Pharmacode position may change as per Supplier's m/c requirement & additional small pharma code may appear on the front / back panel

**APPROVED**
By Telanie Venter at 10:06 am, Jul 29, 2020

**APPROVED**
By Corinda Gaigher at 1:49 pm, Jul 28, 2020

**NOVAGEN** PHARM

**PROFESSIONAL INFORMATION**

**SCHEDULING STATUS**
S4

**1. NAME OF THE MEDICINE**
NOVALUTE (50 mg, film-coated tablet)

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir.
Each 50 mg tablet contains 4 mg sodium and 145.4 mg mannitol.
For full list of excipients, see section 6.1

**3. PHARMACEUTICAL FORM**
Film-coated tablets
NOVALUTE:
Reddish brown coloured, round, biconvex, film-coated tablets debossed with "T over 50" on one side and plain on the other side.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**
NOVALUTE is indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral medicines in adults aged 18 years and older.

**4.2 Posology and method of administration**
NOVALUTE therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

**Posology**

***Adults***
*Treatment-naïve:*
For patients initiating antiretroviral therapy for the first time (treatment-naïve) the recommended dose of NOVALUTE is 50 mg once daily.

*Treatment-experienced, and integrase inhibitor naïve:*
For patients who are treatment-experienced and have not previously been treated with an integrase inhibitor, the recommended dose of NOVALUTE is 50 mg once daily.

*Integrase inhibitor resistant:*
For patients with integrase inhibitor resistance, the recommended dose of NOVALUTE is 50 mg twice daily.

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be administered to patients taking rifampicin.

There is evidence that the concentration of isoniazid is increased by dolutegravir, as contained in NOVALUTE.

***Elderly***
There are limited data available on the use of NOVALUTE in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2 – Special Patient Populations).

***Renal impairment***
No dosage adjustment is required in patients with mild, moderate or severe (CrCl < 30 ml/min, not on dialysis) renal impairment. No data are available in subjects receiving dialysis, although differences in pharmacokinetics are not expected in this population.
Treatment with NOVALUTE resulted in an early small increase of mean serum creatinine levels by 10 - 14 % which remained stable over time and is not considered a renal clinically relevant (see section 4.8 – clinically relevant adverse reactions).

***Hepatic impairment***
No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh grade A or B). NOVALUTE is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

***Paediatric Population***
The safety and efficacy of NOVALUTE in children under the age of 18 years has not been established.

**Method of administration**
Oral use.
NOVALUTE can be taken with or without food.
In the presence of integrase class resistance, NOVALUTE should preferably be taken with food to enhance exposure (particularly in patients with G140 mutations) (see section 5.2 - Absorption)

**4.3 Contraindications**
NOVALUTE is contraindicated in:
- patients with known hypersensitivity to dolutegravir or to any of the excipients
- combination with dofetilide and pilsicainide (see section 4.5)
- patients with moderate and severe hepatic impairment (see section 4.4)
- women planning to become pregnant, are pregnant or breastfeeding their babies
- women of childbearing age not on effective contraception.

Metformin is contraindicated in patients taking NOVALUTE.

**4.4 Special warnings and precautions for use**

***Integrase class resistance of particular concern:***
The decision to use NOVALUTE in the presence of integrase class resistance should take into account that the activity of dolutegravir is considerably compromised for viral strains harbouring Q148/H/K/R substitutions from G140A/C/S, E138A/K/T, L74I. To what extent dolutegravir should provide added efficacy in the presence of such integrase class resistance is uncertain.

***Hypersensitivity reactions:***
Hypersensitivity reactions have been reported with NOVALUTE and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury. NOVALUTE and other suspect medicinal products should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia and angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored and appropriate therapy initiated. Delay in stopping treatment with NOVALUTE or other suspect active substances after the onset of hypersensitivity may result in a life-threatening reaction.

***Lipodystrophy and metabolic abnormalities:***
Combination antiretroviral therapy has 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. During combination antiretroviral treatment a redistribution of body fat may be evident in patients with lipodystrophy should have a thorough cardiovascular risk assessment.

***Immune Reconstitution Inflammatory Syndrome:***
In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause more severe clinical conditions or aggravation of symptoms.
Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are tuberculosis, cytomegalovirus retinitis, generalised and/or focal atypical mycobacterial infections and *Pneumocystis jiroveci (P. carinii)* pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.
Auto-immune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable and can occur many months after initiation of treatment and sometimes can be an atypical presentation.
Any inflammatory symptoms in patients with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of NOVALUTE therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. Particular attention should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients (see section 4.8 – Description of selected adverse reactions).

***Osteonecrosis:***
Although the aetiology is considered to be multifactorial (including corticosteroid use, hypophosphaemia, 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). 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 NOVALUTE should be advised that NOVALUTE or any other antiretroviral therapy does not cure HIV infection and that they may continue to develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close medical supervision by healthcare professionals experienced in the treatment of these associated HIV diseases. Regular monitoring of viral load and CD4 count needs to be done.

***The risk of HIV transmission to others:***
Patients should be advised that current antiretroviral therapy, including NOVALUTE, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

***Hepatic impairment:***
The unbound fraction of NOVALUTE in the blood is doubled in patients with moderate hepatic impairment. NOVALUTE is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

***Interactions:***
Caution should be given to co-administering medications (prescription and non-prescription) that may change the exposure of NOVALUTE or of medications that may have their exposure changed by NOVALUTE (see section 4.3 and section 4.5).
The combination of NOVALUTE with etravirine (TEE) is not recommended unless the patient is also receiving concomitant atazanavir + ritonavir (ATV + RTV), lopinavir + ritonavir (LPV + RTV) or darunavir + ritonavir (DRV + RTV) (see section 4.5).
The recommended dose of NOVALUTE is 50 mg twice daily when co-administered with atazanavir, nevirapine, lopinavir/ritonavir, or rifampicin (see section 4.5).
NOVALUTE should not be co-administered with polyvalent cation-containing products. NOVALUTE is recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.5).
Metformin concentrations may be increased by NOVALUTE. Metformin is contra-indicated in patients taking NOVALUTE (see section 4.3).

***Co-Infection with Hepatitis B or C:***
In these HIV studies, patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of NOVALUTE therapy, particularly in those whose anti-hepatitis B therapy was withdrawn.

***Effect of NOVALUTE on the Pharmacokinetics of other medicines:***
In vitro, NOVALUTE demonstrated no direct, or weak inhibition (IC50 > 50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, unless dipho sphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT1 or MRP2. In vitro, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, NOVALUTE 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, acute 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, ritoglipton, adefovir).

No clinically relevant effect has been reported with NOVALUTE on the pharmacokinetics of the following: tenofovir, metformin, etravirene, lopinavir, atazanavir, darunavir, ritonavir, lopinavir/ritonavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinyl estradiol.

*In vitro*, NOVALUTE inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) 1. *In vivo*, a 10 – 14 % decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients. *In vivo*, dolutegravir did not may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 or MATE-1 (e.g. dofetilide, metformin) (see Table 1 and section 4.3).
*In vitro*, NOVALUTE inhibited the renal uptake transporters, organic anion transporters (OAT1) and OAT3. Based on the lack of clinical effects in the *vivo* pharmacokinetics of the OAT substrate tenofovir, *in vivo* inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been studied *in vivo*. NOVALUTE may increase plasma concentrations of medicines in which excretion is dependent upon OAT3.

***Effect of other medicines on the pharmacokinetics of NOVALUTE:***
All factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance.
NOVALUTE is eliminated mainly through metabolism by UGT1A1. NOVALUTE is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore, medicines that induce those enzymes may decrease NOVALUTE plasma concentration and reduce the therapeutic effect of NOVALUTE. Co-administration of NOVALUTE and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase NOVALUTE plasma concentration (see Table 1).

Efavirenz, etravirine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of NOVALUTE significantly and require NOVALUTE dose adjustment to 50 mg twice daily. Etravirine also reduced plasma concentrations, but the effect of etravirine was mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir. Therefore, no NOVALUTE dose adjustment is necessary when co-administered with etravirine and either Lopinavir/ritonavir, darunavir/ritonavir, or atazanavir/ritonavir. Etravirine in combination with lopinavir/ritonavir or darunavir/ritonavir is not recommended for use in combination with NOVALUTE (see section 4.5 – Interactions of NOVALUTE. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see Table 1 Medicine Interactions - HIV-1 Antiviral Medicines). The UGT1A1 inhibitor, atazanavir, was not shown to increase the plasma concentrations of NOVALUTE significantly. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, pristinamycin, efavirenz, rifabutin, and rifampicin had no or a minimal effect on dolutegravir pharmacokinetics, therefore no NOVALUTE dose adjustment is required when co-administered with these medicines.

The absorption of NOVALUTE is reduced by certain anti-acid medicines (see Table 1).

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicines are listed in Table 1.

***Table 1: Interaction table***
Interactions between NOVALUTE and co-administered medicinal products are listed in Table 1 (increase is indicated as ↑, decrease as ↓, no change as ↔, area under the concentration versus time curve as AUC, maximum observed concentration as $C_{max}$, concentration at end of dosing interval as $C_{τ}$).

| Concomitant Medicine Class: Medicine Name | Effect on Concentration of NOVALUTE or Concomitant Medicine | Clinical Comment |
|---|---|---|
| ***HIV-1 Antiviral Medicines*** | | |
| ***Non-nucleoside Reverse Transcriptase Inhibitors:*** | | |
| Etravirine (ETR) without boosted protease inhibitors | $C_{min}$ ↓ 52 %<br>$C_{τ}$ ↓ 86 %<br>ETR ↔ | Etravirine without boosted protease inhibitors decreased dolutegravir plasma concentration, which may result in loss of virologic response and possible resistance to dolutegravir. NOVALUTE should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir (see further below in table). |
| Lopinavir/ritonavir + etravirine | Dolutegravir ↔<br>AUC ↑ 11%<br>$C_{max}$ ↑ 7%<br>$C_{τ}$ ↑ 28%<br>LPV ↔<br>RTV ↔<br>ETR ↔ | No dose adjustment is necessary. |
| Darunavir/ritonavir + etravirine | Dolutegravir ↓<br>AUC ↓ 20%<br>$C_{max}$ ↓ 12%<br>$C_{τ}$ ↓ 38%<br>DRV ↔<br>RTV ↔ | No dose adjustment is necessary |
| Efavirenz (EFV) | Dolutegravir ↓<br>AUC ↓ 57 %<br>$C_{max}$ ↓ 39 % $C_{τ}$ ↓ 75 % EFV ↔ (historical controls)<br>(induction of UGT1A1 and CYP3A enzymes) | Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of NOVALUTE 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 ↓<br>(Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction) | The recommended dose of NOVALUTE 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. |
| Rilpivirine | Dolutegravir ↔<br>AUC ↑ 12 %<br>$C_{max}$ ↑ 13 %<br>$C_{τ}$ 22 %<br>Rilpivirine ↔ | No dose adjustment is necessary. |
| ***Nucleoside Reverse Transcriptase Inhibitors:*** | | |
| Tenofovir (TDV) | Dolutegravir ↔<br>AUC ↑ 1 %<br>$C_{max}$ ↓ 3 %<br>$C_{τ}$ ↑ 6 %<br>TDV ↔ | Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary. |
| Emtricitabine (FTC) | Dolutegravir ↔<br>AUC ↑ 5 %<br>$C_{max}$ ↓ 5 %<br>$C_{τ}$ ↔<br>FTC ↔ | Emtricitabine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary. |
| Lamivudine (3TC) | Dolutegravir ↔<br>AUC ↑ 3 %<br>$C_{max}$ ↓ 15 %<br>$C_{τ}$ ↔<br>3TC ↔ | Lamivudine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary. |
| Abacavir (ABV) | Dolutegravir ↑<br>AUC ↑ 91 %<br>$C_{max}$ ↑ 40 %<br>$C_{τ}$ ↔ (historical controls)<br>(inhibition of UGT1A1 and CYP3A enzymes) | Abacavir increased dolutegravir plasma concentration. No dose adjustment is necessary.<br>NOVALUTE should not be dosed higher than 50 mg twice daily in combination with atazanavir due to lack of data. |
| Atazanavir/ritonavir (ATV + RTV) | Dolutegravir ↑<br>AUC ↑ 62 %<br>$C_{max}$ ↑ 33 % $C_{τ}$ ↑ 121 %<br>ATV ↔<br>RTV ↔<br>(inhibition of UGT1A1 and CYP3A enzymes) | Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.<br>NOVALUTE should not be dosed higher than 50 mg twice daily in combination with atazanavir due to lack of data. |
| Tipranavir/ritonavir (TPV + RTV) | Dolutegravir ↓<br>AUC ↓ 59 %<br>$C_{max}$ ↓ 47 % $C_{τ}$ ↓ 76 %<br>TPV ↔<br>RTV ↔<br>(induction of UGT1A1 and CYP3A enzymes) | Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of NOVALUTE 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 ↓<br>AUC ↓ 35 %<br>$C_{τ}$ ↓ 24 % $C_{τ}$ ↓ 49 %<br>FPV ↔<br>RTV ↔<br>(induction of UGT1A1 and CYP3A enzymes) | 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) | DTG ↔<br>AUC ↔<br>$C_{max}$ ↔<br>$C_{τ}$ ↔<br>LPV ↔<br>RTV ↔ | Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary. |
| Darunavir/ritonavir (DRV/RTV) | Dolutegravir ↔<br>AUC ↑ 32 %<br>$C_{max}$ ↑ 11 % $C_{τ}$ ↓ 38 %<br>DRV ↔<br>RTV ↔<br>(induction of UGT1A1 and CYP3A enzymes) | Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary. |
| ***Other antiviral medicines*** | | |
| Bocepravir | Dolutegravir ↓<br>AUC ↓ 33 %<br>$C_{max}$ ↓ 18%<br>$C_{τ}$ ↓ 8%<br>Bocepravir ↔<br>(historical controls) | No dose adjustment is necessary. |
| Daclatasvir | Dolutegravir ↔<br>AUC ↑ 53%<br>$C_{max}$ ↑ 29%<br>$C_{τ}$ ↑ 45%<br>Daclatasvir ↔ | Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. NOVALUTE did not change daclatasvir plasma concentration. No dose adjustment is necessary. |
| ***Other Medicines*** | | |
| ***Antisyntrhymics*** | | |
| Dofetilide Pilsicainide | Dofetilide ↑<br>Pilsicainide ↑ | Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter, co-administration with NOVALUTE is contraindicated. If dolutegravir co-administration with NOVALUTE is considered to be clinically beneficial, life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3). |
| ***Anticonvulsants*** | | |
| Carbamazepine | Dolutegravir ↓<br>AUC ↓ 49 %<br>$C_{max}$ ↓ 33 %<br>$C_{τ}$ ↓ 75 % | The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. Alternatives to carbamazepine should be used where possible for INI resistant patients. |
| Oxcarbazepine<br>Phenytoin<br>Phenobarbitone | Dolutegravir ↓ | Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided. |
| ***Azole and anti-fungal medicines*** | | |
| Ketoconazole<br>Fluconazole<br>Itraconazole<br>Posaconazole<br>Voriconazole | Dolutegravir ↔<br>(Not studied) | No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected. |
| ***Antituberculosis*** | | |
| Rifampicin | Dolutegravir ↓<br>AUC ↓ 54 %<br>$C_{max}$ ↓ 43 %<br>$C_{τ}$ ↓ 72 %<br>(induction of UGT1A1 and CYP3A enzymes) | Rifampicin decreased dolutegravir plasma concentration. The recommended dose of NOVALUTE is 50 mg twice daily when co-administered with rifampicin. Alternatives to rifampicin should be used where possible for INI resistant patients. |
| Rifabutin | Dolutegravir ↔<br>AUC ↓ 16 %<br>$C_{max}$ ↓ 16 %<br>$C_{τ}$ ↓ 30 %<br>(induction of UGT1A1 and CYP3A enzymes) | No dose adjustment is necessary. |
| ***Oral contraceptives*** | | |
| Oral contraceptives (Ethinyl estradiol (EE) and Norgestiromin (NGMN)) | EE ↔<br>AUC ↑ 3 %<br>$C_{max}$ ↑ 5 %<br>$C_{τ}$ ↑ 2 %<br>NGMN ↔<br>AUC ↓ 2 %<br>$C_{max}$ ↓ 11 %<br>$C_{τ}$ ↓ 7 % | Dolutegravir did not change ethinyl estradiol and norgestiromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with NOVALUTE. |
| ***Analgesics*** | | |
| Methadone | Dolutegravir ↔<br>Methadone ↔<br>AUC ↓ 2 %<br>$C_{max}$ ↔<br>$C_{τ}$ ↓ 1 % | Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone or NOVALUTE are necessary when co-administered. |
| ***Antibiotics*** | | |
| Metformin | Metformin ↑ | Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contraindicated in patients taking NOVALUTE (see section 4.3) |
| ***Antimycobacterials*** | | |
| Rifampicin | Dolutegravir ↓<br>AUC ↓ 54 %<br>$C_{max}$ ↓ 43 %<br>$C_{τ}$ ↓ 72 %<br>(induction of UGT1A1 and CYP3A enzymes) | Rifampicin decreased dolutegravir plasma concentration. The recommended dose of NOVALUTE is 50 mg twice daily when co-administered with rifampicin. Alternatives to rifampicin should be used where possible for INI resistant patients. |
| Rifabutin | Dolutegravir ↔<br>AUC ↓ 16 %<br>$C_{max}$ ↓ 16 %<br>$C_{τ}$ ↓ 30 %<br>(induction of UGT1A1 and CYP3A enzymes) | No dose adjustment is necessary. |
| ***Oral contraceptives*** | | |
| Oral contraceptives (Ethinyl estradiol (EE) and Norgestiromin (NGMN)) | EE ↔<br>AUC ↑ 3 %<br>$C_{max}$ ↑ 5 %<br>$C_{τ}$ ↑ 2 %<br>NGMN ↔<br>AUC ↓ 2 %<br>$C_{max}$ ↓ 11 %<br>$C_{τ}$ ↓ 7 % | Dolutegravir did not change ethinyl estradiol and norgestiromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with NOVALUTE. |
| ***Analgesics*** | | |
| Methadone | Dolutegravir ↔<br>Methadone ↔<br>AUC ↓ 2 %<br>$C_{max}$ ↔<br>$C_{τ}$ ↓ 1 % | Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone or NOVALUTE are necessary when co-administered. |

**4.5 Overdose**
There is currently limited experience with overdosage in dolutegravir contained in NOVALUTE.
Limited experience of single higher doses (up to 250 mg in healthy subjects) revealed no specific symptoms or signs, apart from those listed as adverse reactions.
Management should be as clinically indicated or as recommended by the national poisons centre, where available.
There is no antidote for an overdose of NOVALUTE. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As NOVALUTE is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**
*A 20.2.8 Antiviral agents*
Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05AX12

***Mechanism of action***
*Dolutegravir* inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

***Pharmacodynamic effects***
*In vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex (t½ 71 hours).

***Resistance***
*Resistance in vitro:*
*Wild type HIV-1:* Viruses highly resistant to dolutegravir were not 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 in strain NL4-32. Additional passage of wild type subtype B, C, and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T.

*Antiviral Activity Against Resistant Strains:* Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: *Dolutegravir* demonstrated equivalent potency against 2 non-nucleoside (NNI)-RTI-resistant, 3 nucleoside (N)-RTI-resistant and 2 P-resistant HIV-1 mutant clones (1 triple and 1 setuple) 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 viruses with single substitutions including T66A/K, E92Q/V, T124Σ/H/R, Q148H/K/R, and N155H.

*Integrase Inhibitor-Resistant HIV-2 Strains:* Site directed mutant HIV-2 viruses were constructed based on subjects 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.

*Clinical isolates from Treatment Virologic Failure Subjects:* Seven hundred and five raltegravir resistant clinical isolates were analysed for susceptibility to dolutegravir using the Monogram Biosciences PhenoSense assay. Dolutegravir has a ≤ 10 FC against 93.9 % of the 705 clinical isolates.

*Resistance in vivo: integrase inhibitor naïve patients:*
No integrase inhibitor-resistance mutations or treatment-emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment-naïve studies. In a study for treatment-experienced (and integrase-naïve) patients, treatment-emergent integrase resistance was reported in 2 of 9 subjects with virologic failure. In both cases, a unique R263K integrase substitution was observed, with a maximum FC of 1.93.

*Resistance in vivo: integrase inhibitor resistant patients:*
Reports from a study evaluating dolutegravir (plus optimised background therapy) in subjects with pre-existing INI resistance showed that twenty-six subjects (26/114) experienced protocol defined virologic failure through to Week 24. Of these, 25 had paired baseline and PDVF resistance data for integrase. Twenty-three subjects developed dolutegravir resistance mutations. Treatment-emergent mutations or mixtures of mutations observed were E92Q, T97A, E138K/A, G140S, T143R/I, G148R/H/R, and N155H. Eleven of the 13 subjects with virus exhibiting treatment-emergent mutations harboured Q148 pathway virus present at baseline or historically.

***Effects on Renal Function***
Serum creatinine and 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-aminopurate (PAH) as the probe, a small decrease of 10 - 14 % in mean serum creatinine clearance (CrCl) was reported with dolutegravir within the first week of treatment. No significant effect on glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF) was observed. It was suggested that the increases in creatinine observed 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.

**5.2 Pharmacokinetic properties**
Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is between low to moderate. In healthy subjects, between-subject CVb % for AUC and $C_{max}$ ranged from ~20 to 46 % and Cr from 30 to 65 %. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw %) is lower than between-subject variability.

***Absorption:***
Dolutegravir is rapidly absorbed following oral administration, with median $T_{max}$ at 2 to 3 hours post dose for the tablet formulation. Following oral administration of the tablet formulation, 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.

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 AUC20 (+) by 33 %, 41 %, and 66 %, increased $C_{max}$ by 46 %, 52 % and 87 %, prolonged $T_{max}$ to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, NOVALUTE should preferably be taken with food to enhance exposure (see section 4.2).
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 (VdF) is 17 L to 20 L in HIV-1 infected subjects with pharmacokinetic data following oral administration. Dolutegravir distributes into cerebrospinal fluid (CSF) and the concentration in CSF was reported to be approximately 18 ng/ml (compatible to unbound plasma concentration, and above the IC50). CSF; plasma ratio was observed during a study of dolutegravir 50 mg (n=9) and 100 mg (n=9) administered once daily. Dolutegravir concentrations in CSF exceeded the IC50, supporting the median reduction from baseline in CSF HIV-1 RNA of 2.1 log after 2 weeks of therapy (see section 5.1).

Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue and vaginal tissue were 6 – 10 % of those in corresponding female genital steady state. AUC in rectum was 7 % and 17 % in rectal tissue of those in corresponding plasma at steady state.

***Biotransformation:***
Dolutegravir is primarily metabolised via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine is low (< 1 % of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed medicine or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two percent of the total oral dose is excreted in the urine, represented by either glucuronide of dolutegravir (18.9 % of total dose), N-dealkyl-metabolite (3.6 % of total dose) and a metabolite formed by oxidation at the benzylic carbon (3.0 % of total dose).

***Elimination:***
The terminal phase has a terminal half-life of ~14 hours.
The apparent oral clearance (CL/F) is approximately 1 L/hr in HIV-infected patients based on a population pharmacokinetic analysis.

***Special patient populations:***
*Adolescents:*
Pharmacokinetics of dolutegravir 50 mg once daily dosage in antiretroviral treatment-experienced HIV-1 infected adolescents (12 to < 18 years of age) is comparable to that observed in adults who received dolutegravir 50 mg once daily.
However, in treatment-naïve adolescents contained in NOVALUTE, is not recommended for use in patients under 18 years of age (see section 4.2).

**Table 3: Adolescent pharmacokinetic parameters**

| Age/weight | Dolutegravir Dose | Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (CV %) | | |
|---|---|---|---|---|
| | | AUC$_{(0-\tau)}$ µg·hr/ml | $C_{max}$ µg/ml | $C_{\tau}$ µg/ml |
| 12 to <18 years ≥ 40 kg* | 50 mg once daily * | 46 (43) | 3.49 (38) | 0.90 (59) |
| * One subject 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 subjects of > 65 years old are limited.

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

*Hepatic impairment:*
Dolutegravir is primarily metabolised and eliminated by the liver. In subjects with moderate hepatic impairment (Child-Pugh category B), a single 50 mg dose exposure of dolutegravir was similar to that observed in healthy adults. No dosage adjustment is 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 pharmacogenetic polymorphisms in metabolising enzymes after dolutegravir pharmacokinetics to a clinically meaningful extent. In healthy subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32 % lower clearance of dolutegravir and 46 % higher AUC of plasma concentration compared with genotypes associated with normal metabolism via UGT1A1. *Polymorphisms in CYP3A4, CYP3A5, and NR1I2* were not associated with differences in the pharmacokinetics of dolutegravir.

*In vitro* cell lines with Hepatitis *B or C:*
Hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited data on subjects with hepatitis B co-infection.

**5.3 Preclinical safety data**
Dolutegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Dolutegravir was not carcinogenic in the mouse or rat.
Dolutegravir did not affect male or female fertility in rats at doses up to 1 000 mg/kg/day, the highest dose tested (24 times the 50 mg twice daily human clinical exposure based on AUC).
Oral administration of dolutegravir to pregnant rats at doses up to 1 000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, embryotoxicity or teratogenicity (0.40 times the 50 mg twice daily human clinical exposure based on AUC).
Oral administration of dolutegravir to pregnant rats at doses up to 1 000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (0.40 times the 50 mg twice daily human clinical exposure based on AUC).
In rabbits, maternal toxicity (decreased food consumption, scant/ pale/ soft faeces curine, suppressed body weight gain) was observed at 1 000 mg/kg (0.40 times the 50 mg twice daily human clin

# NOVAGEN
FILMDEK

**PROFESSIONELE INLIGTING**

**SKEDULERINGSTATUS**

S4

**1. NAAM VAN DIE MEDISYNE**

NOVALUTE (50 mg, filmbedekte tablet)

**2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING**

Elke filmbedekte tablet bevat novelgemiddelde aspartaat aan 50 mg dolutegravir.
Elke 50 mg tablet bevat 4 mg natrium en 145,4 mg mannitol.
Vir 'n volledige lys van hulpstowwe, sien afdeling 6.1

**3. FARMASEUTIESE VORM**

Filmbedekte tablette
NOVALUTE
Rooibruin, ronde, bikonvekse, filmbedekte tablette, aan die een kant gedruk met 'T over 50', en gewoon aan die ander kant.

**4. KLINIESE BESONDERHEDE**

**4.1 Terapeutiese indikasies**

NOVALUTE is aangedui vir die behandeling van menslike immuniteitsgebreksvirus (MIV) infeksie in kombinasie met ander antiretrovirale middels by volwassenes van 18 jaar en ouer.

**4.2 Posologie en metode van toediening**

NOVALUTE-terapie moet deur 'n mediese praktisyn wat ervaring het met die hantering van MIV-infeksie.

*Posologie*

*Volwassenes*

*Behandelingsnaïewe:*
Vir pasiënte wat vir die eerste keer antiretrovirale terapie (behandelingsnaïewe) begin, is die aanbevole dosis NOVALUTE 50 mg een keer per dag.

*Behandelingservaren, en integrase-inhibeerder-naïewe:*
Vir pasiënte wat behandelingservaren is, en nog nie voorheen met 'n integrase-inhibeerder behandel is nie, is die aanbevole dosis NOVALUTE 50 mg een keer per dag.

*Integrase-inhibeerder-weerstandig:*
Vir pasiënte met weerstand teen integrase-inhibeerders, is die aanbevole dosis NOVALUTE 50 mg twee keer per dag.

Rifampisien verlaag die bioskiwiteit van dolutegravir. 'n Aanvullende dosis dolutegravir moet gegee word aan pasiënte wat rifampisien neem.

Daar is bewyse dat die konsentrasie isoniasied verhoog word deur dolutegravir, soos bevoel in Afdeling 5.2.

*Bejaardes*
Daar is beperkte inligting beskikbaar oor die gebruik van NOVALUTE by pasiënte van 65 jaar en ouer. Daar is geen bewyse dat ouer pasiënte 'n ander dosis benodig as jonger volwasse pasiënte nie (sien afdeling 5.2 - Spesiale Populasiegroepe).

*Renale inskrywing*
Geen dosisaanpassing is nodig by pasiënte met lighe, matige of ernstige (CrCl > 30 ml/min, nie op dialysis) renale inskrywing nie. Geen data is beskikbaar by persone wat dialise ontvang nie, hoewel verskille in farmakokinetika nie in hierdie populasie verwag word nie.
Behandeling met NOVALUTE het gelei tot 'n vinnier kleiner toenemende serumkreatiniewaardes van 10 - 14 % wat meltertyd stabiel gebly het en wat nie as kliniese relevant beskou word nie (sien afdeling 4.8 - Beskrywing van geselekteerde nevre-reaksies).

*Hepatiese inskrywing*
Geen dosisaanpassing is nodig by pasiënte met lighe hepatiese inskrywing (Child-Pugh graad A of B) nie. NOVALUTE is teenaangedui by pasiënte met matige of ernstige hepatiese inskrywing (sien afdeling 4.3).

*Pediatriese Populasie*
Die veiligheid en doeltreffendheid van NOVALUTE by kinders onder 18 jaar is nie vasgestel nie.

*Metode van toediening*
Oraal gebruik.
NOVALUTE kan met of sonder voedsel geneem word.
In die teenwoordigheid van integrase klasweerstand, moet NOVALUTE verkieslik saam met voedsel geneem word om blootstelling te verhoog (veral by pasiënte met D146-mutasies) (sien afdeling 5.2 - Farmakokinetiek).

**4.3 Kontraindikasies**

NOVALUTE is teenaangedui by:
- pasiënte met 'n bekende hipersensitiwiteit vir dolutegravir of vir een van die hulpstowwe
- kombinasie met dofetilide en pilsakiesel (sien afdeling 5.2)
- pasiënte met matige en ernstige hepatiese inskrywing (sien afdeling 4.4)
- vrouwe van vruigbare ouderdom wat nie 'n effektiewe voorbehoedmiddel gebruik nie.
- vrouwe van bevruigbare ouderdom wat nie op effektiewe voorbehoedmiddels is nie.

Metformien is teenaangedui by pasiënte met NOVALUTE neem.

**4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik**

*Integrase klasweerstand van besondere belang:*
Voor die aanvang van NOVALUTE is die bewoordingsel van 'n integrase klasweerstand te gebruik, moet daar in ag geneem word dat die werking van dolutegravir aanwesig is in die gedrang kom vir vinustamme wat Q148 + ≥2 sekondêre mutasies van G140A/C/S, E138A/K/T, L74I beoot. Tot watter mate dolutegravir aktief is effektiewel is die bewoordingsel van sulke mutasies nog onseker.

*Hipersensitiwiteitsreaksies:*
Daar is hipersensitiwiteitsreaksies geapporteer met NOVALUTE en is gekenmerk deur uitslag, bevindings van die hele gestel en soms, organdisfunksie, insluitend leweribeskadiging. NOVALUTE en ander vrategte medisyne moet onmiddellik gestaak word as daar teken of simptome van hipersensitiwiteitsreaksies ontstaan (insluitend, maar nie beperk nie tot, ernstige uitslag of uitslag wat gepaard gaan met verhoogde kwesmetenes, koors, algemene probleme, moegheid, spier- of gewrigpyn, blase, mondsteek, konjunktiwitis, gesigoedeem, eosinofilie en angioedeem). Die kliniese status, insluitende leweringsfunksies moet dadelik geëvalueer word en moet, nadat geëmotief word en toepaslike terapie moet begin word. Verhaging om die bewoordingsel met NOVALUTE of ander vrategte aktiewe stowwe te stop na die aanvang van hipersensitiwiteit, kan tot 'n lewensbedreigende reaksie.

*Lipodistrofie en metabolese abnormaliteite:*
Kombinasie-antiretrovirale terapie word geassosieer met die herverdeling/opeenhoping van ligaamvet, insluitend sentrale vetsug, verspreiding van dorsocervikale vetweefselweefsel, perifere uitmerging, gesichtsverlies, borsverlies en gedusvoedsel by pasiënte met MIV-infeksie. 'n Kliniese ondersoek moet die fisiese teekens van vetherverdeling insluit. Pasiënte met bevoye van lipodistrofie moet 'n degelike kardiovaskulêre risikobepaling ondergaan.

*Immuunrekonstitusie-inflammatoriese Sindroom:*
By MIV-geïnfekteerde pasiënte met 'n ernstige immunogebrek ten tyde van die aanvang van die antiretrovirale terapie (ART), kan 'n inflammatoriese reaksie op asimptomatiese of residuele opportunistiese infeksies ontstaan en ernstige kliniese toestande veroorsaak, of die simptome verergr. Dikwyls word hierdie reaksies waargeneem binnen die eerste weke of maande na die aanvang van ART. Relevante voorbeelde is tuberkulose, sytomegalovirus retinitis, verspreidende en/of fokale atipiese mycobacteriële infeksies en Pneumocystis jirovecii (P. carinii) longontsteking. Enige inflammatoriese simptome moet sonder vertraan geëvalueer word en die behandeling moet, indien nodig, begin word.
Outoimmuunafwykings (soos Grave se siekte, polimiositis en Guillain-Barre-sindroom) is ook gerapporteer om voor te kom by die inisiëring van immuunrekonstitusie, maar die tyd tot aanvang is veranderlik en kan baie maande na die aanvang van die behandeling plaasvind en soms kan dit atipies presenteer.
Verhoogde ALT- en AST-waardes, saam met die immuunrekonstitusiesindroom, is by sommige pasiënte met met hepatitis B en/of C-infeksie gerapporteer. In sulke gevalle moet NOVALUTE terapie waargeneem. Monitering van leweranomaliewaardes word aanbeveel by pasiënte met hepatitis B en/of C-infeksie. Besondere nouwkeurigheid moet gegeeu word by die aanvang of indanbodiuing van effektiewe hepatitis B-terapie (vereys na die behandelingsrigtlyne) wanneer met dolutegravir-gebaseerde terapie begin word by pasiënte wat ook met hepatitis B besmet is (sien afdeling 4.8 - Beskrywing van geselekteerde neve-reaksies).

*Osteonekrose:*
Afsweel die etiologie as multifaktoriel beskou word (insluitend gebruik van kortikosteroiede, bisfosfonate, alkoholverbruik, ernstige immuunonderdrukking, hoër liggaamsmassa-indeks), is gevalle van osteonekrose aangemeld, veral by pasiënte met gevorderde MIV-siekte enlof langtermyn blootstelling aan kombinasie antiretrovirale terapie (ART). Pasiënte moet aangeraai word om mediese advies in te win as hulle gewrigpyn en skete, gewrigstyfheid of probleme met bewyging ondervind.

*Oksidatiewe stres:*
Pasiënte met NOVALUTE ontvang, moet in kennis gestel word dat NOVALUTE of enige ander antiretrovirale terapie nie MIV-infeksie genees nie en dat hulle steeds opportunistiese infeksies en ander komplikasies van MIV-infeksie kan ontwikkel. Daarom moet pasiënte onder noukeurige kliniese versorg bly deur professionele persone in die geneesheidsorg wat ervare is in die behandeling van hierdie MIV-siektes. Gereelde monitering van visualisiëring en CD4-telling moet gedoen word.

*Die risiko van MIV-ontwing aan ander:*
Pasiënte moet in kennis gestel word dat die huidige antiretrovirale terapie, insluitend NOVALUTE, nie die risiko van oordrag van MIV aan ander deur seksuele kontak of bloedbesmetting voorkom nie. Toepaslike voorsorgmaatreëls moet steeds gebruik word.

*Hepatiese inskrying:*
Die ongebonde fraksie NOVALUTE in die bloed word verdubbel by pasiënte met matige hepatiese inskrying. NOVALUTE is teenaangedui by pasiënte met matige of ernstige hepatiese inskrying (sien afdeling 4.3).

*Interaksies:*
Omsigtigheid moet gebruik word wanneer medisyne saam toegedien word (voorskrif en ten-voorskrif) wat die bioskiwiteit van NOVALUTE kan verander of medisyne wat deur blootstelling aan NOVALUTE kan verander (sien afdeling 4.5 en 5.2).
Die gelyktydige toediening van NOVALUTE met etravirien (ETR) word nie aanbeveel nie, tenty die pasiënt ook gepaardgaande atasanavir + ritonavir (ATV + RTV) of darunavir + RTV (DRV + RTV) ontvang, wat 'n vermindering van die bioskiwiteit van dolutegravir veroorsaak.
Die aanbevole dosis NOVALUTE is 50 mg twee keer per dag as dit saam met etravirien, nevirapien, fosravaviritonavir, of rifampisien toegedien word (sien afdeling 4.5).
NOVALUTE moet nie saam met pofivalente katoon-bevatbare teensuurmiddels toegedien word nie. Daar word aanbeveel dat NOVALUTE toegedien word 2 uur voor of 6 uur na hierdie middels (sien afdeling 4.5).
Metformien kreatinien kan 'n rol speel in die vinnier kleiner toenemende van serum kreatinien. Metformien is teenaangedui by pasiënte wat NOVALUTE neem (sien afdeling 4.3).

*Gelyktydige infeksie met Hepatitis B of C:*
In Fase III-studies is pasiënte met Hepatitis B en/of C-ko-infeksie toegelaat om in te skryf, mits die basislyn leverchemiesetoe die boonste normale norm (ULN) met 5 maal oorskry het nie. Ook die algemeen was die veiligheidsprofiel by pasiënte wat gesamenlik met hepatitis B en/of C geïnfekteer was, soortgelik aan die wat waargeneem is onder pasiënte sonder gelyktydige hepatitis B of C infeksie, hoewel die kiesie van AST- en ALT-abnormaliteite hoër was in die subgroep met gelyktydige hepatitis B enlof C infeksie vir alle behandelingsgroepe. Verhoogtes in leverchemie, koekwaret met immuunrekonstitusiesindroom, is by sommige proefpersone met gelyktydige hepatitis B enlof C infeksie aan die begin van die NOVALUTE-terapie waargeneem, veral by diegene waar anti-hepatitis B-terapie ontvies is.
NOVALUTE moet onder as 1 mmol natrium (23 mg) per doseringseenheid, dit wil sê in wese "natriumvry".

**4.5 Interaksie met ander medisyne en ander vorme van interaksie**

*Effek van NOVALUTE op die farmakokinetika van ander middels:*
In vitro het NOVALUTE geen direkte, of swak inhibisie (IK50>50 µM) van die ensieme sitochroom P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, CYP2B6, uridienifosfaat glukuronosiltransferase (UGT)1A1 of UGT2B7, of die transporteiers Pgp, BCRP, OATP1B1, OATP1B3, OCT1 of MRP2 geëmoniseer nie. In vitro het dolutegravir nie CYP1A2, CYP2B6 of CYP3A4 geïnduseer nie. In vivo het dolutegravir geen effek op midazolam, 'n CYP3A4-onderskeiwidel gebruik nie. Gebaseer op hierdie data, word daar nie verwag dat NOVALUTE die farmakokinetika van medisyne wat deur hierdie ensieme of transporteiers gemetaboliseer word, betekenisvol sal verander nie (sien afdeling 5.2 - Farmakokinetiese Studies). Die UGT1A1-inhibeerder, statiene, kasoel-antifungale middels (soos fluikonasol, itrakonasol, kloitrimasol), protoonpompinhibeerders (soos esomeprasol, lansoprasol, omeprasol), anti-erektiele disfunksiemiddels (soos sildenafil, tadalafil, vardenafil), asikloviir, valasikloviir, sitagliptien en azefovir sal effekte nie.

Geen kliniese relevante effekte is geraporteer met NOVALUTE op die farmakokinetika van die volgende: ran- tenofovir, metadon, etravirens, lopinavir, atasanavir, darunavir, etravirien, fosamprenavir, tipranavir, ritonavir en orale voorbehoedmiddels met progestiene en/of estrogene.

*In vitro* het NOVALUTE die renale organiese kation-transporteier 2 (OCT2) en multi-geneesmiddel en toksiek ekstruksie-transporteur (MATE) geïnhibeer. In vivo, is 'n 10 - 14 % verlaging in kreatinesynthesing (gebaseerdgrafiek as afhanklik van OCT2 en MATE-1 -ensiem) waargeneem by pasiënte. In vivo kan dolutegravir die plasmakonsentrasies van medisyne vehoog waar uitskeiding afhanklik is van OCT2 of MATE-1 (bv. dofetilide), metformien of serum kreatinien (sien afdeling 4.3).
In vitroenin NOVALUTE die vloeiing van metformien, organiese anioontransporteiers (OAT) en OAT3, geïnhibeer. Gebaseer op die gebrek aan effek op die farmakokinetika van ander substrate van die OAT-substraat tenofovir, is in vivo-inhibisie van OAT1 onwaarskynlik. Die inhibisie van OAT3 is nie in vivo bestuiwer nie. NOVALUTE kan die plasmakonsentrasie van medisyne verhoog wat vir hul uitskeiding van OAT3 afhanklik is.

*Effek van ander middels op die farmakokinetika van NOVALUTE:*
Alle faktore wat die bioskiwiteit van dolutegravir verminder, moet vermy word in die kombinasie met NOVALUTE. Dolutegravir is 'n substraat van UGT1A1, UGT1A3, UGT1A9, CYP3A en OAT-substraat tenofovir, is in vivo-inhibisie van UGT1A1, UGT1A3, UGT1A9, CYP3A4, Pgp en BCRP; dus kan medisyne wat daardie ensieme induseer, NOVALUTE plasmavlakke verlaag en die terapeutiese effek van NOVALUTE verminder.
Gelyktydige toediening van NOVALUTE en ander medisyne wat UGT1A1, UGT1A3, UGT1A9, CYP3A4 enlof Pgp inhibeer, kan die NOVALUTE-plasmakonsentrasie verhoog (sien Tabel 1).

Etravirens, nevirapien, rifampisien en fenobarbiton is minder huweel het elkaar die plasmakonsentrasies van NOVALUTE beduidend verminder en weg 'n doseraanpassing na NOVALUTE 50 mg twee keer daagliks. Etravirien het ook die plasmakonsentrasies verminder, maar die effek van etravirien is vermoed die gelyktydige toediening van die CYP3A4-inhibeerders lopinavir/ritonavir, atanavir/ritonavir en ook na verwagting ook deur darunavir/ritonavir verwag word. Daarom is geen NOVALUTE-dosisaanpassing nodig as dit saam met etravirien en lopinavir/ritonavir, darunavir/ritonavir of atasanavir/ritonavir toegedien word nie. 'n Ander induseerder, fosamprenavir in kombinasie met ritonavir, het die plasmakonsentrasies van NOVALUTE verminder, maar die doseringsaanpassing van NOVALUTE is nie nodig nie. Verslightheid is nodig en kliniese monitering word aanbeveel wanneer hierdie kombinasies toegedien word wanneer dolutegravir saam met 'n CYP3A-induseerder (bv. Rifampisien, Etravirine Middels). Die UGT1A1-inhibeerder, atasanavir, kan die plasmakonsentrasies van NOVALUTE aansienlik verhoog nie. Tenofovir, disoproksil fumaraat, darunavir/ritonavir, darunavir/cobisistat, rilpivirien, boosprasvir, telaprevir, predniso(lon), rifabutien en omeprasol het geen of minimale effek op die farmakokinetika van dolutegravir gehad, en daarom word geen dosisaanpassing van NOVALUTE benodig wanneer dit saam met hierdie medisyne toegedien word nie.

Die opname van NOVALUTE word verminder deur sekere antisuurmiddels (sien Tabel 1).

Gevestiges en teoretiese interaksies met geselekteerde antiretrovirale middels en nie-antiretrovirale middels word gelys in Tabel 1.

*Tabel 1: Interaksiestabel*
Interaksies tussen NOVALUTE en medisyne wat saam toegedien word, word in Tabel 1 gelys (toename word aangedui as ↑, afname as ↓, geen verandering as ↔, area onder die konsentrasie teenoor tydskurwe as AOK, maksimum waargenome konsentrasie as $K_{max}$, konsentrasie aan die einde van doseringsinterval as $K_t$).

| Gelyktydige Medisyne Klas:<br>Naam van Medisyne | Effek op Konsentrasie van NOVALUTE of Gepaardgaande Medisyne | Kliniese Kommentaar |
|---|---|---|
| *Nukleoside/ Tru Transkriptase Inhibeerders:* | | |
| Etravirien (ETR) sonder versterkte protease-inhibeerders | $K_{max}$ ↓ 52 %<br>AOK ↓ 88 %<br>ETR ↔ | Etravirien sonder versterkte protease-inhibeerders verlaagde NOVALUTE-blootstelling aansienlik en die verlies van strategiese realiste en moontlike weerstand teenoor dolutegravir. NOVALUTE moet nie gebruik word met etravirien sonder gelyktydige toediening van atasanavir/ritonavir, darunavir/ritonavir of lopinavir/ritonavir nie (sien inligting wat volg in tabel). |
| Lopinavir/ritonavir + etravirien | Dolutegravir ↔<br>AOK ↓ 11 %<br>$K_{max}$ ↓ 7 %<br>$K_t$↓ 28 %<br>LPV ↔<br>RTV ↔<br>ETR ↔ | Geen dosisaanpassing is nodig nie |
| Darunavir/ritonavir + etravirien | Dolutegravir ↓<br>AOK ↓ 25 %<br>$K_{max}$ ↓ 18 %<br>$K_t$ ↓ 36 %<br>DRV ↔<br>RTV ↔ | Geen dosisaanpassing is nodig nie |
| Efavirens (EFV) | Dolutegravir ↓<br>AOK ↓ 57 %<br>$K_{max}$ ↓ 39 %<br>$K_t$ ↓ 75 % EFV ↔ historiese kontroles<br>(indukse van UGT1A1 en CYP3A ensieme) | Efavirens verlaag dolutegravir plasmakonsentrasies. Die aanbevole dosis NOVALUTE is 50 mg twee keer per dag wanneer toegedien word met efavirens. Alternatiewe kombinasies wat die efavirens bevat nie moet, waar moontlik, gebruik word by INI-weerstandige pasiënte. |
| Nevirapien | Dolutegravir ↔<br>(Ilete bestuiber nie, 'n soortgelyke afname in blootstelling sous waargeneem word met etravirens word verwag, as gevolg van induksie) | Die aanbevole dosis NOVALUTE is 50 mg twee keer per dag wanneer toegedien word met nevirapien. Alternatiewe kombinasies wat nie nevirapien insluit nie moet, waar moontlik, gebruik word by INI-weerstandige pasiënte. |
| Rilpivirien | Dolutegravir ↔<br>AOK ↑ 12 %<br>$K_{max}$ ↔ 13 %<br>Kt↑ 22 %<br>Rilpivirien ↔ | Geen dosisaanpassing is nodig nie |
| *Nukleotide Transkriptase Inhibeerders:* | | |
| Tenofovir (TDF) sonder versterkte proteasie-inhibeerders | Dolutegravir ↓<br>AOK ↓ 10 %<br>$K_{max}$ ↓ 1 %<br>$K_t$ ↓ 6 %<br>TDF ↔ | Tenofovir het nie blootgelyk plasmakonsentrasie verander tot 'n kliniese merkbare omvang nie. Geen dosisaanpassing is nodig nie. |
| *Protease-inhibeerders:* | | |
| Atasanavir (ATV) | Dolutegravir ↑<br>AOK ↑ 91 %<br>$K_{max}$ ↑ 48 %<br>Kt↑ 180 %<br>ATV ↔ (historiese kontroles)<br>(inhibisie van UGT1A1 en CYP3A ensieme) | Atasanavir verhoog dolutegravir plasmakonsentrasies. Geen dosisaanpassing is nodig nie.<br>NOVALUTE dosis moet nie hoër as 50 mg twee keer per dag wees wanneer gebruik word in kombinasie met atasanavir nie as gevolg van 'n gebrek aan data. |
| Atasanavir/ ritonavir (ATV + RTV) | Dolutegravir ↑<br>AOK ↑ 62 %<br>$K_{max}$ ↑ 33 % Kt ↑ 121 %<br>ATV ↔<br>RTV ↔<br>(inhibisie van UGT1A1 en CYP3A ensieme) | Atasanavir/ritonavir verhoog dolutegravir plasmakonsentrasie<br>Geen dosisaanpassing is nodig nie<br>NOVALUTE dosis moet nie hoër as 50 mg twee keer per dag wees wanneer gebruik word in kombinasie met atasanavir nie as gevolg van 'n gebrek aan data. |
| Tipranavir/ ritonavir (TPV + RTV) | Dolutegravir ↓<br>AOK ↓ 59 %<br>$K_{max}$ ↓ 47 % Kt ↓ 76 %<br>TPV ↔<br>RTV ↔<br>(indukse van UGT1A1 en CYP3A ensieme) | Tipranavir/ritonavir verminder dolutegravir konsentrasies. Die aanbevole dosis NOVALUTE is 50 mg twee keer per dag wanneer toegedien word met tipranavir/ritonavir. Alternatiewe kombinasies wat nie tipranavir/ritonavir bevat nie moet, indien moontlik, gebruik word by INI-weerstandige pasiënte. |
| Fosamprenavir/ ritonavir (FPV + RTV) | Dolutegravir ↓<br>AOK ↓ 35 %<br>$K_{max}$ ↓ 24 %<br>Kt ↓ 46 %<br>FPV ↔<br>RTV ↔<br>(indukse van UGT1A1 en CYP3A ensieme) | Fosamprenavir/ritonavir verlaag dolutegravir konsentrasies, maar het nie 'n verminderde effekbeheid in Fase III studies tot gevolg gehad nie, gebaseer op beperkte data. Geen dosisaanpassing is nodig by INI-naïewe pasiënte nie. Alternatiewe kombinasies, wat nie fosamprenavir/ ritonavir bevat nie, behoort gebruik te word, waar moontlik, by INI weerstandige pasiënte. |
| Nelfinavir | Dolutegravir ↔ | Hierdie interaksie is nie bestuiber nie. Hoewel dit 'n inhibeerder van CYP3A4 is, word 'n verhoging, gebaseer op data van ander inhibeerders, nie verwag nie. Geen dosisaanpassing is nodig nie. |
| Lopinavir/ritonavir (LPV + RTV) | DTG ↔<br>AOK ↔<br>$K_{max}$ ↔<br>$K_t$ ↔<br>LPV ↔<br>RTV ↔ | Lopinavir/ritonavir het nie die dolutegravir plasma-konsentrasie verander tot 'n klinies relevante graad nie. Geen dosisaanpassing is nodig nie. |
| Darunavir/ ritonavir (DRV/RTV) | Dolutegravir ↔<br>AOK ↓ 32 %<br>$K_{max}$ ↓ 11 %<br>$K_t$ ↓ 38 %<br>DRV ↔<br>RTV ↔<br>(indukse van UGT1A1 en CYP3A ensieme) | Darunavir/ritonavir het die dolutegravir plasma-konsentrasie verander tot 'n klinies relevante graad nie. Geen dosisaanpassing is nodig nie. |
| *Ander antiviralemiddels* | | |
| Boseprevir | Dolutegravir ↔<br>AOK ↑ 7 %<br>$K_{max}$ ↓ 5 %<br>Kt ↑ 8 %<br>Boseprevir ↔<br>(historiese kontroles) | Geen dosisaanpassing is nodig nie |
| Daklatasvir | Dolutegravir ↔<br>AOK ↓ 33 %<br>$K_{max}$ ↓ 29 %<br>Kt↑ 46 %<br>Daklatasvir ↔ | Daklatasvir het nie die dolutegravir plasmakonsentrasie verander tot 'n klinies relevante graad nie. NOVALUTE het nie die daklatasvir plasmakonsentrasie verander nie. Geen dosisaanpassing is nodig nie. |
| *Ander Medisyne* | | |
| *Anti-diurtiimiese middels* | | |
| Dofetilied Pilsikaliesied | Dofetilied ↑<br>Pilsikaliesied ↑ | Gelyktydige toediening van dolutegravir het die potensiaal om dofetilied- of pilsikaliesied-blootstellingsvlakke te verhoog deur inhibisie van OCT2 transporteier; gelyktydige toediening van NOVALUTE en OCT2-substrate moet gebruik word met dofetilied of pilsikaliesied wanneer NOVALUTE is teenaangedui as gevolg van die potensiële kwesbaredigende toksisiteit wat vervorsaak word deur hoë dofetilied of pilsikaliesied konsentrasie (sien afdeling 4.3). |
| *Antikonvulsante* | | |
| Karbamasepien | Dolutegravir ↓<br>AOK ↓ 49 %<br>$K_{max}$ ↓ 33 %<br>$K_t$ ↓ 73 % | Die aanbevole vloeiende dosis dolutegravir is 50 mg twee keer per dag wanneer dit gelyktydig toegedien word met karbamasepien. Alternatiewe kombinasies wat nie karbamasepien bevat nie moet, waar moontlik, aan INI weerstandige pasiënte. |
| Oksarbasepien<br>Fenitoïen<br>Fenobarbiton | Dolutegravir ↓ | Gelyktydige toediening kan die dolutegravir plasmakonsentrasie verlaag en is nie bestuiber nie. Gelyktydige toediening met hierdie metaboliese induserendes moet vermy word. |
| *Asool en anti-fungale medisyne* | | |
| Ketokonasool<br>Itrakonasool<br>Flukonasool<br>Vorikonasool | Dolutegravir ↔<br>(Nie bestuiber nie) | Geen dosisaanpassing is nodig nie.<br>Gebaseer op data van ander CYP3A4 inhibeerders, word 'n merkbare verhoging nie verwag nie. |
| *Bisfosfonaatmiddels* | | |
| St. Janskruid | Dolutegravir ↓ | Gelyktydige toediening kan die dolutegravir plasmakonsentrasie verminder en is nie bestuiber nie. Gelyktydige toediening met hierdie metaboliese induserendes moet vermy word. |
| *Teensuurmiddels en aanvullings* | | |
| Teensuurmiddels wat polivalente kations bevat (bv. Mg, Al of Ca) | Dolutegravir ↓<br>AOK ↓ 74 %<br>$K_{max}$ ↓ 72 %<br>$K_t$ ↓ 38 % | Gelyktydige toediening van teensuurmiddels wat polivalente kations bevat, word nie aanbeveel nie. Daar word aanbeveel dat NOVALUTE 2 uur voor of 6 uur na onsame van teensuurmiddels wat polivalente kations bevat, toegedien word. |
| Katsuamanvullings | Dolutegravir ↓<br>AOK ↓ 39 %<br>$K_{max}$ ↓ 37 %<br>$K_t$ ↓ 38 % | Daar word aanbeveel dat NOVALUTE 2 uur voor of 6 uur na inname van produkte wat kalsium bevat, toegedien word, of as alternatief kan dit saam met voedsel toegedien word. |
| Yisteranvullings | Dolutegravir ↓<br>AOK ↓ 54 %<br>$K_{max}$ ↓ 57 %<br>$K_t$ ↓ 56 %<br>(komplekse binding met polivalente ione) | Daar word aanbeveel dat NOVALUTE 2 uur voor of 6 uur na inname van produkte wat yster bevat, toegedien word, of as alternatief kan dit saam met voedsel toegedien word. |
| Multivitamien | Dolutegravir ↓<br>AOK ↓ 33 %<br>$K_{max}$ ↓ 31 %<br>$K_t$ ↓ 32 %<br>(komplekse binding met polivalente ione) | Daar word aanbeveel dat NOVALUTE 2 uur voor of 6 uur na multivitamiene toegedien word. |
| *Kortikosteroiede* | | |
| Prednison | Dolutegravir ↔<br>AOK ↑ 15 %<br>$K_{max}$ ↔ 14 %<br>Kt↑ 17 % | Geen dosisaanpassing is nodig nie |
| *Antidiabetiese middels* | | |
| Metformien | Metformien ↑ | Gelyktydige toediening van dolutegravir verhoog metformien plasmakonsentrasie. Metformien is teenaangedui by pasiënte wat NOVALUTE neem (sien afdeling 4.3). |
| *Antimikrobiaterskile middels* | | |
| Rifampisien | Dolutegravir ↓<br>AOK ↓ 54 %<br>$K_{max}$ ↓ 43 %<br>Kt↑ 72 %<br>(indukse van UGT1A1 en CYP3A ensieme) | Rifampisien verlaag dolutegravir plasmakonsentrasie. Die voorgestelde dosis NOVALUTE is 50 mg twee keer per dag wanneer dit toegedien word saam met rifampisien. Alternatiewe kombinasies wat rifampisien bevat moet vermy word. |
| Rifabutien | Dolutegravir ↔<br>AOK ↓ 5 %<br>$K_{max}$ ↔ 16 %<br>Kt↑ 30 %<br>(indukse van UGT1A1 en CYP3A ensieme) | Geen dosisaanpassing is nodig nie |
| *Orale voorbehoedmiddels* | | |
| Orale voorbehoedmiddels (Etinielestrad (EE) en Norgestromien (NGMN)) | EE ↔<br>AOK ↑ 6 %<br>$K_{max}$ ↓ 1 %<br>Kt↑ 2 %<br>NGMN ↔<br>AOK ↓ 2 %<br>$K_{max}$ ↓ 11 %<br>$K_t$ ↓ 11 % | Dolutegravir het nie etinielestradiol en norgestromien plasmakonsentrasies verander tot 'n klinies beduidende graad nie. Geen dosisaanpassing van orale voorbehoedmiddels is nodig wanneer dit saam met NOVALUTE toegedien word nie. |
| *Analgetiese middels* | | |
| Metadon | Dolutegravir ↔ Metadon ↔<br>AOK ↓ 2 %<br>$K_{max}$ ↔ 0 %<br>Kt↑ 1 % | Dolutegravir het nie die metadon plasmakonsentrasie verander na 'n klinies beduidende graad nie. Geen dosisaanpassing van metadon of NOVALUTE is nodig wanneer dit saam toegedien word nie. |

**4.6 Fertiliteit, swangerskap en laktasie**

NOVALUTE is teenaangedui by vrouw wat van plan is om swanger te raak, swanger is of hulle baba borsvoed, sowel as by vrouw van bevruigbare ouderdom wat nie doeltreffende voorbehoedmiddels gebruik nie (sien afdeling 4.3).

*Vrouw met swangerskap potensiaal*
Vrouw wat swanger kan word (WOCBP) moet swangerskapstoetsing ondergaan voordat NOVALUTE begin word. WOCBP wat NOVALUTE neem, moet gedurende die hele behandeling effektiewe kontraseptiewe gebruik.

*Swangerskap*
Daar is bewyse van dat dul op 'n verhoogde voorkoms van neurale buisdefekte met die gebruik van dolutegravir in die pre/peri bevruigingsperiode en vroeë swangerskap. Die beskikbare data van bevruigting is beperk en die bydrag van die slutting van die neurale buis te beskeen, moet dolutegravir of dolutegravir bevattende voorbereidings nie in die eerste trimester van swangerskap gebruik word nie. Beskikbare inligting aangaande dolutegravir gebruik in die tweede en derde trimester is nie beperk nie.

Behandeling met NOVALUTE moet nie begin word sonder 'n medese en/of negatiewe swangerskapstoets (bloed en urine) onder laboratorium toesig nie, en moet gewoni herhaal word tydens behandeling om swangerskap uit te sluit.

Laat aanvang neurotoksiese afwykings met mitochondriale disfunksie is waargeneem by kinders wat in utero en/of postnataal aan nukleosiedanalose blootgestel is, soos bevoel in NOVALUTE. Daarom moet NOVALUTE nie in enige trimester van die swangerskap gebruik word nie, tenty daar nie 'n veiliger alternatiewe opsie beskikbaar is, behalwe indien dit nie bestuiber word nie, of terwanneer dit is.

*Laktasie*
MIV-geïnfekteerde vrouwes behoort nie hul babas te borsvoed nie, om oordrag van MIV te voorkom. Daar word verwag dat NOVALUTE in menslike melk uitgeskei word. Vrouw wat behandeling met dolutegravir (NOVALUTE) ontvang, moet nie hulle babas borsvoed nie.

*Fertiliteit*
Daar is geen inligting oor die gevolge van dolutegravir op die vrugbaarheid van menslike of nie-menslike mans nie. Dieresteuns dui op geen effek van dolutegravir op mantel of vrouliike vrugbaarheid nie (sien afdeling 5.3).

**4.7 Effekte op die vermoë om te bestuur en masjiene te gebruik**

Pasiënte moet in kennis gestel word dat duiseltigheid tydens die behandeling met NOVALUTE aangemeld is. Die kliniese status van die pasiënt en die nadelige insiderpriëel van NOVALUTE moet in gedagte gehou word as die pasiënt se vermoë om te bestuur of masjiene te gebruik, oorweeg word.

**4.8 Ongewenste effekte**

*Opsomming van die veiligheidsprofiel*
Die mees ernstige newe-effek wat by 'n individuele pasiënt gesien is, was 'n hipersensitiwiteitsreaksie wat uitslag en ernstige leweriffektie insluit (sien afdeling 4.4). Die mees algemene newe-effekte by behandeling was naarheid (13 %), diarree (18 %) en hoofpyn (13 %).

*Tabel 2: Opsomming van nadelige reaksies in tabelvorm*

| | | |
|---|---|---|
| **Immuunsteelsel afwykings** | Minder gereeld | Hipersensitiwiteit (sien afdeling 4.4).<br>*Immuun Rekonstitusie-Sindroom (sien afdeling 4.4)** |
| **Psigiatriese afwykings** | Gereeld | Slapeloosheid, abnormale drome, depressie, angstigheid |
| | Minder gereeld | Selfmoordgedagtes*, selfmoordpoging * (veral by pasiënte met 'n voorafbestaande geskiedenis van depressie of psigiatriese siekte. |
| **Senuweesteelsel afwykings** | Gereeld | Hoofpyn, duiseligheid |
| **Gastrointeslinale afwykings** | Gereeld | Naarheid, diarree, braking, winderigheid, boonste abdominale pyn, abdominale pyn, abdominale ongemak |
| **Hepatobiliêre afwykings** | Minder gereeld | Hepatitis, akute hepatiese verskaring |
| **Vel- en subkutane weefselafwykings** | Gereeld | Uitslag, pruritus |
| **Muuskuloskeletale en konnektiewe weefselafwykings** | Minder gereeld | Artralgie, mialgie |
| **Algemene afwykings en toedieningspiaik kondisies** | Gereeld | Moegheid |
| **Ondersoeke** | Gereeld | Alanienaminotransferase (ALT) enlof Aspartaat-aminotransferase verhogings, kreatien-fosfokinase (CPK) verhogings |

** sien onder "Beskrywing van geselekteerde neve-reaksies"
Die veiligheidsprofiel was soortgelyk in die behandelingsnaïewe, behandelingservare (en integrase-naïewe) en integrase-weerstandige pasiëntpopulasies.

*Beskrywing van geselekteerde neve-reaksies*
Verandertye in laboratoriumafwykings/-reaksies
Verhogings in serumkreatinien het binne die eerste week van NOVALUTE-behandeling voorgekom en het stabiel gebly tot by week 48. Na 48 week van behandeling is 'n gemiddelde verandering vanaf die basislyn van 14 % waargeneem. Kreatinienverhogings was vergelykbaar deur verskillende afgeroongdemiene. Hierdie verandering word nie as klinies relevant beskou nie, aangesien dit nie 'n verandering in glomerulêre filtreasiewerp weerspieël nie (sien afdeling 5.1). Klein toenames in die totale bilisuben (sonder kliniese gevolug) is op die NOVALUTE en rittipravir-tene (maar nie efavirens-bevat nie) in die program waargenomen. Hierdie verandering word nie as klinies relevant beskou nie, aangesien dit waarskynlik medediging tussen NOVALUTE en ongekonjugeerde bilirubien vir 'n gemeenskappike opruimingsroete (UGT1A1) weerspieël (sien afdeling 5.2 - Biotransformasie