SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NUVACO, 300 mg, 300 mg, 50 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **NUVACO** film-coated tablet contains:
Lamivudine 300 mg
Tenofovir disoproxil fumarate 300 mg
Dolutegravir sodium equivalent to dolutegravir 50 mg

Contains sugar (140,4 mg mannitol per tablet).

For the full list of excipients, see section 6.1

WARNING:
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE SECTION 4.4). NUVACO IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. SAFETY AND EFFICACY OF NUVACO HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND HAVE DISCONTINUED THE COMBINATION TABLET. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE NUVACO AND ARE CO-INFECTED WITH HIV AND HBV IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

3. PHARMACEUTICAL FORM

Film-coated tablets

Orange coloured, modified capsule shaped, biconvex film-coated tablets debossed with 'H' on one side, and 'D 17' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NUVACO is indicated for the treatment of HIV-1 infection in adults aged 18 years and older.

4.2 Posology and method of administration

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

NUVACO can be taken with or without food.

Adults:

For treatment-naïve and treatment-experienced patients, the recommended dose of **NUVACO** is one tablet daily.

Special populations

Renal impairment:

Significantly increased exposure occurred when tenofovir disoproxil fumarate, as in **NUVACO**, was administered to patients with renal impairment (see section 4.3).

The pharmacokinetics of tenofovir disoproxil fumarate, as in **NUVACO**, have not been evaluated in non-haemodialysis patients with creatinine clearance < 80 ml/min; therefore, no dosing recommendations are available for these patients.

NUVACO is contraindicated in patients with renal impairment with creatinine clearance less than 80 ml/min.

Paediatric population

NUVACO is not recommended for use in patients younger than18 years of age.

Dosage recommendations with certain concomitant medications

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and require dolutegravir dose adjustment to 50 mg twice daily. A supplementary dose of 50 mg dolutegravir should be given to patients taking **NUVACO**.

There is evidence that the concentration of isoniazid is increased by dolutegravir as contained in **NUVACO**. Patients receiving **NUVACO** while on isoniazid and/or combination regimen containing isoniazid should be carefully monitored. Dosage adjustment of isoniazid should be considered if necessary.

4.3 Contraindications

- Hypersensitivity to lamivudine, tenofovir disoproxil fumarate, dolutegravir or to any of the components of the **NUVACO** tablets listed in section 6.1.
- Moderate and severe hepatic impairment.
- Renal impairment.
- Women planning to become pregnant
- Pregnancy and lactation (see section 4.6).
- Women of childbearing age not using highly effective contraception.

- Concomitant use with adefovir dipivoxil.
- Co-administration with dofetilide and pilsicainide (see section 4.5).
- Co-administration with didanosine (see section 4.5).
- Co-administration with metformin (see section 4.5).
- Patients younger than 18 years of age.

4.4 Special warnings and precautions for use

Safety and efficacy of the individual active ingredients in various antiretroviral combination regimens with similar dosages as contained in **NUVACO** have been established in clinical studies for the treatment of HIV patients. However, safety and efficacy of the fixed-drug combination as in **NUVACO** for the treatment of HIV have not been established in clinical studies.

The complete professional information of the other medicines used in combination should be consulted before initiation of therapy.

Metabolic abnormalities:

Combination antiretroviral therapy, including **NUVACO** has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Lipodystrophy:

Combination antiretroviral therapy, including **NUVACO**, has also been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients.

A higher risk of lipodystrophy has been associated with individual factors such as older age, and with medicine related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Fasting serum lipids and blood glucose levels should be monitored. Lipid disorders should be managed as clinically appropriate.

Patients with evidence of lipodystrophy should also have a thorough cardiovascular risk assessment.

Immune reactivation syndrome:

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (cART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of cART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, cryptococcal meningitis and *Pneumocystis jirovecii (carinii)*

pneumonia. Any inflammatory symptoms should be evaluated, treatment instituted when necessary and ART continued.

Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease, Guillain-Barre syndrome, polymyositis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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

Opportunistic infections:
Patients receiving **NUVACO** may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by healthcare providers experienced in the treatment of patients with HIV-associated disease.

The risk of HIV transmission to others:
Patients must be advised that treatment with **NUVACO**, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used.

Lactic acidosis/ severe hepatomegaly with steatosis:
Lactic acidosis, usually associated with hepatic steatosis, including fatal cases, has been reported with the use of nucleoside analogues, such as in **NUVACO**. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure.

Lactic acidosis generally occurs after a few or several months of treatment. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and respond as follows:

- Lactate 2 – 5 mmol/L: monitor regularly, and be alert for clinical signs.
- Lactate 5 – 10 mmol/L without symptoms: monitor closely.
- Lactate 5 – 10 mmol/L with symptoms: Stop all therapy. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, hyperthyroidism, lymphoma).
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality in case studies).

The above lactate values may not be applicable to paediatric patients.

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any acidotic patient with a raised lactate level.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of **NUVACO** alone or in combination, in the treatment of HIV infection. Most cases were women.

Caution should be exercised when administering **NUVACO** to patients with known risk factors for liver disease.

Treatment with **NUVACO** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Caution should be exercised when administering nucleoside analogues as contained in **NUVACO** to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicines and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk. Patients at increased risk should be followed closely. However, cases have also been reported in patients with no known risk factors.

There are no study results demonstrating the effect of **NUVACO** on clinical progression of HIV-1.

Mitochondrial dysfunction:
Nucleoside and nucleotide analogues as contained in **NUVACO** 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. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia) and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and

laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs and symptoms.

Pancreatitis:
Pancreatitis has been observed in some patients receiving lamivudine, as in **NUVACO**. It is unclear whether this is due to lamivudine or to underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **NUVACO** until diagnosis of pancreatitis is excluded.

Patients with renal impairment:
In patients with renal impairment, the terminal half-life of **NUVACO** is increased due to decreased clearance (see section 4.3).

Renal impairment:
NUVACO is a combination medicine and the dose of the individual components cannot be altered. Tenofovir disoproxil fumarate and lamivudine are principally eliminated by the kidney. **NUVACO** is not recommended for patients with creatinine clearance < 50 ml/min or patients who require haemodialysis. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with the use of tenofovir disoproxil fumarate in clinical practice. Careful monitoring of renal function (serum creatinine and serum phosphate) is therefore recommended before taking **NUVACO**.

Renal function:
Since **NUVACO** is primarily eliminated by the kidneys, co-administration of **NUVACO** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of **NUVACO** and/or increase the concentrations of other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, aciclovir, valaciclovir, ganciclovir and valganciclovir.

Renal safety with tenofovir has only been studied to a very limited degree in adult patients with impaired renal function (creatinine clearance < 80 ml/min).

Renal monitoring:
It is recommended that renal function (creatinine clearance and serum phosphate) is assessed in all patients prior to initiating therapy with tenofovir disoproxil fumarate and that it is also monitored every four weeks during the first year of tenofovir disoproxil fumarate therapy, and then every three months. In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.

Co-administration and risk of renal toxicity:
Use of tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicine (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir,

pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil fumarate and nephrotoxic medicines is unavoidable, renal function should be monitored weekly.

Tenofovir disoproxil fumarate has not been clinically evaluated in patients receiving medicines which are secreted by the same renal pathway, including the transport proteins human organic anion transporter (hOAT) 1 and 3 or MRP 4 (e.g. cidofovir, a known nephrotoxic medicine). These renal transport proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir and cidofovir.

Consequently, the pharmacokinetics of these medicines, which are secreted by the same renal pathway including transport proteins hOAT 1 and 3 or MRP 4, might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicines which are secreted by the same renal pathway is not recommended, but if such use is unavoidable, renal function should be monitored weekly.

NUVACO should be avoided with concurrent or recent use of a nephrotoxic medicine. Patients at risk of, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic substances should be carefully monitored for changes in serum creatinine and phosphorus.

K65R mutation:
NUVACO should be avoided in antiretroviral experienced patients with HIV-1 harbouring the K65R mutation.

Bone mineral density:
Decreases in bone mineral density of spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate as contained in **NUVACO**. Decreases in bone mineral density of the hip are significantly greater. Clinically relevant bone fractures are reported. If bone abnormalities are suspected, then appropriate consultation should be obtained. Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk of osteopenia.

NUVACO may cause a reduction in bone mineral density. The effects of tenofovir disoproxil fumarate-associated changes in bone mineral density on long-term bone health and future fracture risk are currently unknown.

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

Liver disease:
Use of **NUVACO** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis).The safety and efficacy of **NUVACO** has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant professional information for these medicines.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients with HIV and hepatitis B or C virus co-infection:
NUVACO is not indicated for the treatment of chronic HBV infection. The safety and efficacy of **NUVACO** has not been established for the treatment of patients co-infected with HBV and HIV.

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant professional information for these medicines.

Patients co-infected with HIV and HBV who discontinue **NUVACO** should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Discontinuation of **NUVACO** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Exacerbations of hepatitis:
Flares on treatment:
Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Flares after treatment discontinuation:
Acute exacerbations of hepatitis have been reported in patients after the discontinuation of hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

Hypersensitivity reactions:
Dolutegravir, as in **NUVACO** is associated with a risk for hypersensitivity reactions (HSR) and share some common features such as fever and/or rash with other symptoms indicating multi-organ involvement.

Discontinue dolutegravir, as in **NUVACO** and other suspect agents if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema).

Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with dolutegravir, as in **NUVACO** and other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Paediatric use:
Safety and effectiveness in paediatric patients and patients < 18 years of age have not been established.

Use in the elderly:
Clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

4.5 Interaction with other medicines and other forms of interaction
Lamivudine
The likelihood of metabolic interactions is low due to limited metabolism as plasma protein binding and almost complete renal clearance.

Zidovudine plasma levels are not significantly altered when co-administered with lamivudine, as in **NUVACO**. Zidovudine has no effect on the pharmacokinetics of lamivudine, as in **NUVACO**.

Table 1: Medicine interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of lamivudine

Co-administered medicine	**Dose of co-administered medicine**	**Change of co-administered medicine pharmacokinetic parameters**	
Zidovudine	No dosage adjustments necessary	13 % ↑ in zidovudine exposure 28 % ↑ in peak plasma levels	
Zalcitabine	Do not use in combination	May inhibit intracellular phosphorylation of zalcitabine	
Trimethoprim (a constituent of co-trimoxazole)	No dosage adjustments necessary, unless the patient has renal impairment. **NUVACO** has no effect on the pharmacokinetics of co-trimoxazole.	↑ in **NUVACO** plasma levels	↔
Etravirine (ETR)	Co-administration is not recommended, unless the patient is also receiving concomitant atazanavir + ritonavir (ATV + RTV), lopinavir + ritonavir (LPV + RTV) or darunavir + ritonavir (DRV + RTV)		
Emtricitabine	Due to similarities, lamivudine as in **NUVACO** should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, lamivudine as in **NUVACO** should not be taken with any other medicinal products containing lamivudine.		
Cladribine	*In vitro,* lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended.		
Ranitidine or cimetidine	Do not interact with lamivudine. No dosage adjustments necessary.		
Products containing sorbitol or osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol).	Studies conducted demonstrated that co-administration of sorbitol solution (3,2 g, 10,2 g, 13,4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14 %, 32 %, and 36 % in lamivudine exposure (AUC_{∞}) and 28 %, 52 %, and 55 % in the C_{max} of lamivudine in adults. Where possible, avoid chronic co-administration of lamivudine, as in **NUVACO**, with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol,		

Co-administered medicine	Dose of co-administered medicine	Change of co-administered medicine pharmacokinetic parameters
	maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.	

Abbreviations: ↑ = increase; ↓ = decrease; ↔ = no effect

The possibility of interactions with other medicines administered concurrently should be considered, particularly when the main route is renal.

Tenofovir disoproxil fumarate

No medicine interaction studies have been conducted using **NUVACO**. As **NUVACO** contains tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with these individual medicines may occur with **NUVACO**. Important medicine interaction information for **NUVACO** is summarised in Tables 2, 3, 4 and 5.

The medicine interactions described are based on studies conducted with tenofovir disoproxil fumarate or lamivudine as individual medicines or are potential medicine interactions. While the tables include potentially significant interactions, they are not all inclusive. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir disoproxil fumarate, the potential for CYP450 mediated interactions involving tenofovir with other medicines is low. An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with the lamivudine/zidovudine combination in patients with renal impairment should be carefully assessed.

Renally eliminated medicines:

Tenofovir disoproxil fumarate is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of tenofovir disoproxil fumarate with medicines that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir disoproxil fumarate or the co-administered medicines, due to competition for this elimination pathway. Medicines that decrease renal function may also increase serum concentrations of tenofovir disoproxil fumarate, as in **NUVACO**.

Tenofovir disoproxil fumarate has been evaluated in healthy volunteers in combination with abacavir, adefovir dipivoxil, atazanavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, oral contraceptives and ribavirin. Tables 3 and 4 summarise pharmacokinetic effects of co-administered medicine on tenofovir disoproxil fumarate pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of co-administered medicine.

When administered with multiple doses of tenofovir disoproxil fumarate, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown.

When didanosine 250 mg enteric-coated capsules were administered with tenofovir, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Table 2: Medicine interactions: Changes in pharmacokinetic parameters for tenofovir[1] in the presence of co-administered medicines:

Co-administered medicine	Dose of co-administered medicine (mg)	N	% Changes of tenofovir pharmacokinetic parameters[2] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↔	↔	NC
Adefovir dipivoxil	10 once	22	↔	↔	↔
Atazanavir	400 once daily x 14 days	33	↑14 (↑8 to ↑20)	↑24 (↑21 to ↑28)	↑22 (↑15 to ↑30)
Didanosine (enteric-coated)	400 once	25	↔	↔	↔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	↔	↔	↔
Efavirenz	600 once daily x 14 days	29	↔	↔	↔
Emtricitabine	200 once daily x 7 days	17	↔	↔	↔
Indinavir	800 three times daily x 7 days	13	↑14 (↓ 3 to ↑33)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↔	↔	↔
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	↔	↑32 (↑25 to ↑38)	↑51 (↑37 to ↑66)
Nelfinavir	1 250 twice daily x 14 days	29	↔	↔	↔
Saquinavir/ Ritonavir	1 000/100 twice daily x 14 days	35	↔	↔	↑23 (↑16 to ↑30)

[1] Patients received tenofovir disoproxil fumarate 300 mg once daily

[2] Increase = ↑; Decrease = ↓; No effect = ↔; NC = Not calculated

Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy, oral contraceptives, or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating a lack of clinically significant medicine interactions between these medicines and tenofovir disoproxil fumarate.

Table 3: Medicine interactions: Changes in pharmacokinetic parameters for co-administered medicines in the presence of tenofovir disoproxil fumarate

Co-administered medicine	**Dose of co-administered medicine (mg)**	**N**	**%Change of co-administered medicine pharmacokinetic parameters [1] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑12 (↓1 to ↑26)	↔	NA
Adefovir dipivoxil	10 once	22	↔	↔	NA
Efavirenz	600 once daily x 14 days	30	↔	↔	↔
Emtricitabine	200 once daily x 7 days	17	↔	↔	↑20 (↑12 to ↑29)
Indinavir	800 three times daily x 7 days	12	↓11 (↓30 to ↑12)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↓24 (↓34 to ↓12	↔	↔
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	21	↔	↔	↔
Methadone[2]	40 – 110 once daily x 14 days[3]	13	↔	↔	↔
Oral contraceptives[4]	Ethinyl oestradiol/ norgestimate once daily x 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	NA
Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	↔	↔	↔

Atazanavir[5]	400 once daily x 14 days	34	↓21 (↓27 to ↓14)	↓25 (↓30 to ↓19)	↓40 (↓48 to ↓32)
Atazanavir[5]	Atazanavir/Ritonavir 300/100 once daily x 42 days	10	↓28 (↓50 to ↑5)	↓25 (↓42 to ↓3)	↓23[6] (↓46 to ↑10)
Saquinavir	Saquinavir/ Ritonavir 1 000/100 twice daily x 14 days	32	↑22 (↑6 to ↑41)	↑29[7] (↑12 to ↑48)	↑47[7] (↑23 to ↑76)
Ritonavir			↔	↔	↑23 (↑3 to ↑46)

1. Abbreviations: ↑ = increase; ↓ = decrease; ↔ = no effect; NA = Not applicable
2. *R*-(active), *S*-and total methadone exposures were equivalent when dosed alone or with tenofovir as tenofovir disoproxil fumarate 300 mg.
3. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms were reported).
4. Ethinyl oestradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir as tenofovir disoproxil fumarate 300 mg.
5. REYATAZ US Prescribing Information (Bristol-Myers Squibb).
6. In HIV-infected patients, addition of tenofovir disoproxil fumarate to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2,3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
7. Increase in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir disoproxil fumarate and ritonavir-boosted saquinavir are co-administered.

Dolutegravir:
Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given to patients taking **NUVACO**.

There is evidence that the concentration of isoniazid is increased by dolutegravir as contained in **NUVACO**.

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

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

Effect of NUVACO on the pharmacokinetics of other medicines:
In vitro, **NUVACO** demonstrated no direct, or weak inhibition (IC_{50} > 50 µM) of the cytochrome P450 enzymes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase UGT1A1 or UGT2B7, or the transporters Pgp, BCRP, OATP1B1, OATP1B3, OCT1 or MRP2. *In vitro*, dolutegravir as in **NUVACO** did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir as in **NUVACO** did not have an effect on midazolam, a CYP3A4 probe.

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

Dolutegravir, as in **NUVACO**, did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir disoproxil fumarate, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinylestradiol.

In vitro, dolutegravir as in **NUVACO** inhibited the renal organic cation transporter 2 (OCT2). Based on this observation, dolutegravir as in **NUVACO** may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin) (see Table 5).

Effect of other medicines on the pharmacokinetics of NUVACO
Dolutegravir, as in **NUVACO**, is eliminated mainly through metabolism by UGT1A1. Dolutegravir as in **NUVACO**, is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp and BCRP; therefore, medicines that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir (see Table 5).

Co-administration of dolutegravir, as in **NUVACO** and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration.

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and require dolutegravir dose adjustment to 50 mg twice daily.

Etravirine also reduced plasma concentrations, but the effect of etravirine was mitigated by co-administration of CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir.

Therefore, no dolutegravir as in **NUVACO** dose adjustment is necessary when co-administered with etravirine and either lopinavir/ritonavir, darunavir/ritonavir, or

atazanavir/ritonavir. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment of dolutegravir as in **NUVACO**. Caution is warranted, and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see Table 5: Medicine Interactions – HIV-1 Antiviral medicines). A medicine interaction study with the UGT1A inhibitor, atazanavir, did not result in clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir disoproxil fumarate, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin and omeprazole had no or minimal effect on dolutegravir pharmacokinetics, therefore no dolutegravir as in **NUVACO** dose adjustment is required when co-administered with these medicines.

Table 4: Medicine interactions

Concomitant medicine class: Medicine name	**Effect on concentration of NUVACO or concomitant medicine**	**Clinical comment**
HIV-1 Antiviral medicines		
Non-nucleoside reverse transcriptase inhibitors		
Etravirine (ETR)	Dolutegravir ↓ AUC ↓ 71 % C_{max} ↓ 52 % C_T ↓ 88 % ETR ↔	Etravirine decreased dolutegravir plasma concentration, which may result in loss of virologic response and possible resistance to dolutegravir. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ ritonavir, darunavir/ritonavir or lopinavir/ritonavir.
Efavirenz (EFV)	Dolutegravir ↓ AUC ↓ 57 % C_{max} ↓ 39 % C_T ↓ 75 % EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients.
Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. Alternative combinations that do not include nevirapine

		should be used where possible in INI-resistant patients.
Protease inhibitors		
Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 49 % C_T ↑ 180 % ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 33 % C_T ↑ 121 % ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % C_T ↓ 76 % TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients.
Fosamprenavir / ritonavir (FPV + RTV)	Dolutegravir ↓ AUC ↓ 35 % C_{max} ↓ 24 % C_T ↓ 49 % FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients. Alternative combinations that do not include Fosamprenavir/ritonavir should be used where possible in INI resistant patients.
Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.

Lopinavir/ritonavir (LPV + RTV)	Dolutegravir ↔ AUC ↔ C_{max} ↔ C_{τ} ↔ LPV ↔ RTV ↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Darunavir/ritonavir (DRV + RTV)	Dolutegravir ↓ AUC ↓ 32 % C_{max} ↓ 11 % C_{τ} ↓ 38 % DPV ↔ RTV ↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

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

Dofetilide Pilsicainide	Dofetilide Pilsicainide	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or pilsicainide co-administration with **NUVACO** is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Oxcarbazepine Phenytoin Phenobarbitone Carbamazepine St John's wort	Dolutegravir ↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.
Antacids containing polyvalent cations (e.g. Mg, Al or Ca)	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % C_{24} ↓ 74 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. **NUVACO** is recommended to be administered 2 hours before or 6 hours after taking antacids containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C_{24} ↓ 39 %	**NUVACO** is recommended to be administered 2 hours before or 6 hours after taking products containing calcium, or alternatively, administered with food.
Iron supplements	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 57 % C_{24} ↓ 56 %	**NUVACO** is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administered with food.
Metformin	Metformin ↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contraindicated in patients taking **NUVACO** (see section 4.3).
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % C_{T} ↓ 72 %	Rifampicin decreased dolutegravir plasma concentration. Alternatives to rifampicin should be used where possible for INI-resistant patients.

Oral contraceptives (ethinylestradiol (EE) and norgestromin (NGMN)	Effect of dolutegravir: EE ↔ AUC ↑ 3 % Cmax ↓ 1 % C_T ↑ 2 % Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % Cmax ↓ 11 % C_T ↓ 7 %	Dolutegravir did not change ethinylestradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with **NUVACO**.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % C_T ↓ 1 %	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with **NUVACO**.

Abbreviations: ↑ = increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration; C_T = concentration at the end of dosing interval

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

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

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

Pregnancy

Use of dolutegravir during pregnancy was associated with a small increase in the prevalence of neural tube defects (0,19 %) compared to non-dolutegravir regimens (0,11 %). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

If a pregnancy is confirmed in the first trimester while on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed

with the patient, taking the gestational age and the critical time period of neural tube defect development into account.

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

Breastfeeding
HIV infected women should not breast-feed their infants in order to avoid transmission of HIV or follow appropriate guidelines.

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

Fertility
There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility.

4.7 Effects on ability to drive and use machines
NUVACO may affect the ability to drive a vehicle and use machines (see section 4.8). Patients should ensure that they do not engage in driving or using machines until they know how **NUVACO** affects them.

4.8 Undesirable effects
NUVACO can have side effects.

The following side effects have been reported during therapy for HIV disease with **NUVACO** film-coated tablets alone and in combination with other antiretrovirals.

Lamivudine:

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	*Less frequent*	Neutropenia, anaemia, thrombocytopenia, pure red cell aplasia.
Immune system disorders	*Less frequent*	Immune reconstitution inflammatory syndrome, angioedema.
Metabolism and nutrition disorders	*Frequent*	Hyperlactataemia.
	Less frequent	Lactic acidosis (see section 4.4), lipodystrophy (redistribution/accumulation of body fat) (see section 4.4), including central obesity, dorsocervical fat enlargement (buffalo hump),

		peripheral wasting, cushingoid appearance, hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, hyperlipasaemia.
Psychiatric disorders	*Less frequent*	Abnormal behaviour.
Nervous system disorders	*Frequent*	Headache, insomnia.
	Less frequent	Paraesthesia, peripheral neuropathy (although a causal relationship to treatment is uncertain), convulsions, late onset neurological disorders in children exposed *in utero*.
Respiratory, thoracic and mediastinal disorders	*Frequent*	Cough, nasal symptoms.
Gastrointestinal disorders	*Frequent*	Upper abdominal pain or cramps, nausea, vomiting, diarrhoea.
	Less frequent	Pancreatitis (although a causal relationship to treatment is uncertain), increased serum amylase.
Hepato-biliary disorders	*Less frequent*	Transient increased liver enzymes (AST, ALT), hepatitis.
Skin and subcutaneous tissue disorders	*Frequent*	Alopecia, rash.
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Arthralgia, muscle disorders, musculoskeletal pain.
	Less frequent	Rhabdomyolysis, decrease in bone mineral density, osteopenia, fractures, hypertonia, myalgia, myositis, osteonecrosis.
Reproductive system and breast disorders	*Less frequent*	Breast enlargement.
General disorders and administration site conditions	*Frequent*	Fatigue, fever, malaise.
Investigations	*Less frequent*	Increased serum amylase, increased creatine phosphokinase, increased blood lipids and glucose.

Tenofovir disoproxil fumarate

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	*Less frequent*	Neutropenia, anaemia.
Immune system disorders	*Less frequent*	Allergic reaction including angioedema, immune reconstitution inflammatory syndrome.

Metabolism and nutrition disorders	*Less frequent*	Accumulation or redistribution of fat (lipodystrophy), including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, cushingoid appearance, hypercholesterolaemia, hyperlactataemia, lactic acidosis, anorexia, hypophosphatemia, hypokalaemia.
Psychiatric disorders	*Less frequent*	Abnormal behaviour.
Nervous system disorders	*Frequent*	Headache, dizziness.
	Less frequent	Convulsions.
Respiratory, thoracic and mediastinal disorders	*Frequency unknown*	Dyspnoea, pneumonia.
Gastrointestinal disorders	*Frequent*	Abdominal pain, anorexia, distention, nausea, vomiting, diarrhoea, dyspepsia, flatulence.
	Less frequent	Increased amylase, pancreatitis.
Hepato-biliary disorders	*Less frequent*	Hepatomegaly, steatosis, increased liver enzymes (AST, ALT, gamma-GT) hepatitis.
Skin and subcutaneous tissue disorders	*Less frequent*	Skin rash.
Musculoskeletal, connective tissue and bone disorders	*Less frequent*	Bone pain, osteomalacia, fractures, muscle weakness, myopathy, hypertonia, osteonecrosis.
	Frequency unknown	Muscle disorders (including rhabdomyolysis).
Renal and urinary disorders	*Frequent*	Renal insufficiency, renal failure, proximal renal tubulopathy (including Fanconi syndrome), proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus.
	Less frequent	Nephritis.
Reproductive system and breast disorders	*Less frequent*	Breast enlargement.
General disorders and administration site conditions	*Frequent*	Fatigue, asthenia.
Investigations	*Less frequent*	Increased liver enzymes, increased serum amylase, grade 3 and 4 laboratory abnormalities (in total cholesterol, triglycerides, creatine kinase, haematuria, neutrophil, urine glucose and serum glucose).

Dolutegravir

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	*Less frequent*	Thrombocytopenia, neutropenia.
Immune system disorders	*Less frequent*	Hypersensitivity, immune reconstitution inflammatory syndrome (see section 4.4)
Psychiatric disorders	*Frequent*	Insomnia.
	Less frequent	Anxiety, depression, paranoia, suicidal ideation.
Nervous system disorders	*Frequent*	Headache, dizziness, abnormal dreams.
Ear and labyrinth disorders	*Frequent*	Vertigo.
Gastrointestinal disorders	*Frequent*	Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain.
	Less frequent	Abdominal pain, abdominal discomfort, gastritis.
Hepato-biliary disorders	*Less frequent*	Hepatitis.
Skin and subcutaneous tissue disorders	*Frequent*	Rash, pruritus.
	Less frequent	Stevens-Johnson syndrome, toxic epidermal necrolysis.
Musculoskeletal, connective tissue and bone disorders	*Less frequent*	Myopathy, rhabdomyolysis, arthralgia, myalgia.
Renal and urinary disorders	*Less frequent*	Renal failure, abnormal creatine phosphokinase values.
Pregnancy, puerperium and perinatal conditions	*Frequency unknown*	Neural tube defects, late onset neurological disorders including seizures (see section 4.6).
General disorders and administration site conditions	*Frequent*	Fatigue.

Investigations	*Less frequent*	Increased liver transaminases, increased serum triglyceride concentrations.
	Frequency unknown	Changes in laboratory chemistries as reported in clinical studies: Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 48 weeks. In treatment-naive patients a mean change from baseline of 9,96 µmol/L (range: 53 µmol/L to 54,8 µmol/L) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced patients. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (see section 5.2*, Effects on Renal Function*).

Small increases in total bilirubin (without clinical jaundice) were observed on dolutegravir and raltegravir (but not efavirenz) arms in the programme. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway 9UGT1A1) (see section 5.2).

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
Lamivudine:
Limited data are available on the consequences of ingestion of acute overdoses in humans.

If overdosage occurs, the patient should be monitored, and palliative supportive treatment applied as required.

Tenofovir disoproxil fumarate:
If overdose occurs, the patient must be monitored for evidence of toxicity and palliative supportive treatment be applied as necessary.

Tenofovir disoproxil fumarate can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/min. The elimination of tenofovir disoproxil fumarate by peritoneal dialysis has not been studied.

Dolutegravir:
Management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific treatment for an overdose of **NUVACO**. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As **NUVACO** is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 20.2.8 Antimicrobial (chemotherapeutic) agents. Antiviral agents.
Antivirals for treatment of HIV infections, combinations ATC code: J05AR27

NUVACO is an HIV-1 antiretroviral fixed-dose combination product containing lamivudine, tenofovir disoproxil fumarate and dolutegravir.

Lamivudine:
Lamivudine, a nucleoside reverse transcriptase inhibitor (NRTI), is a selective inhibitor of HIV-1 and HIV-2 replication *in vitro*.

Lamivudine is metabolised intracellularly to the 5'-triphosphate which has an intracellular half-life of 16 – 19 hours.

Lamivudine 5'-triphosphate is a weak inhibitor of the RNA and DNA dependent activities of HIV reverse transcriptase, its mode of action is a chain terminator of HIV reverse transcription.

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received lamivudine therapy.

Lamivudine-resistant HIV-1 mutants are cross-resistant to didanosine and zalcitabine. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

Tenofovir disoproxil fumarate:
Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate and is converted in vivo to tenofovir. It is a nucleoside reverse transcriptase inhibitor.

Tenofovir is phosphorylated by cellular enzymes to form tenofovir diphosphate.

Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase, by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation in DNA, by chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase ɣ.

Resistance:
HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro* and a K65R mutation in reverse transcriptase have been selected *in vitro* and, in some patients, treated with tenofovir in combination with certain antiretroviral medicines.

In treatment-naïve patients treated with tenofovir + lamivudine + efavirenz, viral isolates from 17 % patients with virologic failure showed reduced susceptibility to tenofovir.

In treatment-experienced patients, some of the tenofovir-treated patients with virologic failure through week 96 showed reduced susceptibility to tenofovir.

Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 reverse transcriptase gene resulting in the K65R amino acid substitution.

Cross-resistance:
Cross-resistance among certain reverse transcriptase inhibitors has been recognised. The K65R mutation can also be selected by abacavir, didanosine or zalcitabine and results in reduced susceptibility to these medicines plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil fumarate should be avoided in antiretroviral experienced patients with strains harbouring the K65R mutation. Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil fumarate.

Antiviral activity:
The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 has been assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50 % inhibitory concentration) values for tenofovir were in the range of 0,04 µM to 8,5 µM. In medicine combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed.

Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G, and O (IC_{50} values ranged from 0,5 µM to 2,2 µM). The IC_{50} values of tenofovir against HIV-2 ranged from 1,6 µM to 4,9 µM.

Dolutegravir:
Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration, which is essential for the HIV replication cycle. *In vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex ($t_{½}$ 71 hours).

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

Anti-HIV activity against resistant strains: Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent potency against 2 non-nucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant and 2 PI-resistant HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wild-type strain.

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

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

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

5.2 Pharmacokinetic properties
Lamivudine:
Absorption and bioavailability:
Lamivudine is absorbed following oral administration. Bioavailability is between 80 – 85 % and is not affected by food. Following oral administration, the mean time (T_{max}) to maximum serum concentration (C_{max}) is approximately an hour. At therapeutic dose levels, i.e. 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1 – 1,5 µg/ml.

Distribution:
Intravenous studies with lamivudine showed that the mean apparent volume of distribution is 1,3 L/kg.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin.

Biotransformation and elimination:
The mean terminal half-life of elimination is 5 to 7 hours. Lamivudine elimination will be affected by renal impairment, whether it is disease- or age-related. The mean systemic clearance of lamivudine is approximately 0,32 L/kg/h, with predominantly renal clearance (> 70 %), via active tubular secretion, but little (< 10 %) hepatic metabolism. No dosage adjustment is needed when co-administered with food, as lamivudine bioavailability is not altered, although a delay in T_{max} and reduction in C_{max} have been observed.

Special populations:
Renal impairment: Dose reduction is recommended for patients with creatinine clearance ≤ 80 ml/min.

Tenofovir disoproxil fumarate:
Absorption:
Following oral administration of tenofovir disoproxil fumarate in HIV1- infected patients, tenofovir disoproxil fumarate is absorbed and converted to tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients is approximately 25 %. Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40 % and C_{max} by approximately 14 %. Food delays the time to tenofovir C_{max} by approximately 1 hour.

Distribution:
In vitro binding of tenofovir to human plasma or serum proteins is < 0,7 % and 7,2 %, respectively, over the tenofovir concentration range 0,01 to 25 µg/ml.

Elimination:
Following single dose, oral administration of tenofovir disoproxil fumarate, the reported terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir disoproxil fumarate 300 mg once daily (under fed conditions), 32 % ± 10 % of the administered dose is recovered in urine over 24 hours. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Age and gender:
Tenofovir pharmacokinetics are similar in male and female patients. Pharmacokinetic studies have not been performed in children (< 18 years) or in the elderly (over 65 years).

Special populations:
Paediatrics and the elderly:
Pharmacokinetic studies have not been performed in children (< 18 years) or in the elderly (> 65 years).

Hepatic impairment:
Tenofovir pharmacokinetics after a 300 mg single dose have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. Change in tenofovir dosing is not required in patients with hepatic impairment.

Renal impairment:
Tenofovir pharmacokinetics are altered in patients with renal impairment. In patients with creatinine clearance < 50 ml/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max} and $AUC_{0-\infty}$ of tenofovir were increased.

It is recommended that the dosing interval for tenofovir be modified in patients with creatinine clearance < 50 ml/min or in patients with ESRD who require dialysis (see section 4.2). Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir, a four-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

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

Dolutegravir may be administered with or without food.

Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 34 %, 41 % and 66 %, increased C_{max} by 46 %, 52 % and 67 %, prolonged T_{max} to 3, 4 and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant.

The absolute bioavailability of dolutegravir has not been established.

Distribution:
Dolutegravir is highly bound (> 99 %) to human plasma proteins based on *in vitro* data. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F)

is estimated at 12,5 L. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma medicine-related radioactivity concentration ratios averaged between 0,441 – 0,535; indicating minimal association of radioactivity with blood cellular components. It is reported that free fraction of dolutegravir in plasma is estimated at approximately 0,2 to 1,1 % in healthy patients, approximately 0,4 to 0,5 % in patients with moderate hepatic impairment, and 0,8 to 1, 0 % in patients with severe renal impairment and 0,5 % in HIV-1 infected patients.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve patients on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/ml (comparable to unbound plasma concentration, and above the IC_{50}); CSF plasma concentration ratio of dolutegravir ranged from 0,11 to 0,66 %. Dolutegravir concentrations in CSF exceeded the IC_{50}, supporting the median reduction from baseline in CSF HIV-1 RNA of 2,1 log after 2 weeks of therapy.

Biotransformation:
Dolutegravir is primarily metabolised via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance is low (< 1 % of the dose). 53 % of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. 32 % of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18,9 % of total dose), *N*-dealkylation metabolite (3,6 % of total dose), and a metabolite formed by oxidation at the benzylic carbon (3,0 % of total dose).

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

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

Table 5: Adolescent pharmacokinetic parameters

Age/weight	**Dolutegravir dose**	**Dolutegravir pharmacokinetic parameter estimates Geometric mean (CV %)**		
		$AUC_{(0-24)}$ µg.hr/ml	C_{max} µg/ml	C_{24} µg/ml

12 to 18 years ≥ 40 kg [a]	50 mg once daily [a]	46 (43)	3,49 (38)	0,90 (59)

[a] one patient weighing 37 kg received 35 mg once daily.

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

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

Effects on renal function:
The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated. A small decrease of 10 – 14 % in mean serum creatinine clearance (CrCl) was observed with dolutegravir within the first week of treatment. Dolutegravir had no significant effect on glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). *In vitro* studies suggest that the increases in creatinine observed in clinical studies are due to the non-pathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

Hepatic impairment:
Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh category B score 7 to 9) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. No dosage adjustment is considered necessary for patients with mild hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

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

In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32 % lower clearance of dolutegravir and 46 % higher AUC compared with subjects with

genotypes associated with normal metabolism via UGT1A1 (n = 41). Polymorphisms in CYP3A4, CYP3A5 and NR1I2 were not associated with differences in the pharmacokinetics of dolutegravir.

Co-infection with Hepatitis B or C:
Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited data on patients with hepatitis B co-infection.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Croscarmellose sodium
Hydroxypropyl cellulose
Magnesium stearate
Mannitol
Microcrystalline cellulose
Povidone
Sodium starch glycolate
Sodium stearyl fumarate

Film coating:
Iron oxide red (E172)
Iron oxide yellow (E172)
Macrogol/polyethylene glycol (E1521)
Polyvinyl alcohol (E1203)
Talc (E553b)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.
Keep the container tightly closed.
Keep in the original container until required for use.
Protect from light and moisture.

6.5 Nature and contents of the container

Pack sizes 28, 30, 56, 60, 84, 90, 100, 180 and 750 film-coated tablets:

NUVACO tablets are packed in a white opaque high density polyethylene (HDPE) container with a cotton or rayon coil wadding and a desiccant canister containing silica gel. The HDPE container is closed with a white polypropylene, child-resistant cap with heat seal induction liner or pulp liner. Pack size of 30's is packed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special precautions

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK (232625)

8. REGISTRATION NUMBER(S)
52/20.2.8/0949

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10 October 2018

10. DATE OF REVISION OF TEXT
10 February 2022

This product has been produced under a license from the Medicines Patent Pool. Any other use is not authorised.

adcock ingram

PI 2073506 04/2023 &
31313 06/2022