trade name] and glecaprevir/pibrentasvir not recommended
Interferons (pegylated interferons alfa 2a and alfa 2b) + nevirapine	Interferons have no known effect on CYP3A4 or CYP2B6. No clinically relevant interaction is expected.	Interferons and [HA433 trade name] may be co-administered without dose adjustment
Ombitasvir/paritaprevir/ ritonavir + nevirapine	Co-administration of nevirapine and ombitasvir/paritaprevir/ritonavir has not been studied. Plasma concentrations of ombitasvir/paritaprevir/ritonavir could decrease due to CYP3A4 induction by nevirapine; however, nevirapine exposure could increase due to inhibition by ritonavir	Combination of [HA433 trade name] and ombitasvir/paritaprevir/ritonavir is contraindicated
Ribavirin + zidovudine	Co-administration of ribavirin and zidovudine may exacerbate anemia	Combination of [HA433 trade name] and ribavirin not recommended.
Simeprevir + nevirapine	Interaction between nevirapine and simeprevir has not been studied but simeprevir concentrations are expected to fall due to induction of CYP3A4 by nevirapine.	Combination of [HA433 trade name] and simeprevir not recommended
Sofosbuvir/velpatasvir + nevirapine	Co-administration of nevirapine and sofosbuvir/velpatasvir has not been studied but concentrations of velpatasvir and sofosbuvir could decrease due to CYP3A4 induction by nevirapine	Combination of [HA433 trade name]and sofosbuvir/velpatasvir not recommended
Telaprevir + nevirapine	Telaprevir is metabolised by CYP3A and is a P-glycoprotein substrate. Other enzymes may be involved in the metabolism. Co-administration of telaprevir and inducers of CYP3A or P-gp (or both) may decrease telaprevir plasma concentration. Interaction between telaprevir and nevirapine has not been studied; however, interaction studies of telaprevir with an NNRTI with a similar metabolic pathway as nevirapine found reduced levels of both.	Caution should be exercised when co-administering telaprevir with [HA433 trade name]. If co-administered with [HA433 trade name], an adjustment in the telaprevir dose should be considered
Telbivudine + nevirapine	Telbivudine is not a substrate, inducer or inhibitor of the cytochrome P450 enzyme system. No clinically relevant interaction is expected.	Telbivudine and [HA433 trade name]may be co-administered without dose adjustment

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of** [HA433 trade name]
Antibiotics		
Clarithromycin 500 mg twice daily + nevirapine	Clarithromycin AUC ↓ 0.69 (0.62–0.76) Clarithromycin C_{min} ↓ 0.44 (0.30–0.64) Clarithromycin C_{max} ↓ 0.77 (0.69–0.86) Metabolite 14-OH clarithromycin AUC ↑ 1.42 (1.16–1.73) Metabolite 14-OH clarithromycin C_{min} ↔ 0 (0.68–1.49) Metabolite 14-OH clarithromycin C_{max} ↑1.47 (1.21–1.80) Nevirapine AUC ↑ 1.26 Nevirapine C_{min} ↑ 1.28 Nevirapine C_{max} ↑ 1.24 compared to historical controls	Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex* overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended If clarithromycin is used, at least 2-hour gap is recommended between taking [HA433 trade name]and clarithromycin
Clarithromycin 500 mg twice daily + zidovudine	Zidovudine AUC ↓ 12%	
Rifabutin 150 or 300 mg once daily + nevirapine	Rifabutin AUC ↑ 1.17 (0.98–1.40) Rifabutin C_{min} ↔ 1.07 (0.84–1.37) Rifabutin C_{max} ↑ 1.28 (1.09–1.51) Metabolite 25-*O*-desacetylrifabutin AUC ↑ 1.24 (0.84–1.84) Metabolite 25-*O*-desacetylrifabutin C_{min} ↑ 1.22 (0.86–1.74) Metabolite 25-*O*-desacetylrifabutin C_{max} ↑ 1.29 (0.98–1.68) A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical data was reported.	No significant effect on rifabutin and nevirapine pharmacokinetic parameters. Rifabutin and [HA433 trade name] can be co-administered without dose adjustments. However, due to high variability, rifabutin exposure may rise significantly in some patients who may be at higher risk for rifabutin toxicity. Combination of rifabutin and [HA433 trade name] should be used with caution.
Rifampicin 600 mg once daily + nevirapine	Rifampicin AUC ↔ 1.11 (0.96–1.28) Rifampicin C_{min} ND Rifampicin C_{max} ↔ 1.06 (0.91–1.22) Nevirapine AUC ↓ 0.42 Nevirapine C_{min} ↓ 0.32 Nevirapine C_{max} ↓0.50 compared to historical controls.	Combination of [HA433 trade name] and rifampicin is not recommended. For treating patients co-infected with tuberculosis and who are taking nevirapine, rifabutin can be considered instead.
Rifampicin + zidovudine	Zidovudine AUC ↓ 48%	
Trimethoprim/sulfa-methoxazole 160 mg/800 mg once daily for 5 days + lamivudine 300 mg single dose	Lamivudine: AUC ↑ 40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	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

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of** [HA433 trade name]
Antifungals		
Fluconazole 200 mg once daily + nevirapine	Fluconazole AUC ↔ 0.94 (0.88–1.01) Fluconazole C_{min} ↔ 0.93 (0.86–1.01) Fluconazole C_{max} ↔ 0.92 (0.85–0.99) Nevirapine exposure: ↑100% compared with historical data where nevirapine was administered alone.	Because of the risk of increased exposure to nevirapine and zidovudine, patients should be monitored closely for nevirapine and zidovudine toxicity
Fluconazole + zidovudine	Zidovudine AUC ↑ 74%	
Itraconazole 200 mg once daily + nevirapine	Itraconazole AUC ↓ 0.39 Itraconazole C_{min} ↓ 0.13 Itraconazole C_{max} ↓ 0.62 Nevirapine: there was no significant difference in nevirapine pharmacokinetic parameters.	A dose increase for itraconazole should be considered when used concomitantly with [HA433 trade name]
Ketoconazole 400 mg once daily + nevirapine	Ketoconazole AUC ↓ 0.28 (0.20–0.40) Ketoconazole C_{min} ND Ketoconazole C_{max} ↓ 0.56 (0.42–0.73) Nevirapine: plasma levels: ↑ 1.15–1.28 compared to historical controls.	Combination of [HA433 trade name] and ketoconazole is not recommended
Antimalarials		
Amodiaquine 600 mg once daily (with aretesunate) + lamivudine, nevirapine and zidovudine	Amodiaquine AUC ↓ 29% Desethylamodiaquine AUC ↓ 33%	The patient treated with combination of [HA433 trade name] and amodiaquine/artesunate should be carefully monitored for efficacy and safety. Combined use may increase hepatotoxicity
Atovaquone, chloroquine, mefloquine, proguanil, sulfadoxine, pyrimethamine + nevirapine	No formal interaction study available	On theoretical basis, clinically significant interactions with [HA433 trade name] are not likely
Artemisinin and its derivatives + nevirapine	No formal interaction study available	[HA433 trade name] may reduce the concentration of artemisinin and its derivatives, but clinical consequences are unknown
Halofantrine + nevirapine	No formal interaction study available. Halofantrine is extensively metabolised by CYP3A and an interaction is predicted. Alteration of halofantrine metabolism could affect its plasma concentrations	[HA433 trade name]should be used cautiously with halofantrine, which has a narrow therapeutic index
Lumefantrine + nevirapine	Lumefantrine AUC ↑1.56 Lumefantrine C_{max} ↑1.24	Preliminary studies suggest no increase in adverse effects of lumefantrine. [HA433 trade name]and artemether + lumefantrine can be co-administered without dose adjustment (see also under Artemisinin and its derivatives)

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of** [HA433 trade name]
Quinine + nevirapine	Quinine AUC ↓ 0.67 Quinine C_{max} ↓ 0.64	[HA433 trade name] can reduce the antimalarial effect of quinine. Other antimalarials should be considered
Anticonvulsants		
Carbamazepine, phenobarbital, phenytoin + nevirapine	No formal interaction study available	Concentrations of nevirapine and of the anticonvulsant are expected to be reduced, leading to treatment failure; co-administration should be avoided unless antiretroviral (and antiepileptic) effect can be monitored closely
Phenobarbital + zidovudine	Interaction not studied; Potential for slight fall in zidovudine plasma concentrations	
Phenytoin + zidovudine	Phenytoin concentration may rise or fall	
Valproic acid 250–500 mg three time daily + zidovudine	Zidovudine AUC ↑ 80%	
Antacids		
Cimetidine + nevirapine	Cimetidine: no significant effect on cimetidine pharmacokinetic parameters is seen. Nevirapine: C_{min} ↑ 1.07	Cimetidine and [HA433 trade name]can be co-administered without dose adjustment
Anticoagulants		
Warfarin + nevirapine	The interaction between nevirapine and warfarin is complex, with the potential for both increases and decreases in coagulation time when used concomitantly.	Anticoagulation activity should be closely monitored
Contraceptives		
Depot medroxyprogesterone acetate 150 mg every 3 months + nevirapine	Medroxyprogesterone acetate AUC ↔ Medroxyprogesterone acetate C_{min} ↔ Medroxyprogesterone acetate C_{max} ↔ Nevirapine AUC ↑ 1.20 Nevirapine C_{max} ↑ 1.20	Depot medroxyprogesterone acetate and [HA433 trade name]can be co-administered without dose adjustment
Ethinylestradiol 35 micrograms + nevirapine	Ethinylestradiol AUC ↓ 0.80 (0.67–0.97) Ethinylestradiol C_{min} ND Ethinylestradiol C_{max} ↔ 0.94 (0.79–1.12)	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking [HA433 trade name]. Appropriate doses for hormonal contraceptives (oral or other forms of application) other than depot medroxyprogesterone acetate in combination with [HA433 trade name] have not been established.
Norethisterone 1 mg once daily + nevirapine	Norethisterone AUC ↓ 0.81 (0.70–0.93) Norethisterone C_{min} ND Norethisterone C_{max} ↓ 0.84 (0.73–0.97)	
Drug abuse		
Methadone + nevirapine	Methadone AUC ↓ 0.40 (0.31–0.51) Methadone C_{min} ND Methadone C_{max} ↓ 0.58 (0.50–0.67)	Methadone-maintained patients beginning treatment with [HA433 trade name] should be monitored for zidovudine toxicity and for opioid withdrawal and methadone dose should be adjusted accordingly.
Methadone + lamivudine	Interaction not studied	

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of** [HA433 trade name]
Methadone 30–90 mg once daily + zidovudine	Zidovudine AUC ↑ 43% Methadone AUC ↔	
Gastric acid suppressants		
Cimetidine, ranitidine + lamivudine	Interaction not studied. Clinically significant interaction unlikely. Cimetidine and ranitidine eliminated only in part by renal organic cation transport system.	No dosage adjustment necessary
Cytotoxics		
Cladribine + lamivudine	Clinical findings suggest an interaction between lamivudine and cladribine. In vitro lamivudine inhibits the intracellular phosphorylation of cladribine with potential risk of cladribine loss of efficacy	Combination of [HA433 trade name] and cladribine is not recommended
Herbal products		
St John's wort + nevirapine	Serum levels of nevirapine can be reduced by concomitant use of St John's wort (*Hypericum perforatum*) because St John's wort induces drug metabolism enzymes or transport proteins	St John's wort and [HA433 trade name] must not be co-administered. If a patient is already taking St John's wort, check nevirapine, and if possible viral levels, and stop St John's wort. Nevirapine levels may increase on stopping St John's wort. The dose of nevirapine may need adjusting. The inducing effect may persist for at least 2 weeks after stopping St John's wort

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

No increased risks of birth defects have been reported for lamivudine, nevirapine or zidovudine but risks to the foetus cannot be ruled out. More information is available from www.apregistry.com. The use in pregnant women of either nevirapine or zidovudine, with subsequent treatment of the newborn infants, can reduce the rate of maternal-foetal transmission of HIV-infection. No such data are available for lamivudine.

Breastfeeding

Lamivudine, nevirapine and zidovudine pass into breast milk. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Fertility

Neither zidovudine nor lamivudine have shown evidence of impairment of fertility in studies in male and female rats. There are no data on their effect on human female fertility. In men zidovudine has not been shown to affect sperm count, morphology or motility.

Reproductive toxicology studies have found the nevirapine impairs fertility in rats.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of [HA433 trade name] should be borne in mind when considering the patient's ability to drive or operate machinery

Dizziness and fatigue may affect the ability to drive and operate machinery. Patients should be instructed to avoid potentially hazardous activity if they have these side effects.

4.8 Undesirable effects

Adverse reactions of [HA433 trade name] are those of its components: lamivudine, nevirapine and zidovudine.

The most serious adverse reactions of nevirapine are Stevens-Johnson syndrome, toxic epidermal necrolysis, serious hepatitis or hepatic failure, and drug reaction with eosinophilia and systemic symptoms (DRESS), characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction. The first 18 weeks of treatment is a critical period which requires close monitoring (see section 4.4).

The most serious adverse reactions of zidovudine include anaemia, neutropenia and leucopoenia. Lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis can also occur with zidovudine (see section 4.4).

The most frequently reported adverse reactions are rash, allergic reactions, hepatitis, abnormal liver function tests, nausea, vomiting, diarrhoea, abdominal pain, fatigue, fever, headache and myalgia.

Adverse events considered at least possibly related to lamivudine, nevirapine and zidovudine are listed below by body system, organ class and frequency. Frequencies are defined as very common (up to 1 in 10), common (between 1 in 100 and 1 in 10), uncommon (between 1 in 1000 and 1 in 100), rare (between 1 in 10 000 and 1 in 1000), very rare (less than 1 in 10 000), and 'not known'.

Blood and lymphatic systems disorders

Common	anaemia and neutropenia (both occasionally severe), leucopoenia, granulocytopenia
Uncommon	thrombocytopenia and pancytopenia (with marrow hypoplasia)
Rare	pure red cell aplasia
Very rare	aplastic anaemia

Immune system disorders

Common	hypersensitivity (incl. anaphylactic reaction, angioedema, urticaria)
Rare	drug reaction with eosinophilia and systemic symptoms
Not known	Immune reconstitution syndrome

Metabolism and nutrition disorders

Rare	lactic acidosis in the absence of hypoxaemia, anorexia
Not known	raised blood lipids and glucose, weight increase, loss of subcutaneous fat mainly in the face, limbs and buttocks

Nervous system disorders

Very common	Headache
Common	dizziness, insomnia
Rare	paraesthesia, somnolence, loss of mental acuity, convulsions

Psychiatric disorders

Rare	anxiety and depression

Cardiac disorders

Rare	Cardiomyopathy

Respiratory, thoracic and mediastinal disorders

Common	cough, nasal symptoms
Uncommon	Dyspnoea

Gastrointestinal disorders

Very common	Nausea
Common	vomiting, abdominal pain or cramps, diarrhoea
Uncommon	Flatulence
Rare	oral mucosa pigmentation, taste perversion and dyspepsia, pancreatitis, rises in serum amylase

Hepatobiliary disorders

Common	raised blood levels of liver enzymes and bilirubin, hepatitis (including severe and life-threatening hepatotoxicity)
Uncommon	jaundice, transient rises in liver enzymes (AST, ALT)
Rare	liver disorders such as severe hepatomegaly with steatosis, fulminant hepatitis (which may be fatal)

Skin and subcutaneous tissue disorders

Very common	Rash
Common	Alopecia
Uncommon	pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis (which may be fatal), angioedema, urticarial
Rare	nail and skin pigmentation, urticaria, sweating, angioedema

Musculoskeletal and connective tissue disorders

Common	arthralgia, myalgia, muscle disorders
Rare	Rhabdomyolysis
Not known	Osteonecrosis

Renal and urinary disorders

Rare	urinary frequency

Reproductive system and breast disorders

Rare	Gynaecomastia

General disorders and administration site conditions

Common	fatigue, malaise, fever
Uncommon	generalised pain and asthenia

Rare	chills, chest pain and influenza-like syndrome
Investigations	
Uncommon	blood phosphorus decreased; blood pressure increased

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Symptoms

There is limited experience of overdosage with [HA433 trade name]. No specific signs and symptoms have been identified following acute overdose with zidovudine or lamivudine apart from those listed as undesirable effects. Nevirapine overdose at doses ranging between 0.8 and 6 g daily for up to 15 days has been reported. Patients had oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases and weight loss.

Treatment

There is no antidote for any of the three components. In suspected overdose, patients should be monitored for toxicity (see section 4.8), and standard supportive treatment used as necessary. There is no reliable information on the value of haemodialysis and peritoneal dialysis in eliminating lamivudine and zidovudine. Advice should be sought from specialist centres with experience of managing overdoses.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations.

ATC code: J05AR05

Mechanism of action and pharmacodynamic effects

Lamivudine and zidovudine are nucleoside analogues that have activity against HIV. Additionally, lamivudine has activity against hepatitis B virus. Lamivudine and zidovudine are metabolised intracellularly to their active moieties, lamivudine 5'-triphosphate and zidovudine-triphosphate. Their main modes of action are to act as chain terminators of viral reverse transcription.

Lamivudine 5'-triphosphate and zidovudine-triphosphate have selective inhibitory activity against HIV-1 and HIV-2 replication in vitro. Lamivudine in combination with zidovudine acts synergistically against HIV clinical isolates in cell culture. No antagonistic effects in vitro were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine and nevirapine). No antagonistic effects in vitro were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine and interferon-alfa).

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by inducing a change that disrupts the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by nevirapine. In vitro nevirapine had no antiviral activity in cell culture against group O HIV-1 isolates or HIV-2 isolates.

Clinical efficacy

In clinical trials in adults, combination treatment with lamivudine, zidovudine and nevirapine reduced HIV-1 viral load and increased CD4 cell count. Lamivudine and zidovudine in combination with nevirapine significantly reduced the risk of disease progression and mortality. In two different randomised trials of zidovudine and lamivudine in combination with nevirapine in patients who had not previously received antiretroviral therapy, in 65% and 73% of patients plasma HIV RNA fell to less than 20 copies/ml and less than 50 copies/ml, respectively, after 1 year by intention-to-treat analysis.

In a clinical trial in South Africa, 123 children aged between 3 months and 16 years with HIV infection who had not been treated previously, received combination treatment with lamivudine, zidovudine and nevirapine for 48 weeks. Overall, in 50% of the patients, plasma HIV RNA fell to less than 400 copies/ml at 48 Weeks.

The combination of lamivudine, zidovudine and nevirapine has not been specifically investigated in HIV patients co-infected with HBV.

Resistance

In most cases when combination antiretroviral therapy comprising zidovudine and lamivudine fails, the M184V mutation will be selected for at an early stage. M184V causes high-level resistance to lamivudine (> 300-fold reduced susceptibility). Virus with M184V replicates less well than does wild type virus. M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility). In vitro data suggest that continuing lamivudine despite the development of M184V might provide residual antiretroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. The clinical data are very limited and preclude reliable conclusion in the field. Therefore, maintaining lamivudine therapy despite M184V mutation should only be considered when the activity of the best available NRTI backbone is significantly compromised.

Resistance to zidovudine is developed along two separate pathways. The first includes M41L, L210W and T215F/Y. The second includes D67N, K70R and K219E/Q. Collectively, these mutations are termed thymidine analogue mutations (TAM). In viruses with M184V, two to three TAMs are generally required for phenotypically detectable and clinically significant zidovudine resistance. M41L, L210W, and T215Y have a greater effect on zidovudine susceptibility and cross-resistance to other NRTIs than the other TAMs. Other important mutations selected for by zidovudine include T69 insertion mutations and the Q151M complex, where this mutation appears in combination with mutations at positions 75, 77, and 116. Both of these patterns confer high-level resistance to zidovudine and all other presently available NRTIs.

The likelihood of a gradual accumulation of mutations conferring resistance to the entire NRTI class, upon virological failure with combination therapy including zidovudine and lamivudine, underscores the importance of early detection of virological failure. Delayed detection of virological failure may severely limit the options for next-line therapy.

The most common resistance mutations selected for by nevirapine are Y181C, K103N and G190A. All of these mutations cause high-level resistance to nevirapine. In most patients in whom nevirapine-containing antiretroviral therapy fails, the virus will have developed one or more mutations with high-grade resistance to nevirapine, as well as cross-resistance to efavirenz and delavirdine Patients failing therapy including efavirenz or delavirdine will usually have a virus cross-resistant to nevirapine. If failing therapy is continued, further resistance mutations will accumulate.

High-level resistance to nevirapine is selected for by a single dose in monotherapy, as has been demonstrated by the high prevalence of resistance mutations following nevirapine use for prevention of mother to child transmission. Due to the long half-life of nevirapine, a period of functional monotherapy with nevirapine may follow upon discontinuation of effective nevirapine-containing antiretroviral therapy. This may cause significant nevirapine resistance, and compromise the efficacy of future NNRTI therapy (see section 4.4).

5.2 Pharmacokinetic properties

Absorption of [HA433 trade name]

The absorption characteristics of [HA433 trade name] have been determined after administration of a single dose tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Arithmetic mean value (± standard deviation)		
	Lamivudine	**Nevirapine**	**Zidovudine**
Maximum concentration (C_{max})	0.6793 ± 0.2113 µg/mL	1.3052 ± 0.2147 µg/mL	0.7862 ± 0.2139 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	2.6096 ± 0.7043 µg · h/mL	51.1476 ± 6.7796 µg · h/mL*	0.8799 ± 0.1688 µg · h/mL
Time to attain maximum concentration (Tmax)	0.88 ± 0.45 h	2.37 ± 1.18 h	0.44 ± 0.18 h

* AUC_{0-72h}

Pharmacokinetics of Lamivudine, Nevirapine and Zidovudine

	Lamivudine	**Nevirapine**	**Zidovudine**
Absorption			
Oral bioavailability	80-85%	>90%	60-70%
Distribution			
Volume of distribution (mean)	1.3 L/kg	1.2 L/kg	1.6 L/kg
Plasma protein binding *in vitro*	< 36%	60%	34-38%
Metabolism			
	Only minor route (< 10%)	Cytochrome P450 isozymes CYP3A and CYP2B6, and glucuronidation. Autoinduction resulting in decreased plasma half-life after 2-4 weeks of dosing Three major metabolites:2-hydroxy-nevirapine glucoronide, 3-hydroxy-nevirapine glucoronide and 12-hydroxy-nevirapine glucuronide	Glucuronidation Major metabolite: 5'-zidovudine-glucuronide
Active metabolite(s)	None	None	None
Elimination			
Elimination half life	5-7 h 22 h for intracellular lamivudine triphosphate	45 h after single dose and 25-30 hours after multiple doses (200-400 mg)	1.1 h [IV] 7 h [intracellular zidovudine triphosphate]

Mean systemic clearance (Cl/F)	0.32 L/h/kg	1.6 L/h/kg	0.34 L/h/kg
% of dose excreted in urine	> 70% (predominantly cleared unchanged)	> 80% (<5% excreted unchanged)	> 50-80%
% of dose excreted in faeces	NA*	10%	NA*
Pharmacokinetic linearity	Linear pharmacokinetics	Linear pharmacokinetics	NA*
Drug interactions *(in vitro*)			
Transporters	OCT (organic cationic transporters)	-	-
Metabolizing enzymes	-	CYP3A, CYP2B6, UGT	UGT- Uridine 5'-diphospho-glucuronosyltransferase

* Information not available

Pharmacokinetics in pregnancy

The pharmacokinetics of lamivudine and zidovudine during pregnancy were similar to that of non- pregnant women. Nevirapine clearance increases in pregnant women resulting in lower AUC and C_{max} compared to non-pregnant women. The clinical relevance of this finding is unknown.

Pharmacokinetics in children

A clinical trial in South Africa in 123 treatment-naïve, HIV-1-infected children aged 3 months to 16 years treated with nevirapine in combination with zidovudine and lamivudine indicated that either the weight-based or the body surface area-based dosing produced nevirapine plasma concentrations

5.3 Preclinical safety data

Lamivudine and zidovudine

Neither lamivudine nor zidovudine is mutagenic in bacterial tests, but they show activity in in vitro mammalian tests such as the mouse lymphoma assay. Lamivudine has not shown genotoxic activity in in vivo studies at plasma concentrations up to 40–50 times higher than clinical plasma levels. Zidovudine showed clastogenic effects in an oral repeated dose micronucleus test in mice.

A transplacental genotoxicity study in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at exposures equivalent to those in humans. That study found that fetuses exposed in utero to the combination had a higher level of nucleoside analogue-DNA incorporation into multiple fetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

The carcinogenic potential of a combination of lamivudine and zidovudine has not been tested.

In carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential. In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. An intravaginal carcinogenicity study confirmed the hypothesis that the vaginal tumours resulted

from long-term local exposure of the rodent vaginal epithelium to high concentrations of unmetabolised zidovudine in urine. There were no other zidovudine-related tumours in either sex of either species.

In addition, two transplacental carcinogenicity studies have been conducted in mice. In one study zidovudine was administered at maximum tolerated doses to pregnant mice from day 12 to 18 of gestation. One year post-natally, there was an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest dose level (420 mg/kg term body weight).

In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months, with exposure beginning prenatally on gestation day 10. Treatment-related findings were limited to late occurring vaginal epithelial tumours, which were seen with a similar incidence and time of onset as in the standard oral carcinogenicity study. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen.

In reproductive toxicity studies lamivudine has appeared to increase early embryonic deaths in rabbits at relatively low systemic exposures, comparable to those achieved in man, but not in the rat at very high systemic exposures. Zidovudine had a similar effect in both species, but only at very high systemic exposures. Lamivudine was not teratogenic in animal studies. At maternally toxic doses, zidovudine given to rats during organogenesis resulted in increased incidence of malformations, but there was no evidence of fetal abnormalities at lower doses. Neither lamivudine nor zidovudine had any effect on fertility in non-clinical studies

Nevirapine

Pre-clinical data revealed no special hazard for humans other than that observed in clinical studies based on conventional studies of safety, pharmacology, repeated dose toxicity, and genotoxicity. In reproductive toxicology studies, evidence of impaired fertility was seen in rats. In carcinogenicity studies, nevirapine induced hepatic tumours in rats and mice. In rats these findings are most likely related to nevirapine being a strong inducer of liver enzymes, and not due to a genotoxic mode of action. The mechanism of tumours in mice is not yet clear and therefore relevance to humans remains to be determined.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, povidone K30, colloidal silicon dioxide, sodium starch glycolate, magnesium stearate, ferric oxide yellow, orange flavor, aspartame and acesulfame potassium

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 Months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package, protected from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

White, opaque, wide-mouth HDPE bottle, with a white, opaque cap and containing a desiccant.
Pack size: 60 tablets

6.6 Instructions for use and handling and disposal

No special requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA433

9. DATE OF PREQUALIFICATION

26 October 2009

10. DATE OF REVISION OF THE TEXT

February 2020

References

General references

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection 2nd edition (2016), WHO, available at:

http://www.who.int/hiv/pub/arv/arv-2016/en/

Combivir summary of product characteristics (February 2018) available at:

https://www.ema.europa.eu/documents/product-information/combivir-epar-product-information_en.pdf

Viramune summary of product characteristics (June 2018) available at:

https://www.ema.europa.eu/documents/product-information/viramune-epar-product-information_en.pdf

Section 4.5

HIV Drug Interactions

https://www.hiv-druginteractions.org

Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/ .