REYDIN

21073749

REYDIN

21073749

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

REYDIN (Film-coated tablets)

COMPOSITION:

Each **REYDIN** film-coated tablet contains:
Dolutegravir 50 mg (as dolutegravir sodium).
Lamivudine 300 mg.
Tenofovir disoproxil 300 mg (equivalent to tenofovir disoproxil fumarate).

Inactive ingredients: croscarmellose sodium, hydroxypropyl methyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose, opadry blue (containing polyvinyl alcohol, talc, titanium dioxide, indigo carmine, glycerol esters of fatty acids, sodium lauryl sulfate, brilliant blue aluminium lake), povidone, sodium starch glycolate.

Contains mannitol 145 mg (sugar).

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 "WARNINGS AND SPECIAL PRECAUTIONS"). REYDIN IS NOT INDICATED FOR TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. THE SAFETY AND EFFICACY OF REYDIN 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 ARE CO-INFECTED WITH HIV AND HBV AND WHO DISCONTINUED THE COMBINATION TABLET. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE "WARNINGS AND SPECIAL PRECAUTIONS").

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 – Antimicrobial (chemotherapeutic) medicine. Other than antibiotics. Antiviral medicine.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Dolutegravir:

Dolutegravir inhibits HIV integrase by binding to the integrase active sites 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 ($t_{1/2}$ 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 wildtype 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 (RTI)- and protease inhibitor (PI)-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 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.

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.

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 has 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.

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:

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 into DNA, by chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Medicine 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 % of 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 – 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.

Pharmacokinetic properties:

Dolutegravir:

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is between low to moderate. In Phase 1 studies in healthy subjects, between-subjects CVb % for AUC and C_{max} ranged from -20 to 40 % and C_T from 30 to 56 % across studies. 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:

Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours post-dose. With once-daily dosing, pharmacokinetic steady-state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C_{24h} ranging from 1,2 to 1,5.

Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Dolutegravir is a Pgp substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established.

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 33 %, 41 % and 66 %, increased C_{max} by 46 %, 52 % and 67 % and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant.

Distribution:

Dolutegravir is highly bound (greater than or equal to 98,9 %) to human plasma proteins based on *in vivo* data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50 mg once daily administration is estimated at 17,4 L based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0,441 to 0,535 indicating minimal association of radioactivity with blood cellular components. Free fraction of dolutegravir in plasma is estimated at approximately 0,2 to 1,1 % in healthy subjects with moderate hepatic impairment, and 0,8 to 1,0 % in subjects with severe renal impairment and 0,5 % in HIV-1 infected patients. Dolutegravir is present in cerebrospinal fluid (CSF). In 12 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/ lamivudine, the median dolutegravir concentration in CSF was 13,2 ng/mL (range: 3,74 ng/mL to 18,3 ng/mL) 2 to 6 hours post-dose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Metabolism:

Dolutegravir is primarily metabolised via UGT1A1 with some contribution from CYP3A. Dolutegravir is the predominant circulating compound in plasma. After a single oral dose of [14C] dolutegravir, 53 % of the total oral dose was excreted unchanged in 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-one percent 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). Renal elimination of unchanged drug was low (less than 1 % of the dose).

Elimination:

Dolutegravir has a terminal half-life of ~14 hours and an apparent oral clearance (CL/F) of 1,0 L per hour based on population pharmacokinetic analysis.

Special 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 dosage resulted in dolutegravir exposure comparable to that observed in adults who receive dolutegravir 50 mg once daily.

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 subject weighing 37 kg received 35 mg once daily.

Elderly:

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed there is 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. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr < 30 mL/min). 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_{24} 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 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 necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in 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 are not associated with differences in the pharmacokinetics of dolutegravir.

Co-infection with hepatitis B or C:

Population pharmacokinetic analysis indicate that hepatitis C virus co-infection has no clinically relevant effect on the exposure to dolutegravir. There are limited data on patients with hepatitis B co-infection.

Lamivudine:

Absorption:

Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Absolute bioavailability in 12 adult subjects was 86 % ± 16 % (mean ± SD) for the 150 mg tablet and 87 % ± 13 % for the oral solution. After oral administration of 2 mg/kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration (C_{max}) was 1,5 ± 0,5 µg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0,25 to 10 mg/kg. The accumulation ratio of lamivudine in HIV-1 positive asymptomatic adults with normal renal function was 1,50 following 15 days of oral administration of 2 mg/kg twice daily. The mean time (T_{max}) to maximum serum concentration (C_{max}) is about an hour.

Effects of food on oral absorption:

Lamivudine tablets and oral solution may be administered with or without food. An investigational 25 mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-1 infected subjects on 2 occasions, once in the fasted state and once with food (1,099 kcal; 75 g fat, 34 g protein, 72 g carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max}: 3,2 ± 1,3 hours) compared with the fasted state (T_{max}: 0,9 ± 0,3 hours); C_{max} in the fed state was 40 % ± 23 % (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC_{∞}) in the fed and fasted states.

Distribution:

The apparent volume of distribution after IV administration of lamivudine to 20 subjects was 1,3 ± 0,4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (less than 36 %). *In vitro* studies showed that over the concentration range of 0,1 to 100 µg/mL, the amount of lamivudine associated with erythrocytes ranged from 53 % to 57 % and was independent of concentration.

Metabolism:

Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite of lamivudine is the trans-sulfoxide metabolite (approximately 5 % of an oral dose after 12 hours). Serum concentrations of this metabolite have not been determined. Lamivudine is not significantly metabolised by CYP450 enzymes.

Elimination:

The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300 mg oral dose of lamivudine, renal clearance was 199,7 ± 56,9 mL/min (mean ± SD). In 20 HIV-1 infected subjects given a single IV dose, renal clearance was 280,4 ± 75,2 mL/min (mean ± SD), representing 71 % ± 16 % (mean ± SD) of total clearance of lamivudine.

In most single-dose trials in HIV-1 infected subjects, HBV infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life (t½) ranged from 5 to 7 hours. In HIV-1 infected subjects, total clearance was 398,5 ± 69,1 mL/min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0,25 to 10 mg/kg.

No dose 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. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin. Lamivudine elimination will be affected by renal impairment.

Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary. The likelihood of adverse drug interactions with lamivudine is low due to the limited metabolism and plasma protein binding and almost complete renal clearance.

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 3TC/ zidovudine combination in patients with renal impairment should be carefully assessed. Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The mean ratio CSF / serum lamivudine concentration 2 – 4 hours after oral administration is approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Special populations:

Pharmacokinetics in children:

In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55 – 65 %) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age approaching adult values around 12 years of age. Recent findings indicate that exposure in children 2 to < 6 years of age may be reduced by about 30 % compared with other pharmacokinetic data for patients < 3 months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely due to immature renal function and variable absorption.

Pharmacokinetics in pregnancy:

Following oral administration, lamivudine pharmacokinetics in late-pregnancy were similar to non-pregnant adults. Administration of lamivudine in animal toxicity studies at very high doses was not associated with any major organ toxicity. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia. Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an *in vitro* cytogenic assay.

Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 30 – 40 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed in *in vivo* tests it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment. There is as yet no information on the tumorigenic risk in animals, and therefore any potential risk to humans must be balanced against the expected benefits of treatment.

Tenofovir disoproxil fumarate:

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption:

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients is approximately 25 %. Following oral administration of a single 300 mg dose of tenofovir disoproxil fumarate to HIV-1 infected subjects in the fasted state, maximum serum concentrations (C_{max}) were achieved in 1,0 ± 0,4 hrs (mean ± SD), and C_{max} and AUC values were 0,30 ± 0,09 µg/mL and 2,29 ± 0,69 µg•hr/mL, respectively. The pharmacokinetics of tenofovir are dose-proportional over a dose range of 75 to 600 mg and are not affected by repeated dosing.
In a single-dose bioequivalence study conducted under non-fasted conditions (dose administered with 113,4 g apple sauce) in healthy adult volunteers, the mean C_{max} of tenofovir was 26 % lower for the oral powder relative to the tablet formulation. Mean AUC of tenofovir was similar between the oral powder and tablet formulations.

Effects of food on oral absorption:

Administration of tenofovir following a high-fat meal (~700 to 1000 kcal containing 40 % to 50 % fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40 % and an increase in C_{max} of approximately 14 %. However, administration of tenofovir with a light meal does not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the medicine. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 0,33 ± 0,12 µg/mL and 3,32 ± 1,37 µg•hr/mL following multiple doses of tenofovir disoproxil 300 mg once daily in the fed state, when meal content was not controlled.

Distribution:

In vitro binding of tenofovir to human plasma protein is less than 0,7 % and 7,2 %, respectively over the tenofovir concentration range of 0,01 – 25 µg/mL. The volume of distribution at steady-state is 1,3 ± 0,6 L/kg and 1,2 ± 0,4 L/kg, following intravenous administration of tenofovir 1,0 mg/kg and 3,0 mg/kg.

Metabolism:

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes. Following IV administration of tenofovir, approximately 70 – 80 % of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose oral administration of tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir 300 mg once daily (under fed conditions), 32 ± 10 % of the administered dose is recovered in urine over 24 hours.

Elimination:

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.

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 **"DOSAGE AND DIRECTIONS FOR USE"**). 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.

INDICATIONS:

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

CONTRAINDICATIONS:

REYDIN is contraindicated in:
- Patients with known hypersensitivity to dolutegravir, lamivudine, tenofovir disoproxil fumarate or any of the components of **REYDIN**.
- Uncontrolled renal failure (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).
- Pregnancy and lactation (see **"HUMAN REPRODUCTION"**).
- Women of child-bearing age not using highly effective contraception.
- Concomitant use with adefovir dipivoxil.
- Co-administration with dofetilide and pilsicainide.
- Co-administration with didanosine.
- Co-administration with metformin.
- Patients younger than 18 years of age.
- Moderate and severe hepatic impairment.

WARNINGS AND SPECIAL PRECAUTIONS:

Safety and efficacy of the individual active ingredients in various antiretroviral combination regimens with similar dosages as contained in **REYDIN** have been established in clinical studies for the treatment of HIV patients. However, safety and efficacy of the fixed-drug combination as in **REYDIN** 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 **REYDIN** has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Lipodystrophy:

Combination antiretroviral therapy, including **REYDIN**, has also been associated with the redistribution / accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting and breast enlargement 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 reconstitution inflammatory syndrome:

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination anti-retroviral therapy (cART). Typically, such a reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, atypical mycobacterial infections, cytomegalovirus retinitis, *Pneumocystis jirovecii*, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued, 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 as IRIS reactions; 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 **REYDIN**. 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 **REYDIN** may continue to develop opportunistic infections and other complications of HIV infection and therefore should remain under close clinical observation by doctors experienced in the treatment of patients with HIV associated diseases.

The risk of HIV transmission to others:

Patients must be advised that treatment with **REYDIN**, 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 **REYDIN**. 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, thyrotoxicosis, 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 **REYDIN** alone or in combination, in the treatment of HIV infection. Most cases were women. Caution should be exercised when administering **REYDIN** to patients with known risk factors for liver disease.

Treatment with **REYDIN** 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 **REYDIN**, 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.

Patients at increased risk should be followed closely. There are no study results demonstrating the effect of **REYDIN** on clinical progression of HIV-1.

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues, as contained in **REYDIN**, have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), and metabolic disorders (hyperlactataemia, hyperlipidaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms.

Pancreatitis:

Pancreatitis has been observed in some patients receiving lamivudine, as in **REYDIN**. 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 **REYDIN** until diagnosis of pancreatitis is excluded.

Patients with moderate to severe renal impairment:

In patients with moderate to severe renal impairment, the terminal half-life of **REYDIN** is increased due to decreased clearance. The dose of **REYDIN** should therefore be adjusted (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Liver disease:

Use of **REYDIN** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **REYDIN** has not been established in patients with significant underlying liver disorders. 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.

Renal impairment:

REYDIN is a combination medicine and the dose of the individual components cannot be altered. Tenofovir and lamivudine are principally eliminated by the kidney. **REYDIN** 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 hypophosphataemia) 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 **REYDIN**.

Renal function:

Since **REYDIN** is primarily eliminated by the kidneys, co-administration of **REYDIN** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of **REYDIN** 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.

REYDIN 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:

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

Bone mineral density:

Decreases in bone mineral density of the spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate, as contained in **REYDIN**. 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.

REYDIN 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.

Patients with HIV and hepatitis B or C virus co-infection:

REYDIN is not indicated for the treatment of chronic HBV infection. The safety and efficacy of **REYDIN** 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 with chronic hepatitis B or C treated with **REYDIN** are at an increased risk for severe and potentially fatal hepatic adverse reactions. Doctors should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

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:

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir and were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Discontinue **REYDIN** and other suspect agents immediately 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 **REYDIN**, or 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 elderly:

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Effects on ability to drive and use machines:

REYDIN may cause dizziness, impaired concentration and/or drowsiness and may affect the ability to drive and use machines. Patients should ensure that they do not engage in driving or using machines until they know how **REYDIN** affects them.

INTERACTIONS:

The likelihood of interactions is low due to the limited metabolism and plasma protein binding and almost complete renal clearance. Zidovudine plasma levels are not significantly altered when co-administered with lamivudine. Zidovudine has no effect on the pharmacokinetics of lamivudine. Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine. Administration of trimethoprim, a constituent of co-trimoxazole, causes an increase in lamivudine plasma levels. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of co-trimoxazole. The possibility of interactions with other drugs administered concurrently should be considered, particularly when the main route is renal.

No medicine interaction studies have been conducted using **REYDIN**. As **REYDIN** contains tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with these individual medicines may occur with **REYDIN**. Important medicine interaction information for **REYDIN** is summarised in Table 1, 2 and 3. 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, 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.

Tenofovir:

Renally eliminated medicines:

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

Tenofovir 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 1 and 2 summarise pharmacokinetic effects of co-administered medicine on tenofovir pharmacokinetics and effects of tenofovir on the pharmacokinetics of co-administered medicine.

When administered with multiple doses of tenofovir, 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 1:

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	% Change 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)

1. Patients received tenofovir DF 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 2:

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

Co-administered medicine	Dose of co-administered medicine (mg)	N	% Change of co-administered medicine pharmacokinetic parameters[1]		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 122 (↑ 1 to ↑ 26)	↔	NA
Adefovir dipivoxil	10 once	22	↔	↔	NA
Efavirenz	600 mg once daily x 14 days	30	↔	↔	↔
Emtricitabine	200 mg once daily x 7 days	17	↔	↔	↔
Indinavir	800 mg three times daily x 7 days	12	↑ 14 (↓ 3 to ↑33)	↔	↔
Lamivudine	150 mg twice daily x 7 days	15	↔	↔	↔
Lopinavir/ Ritonavir	400/100 mg twice daily x 14 days	21	↔	↔	↔
Methadone[2]	40 – 110 once daily x 14 days[3]	13	↔	↔	↔
Oral contraceptives[4]	Ethinyl oestradiol/ norgestimate (Ortho-Tricyclen®) 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	29	↔	↔	↔
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)

1. 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-Meyers 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.

Lamivudine:

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

Zidovudine plasma levels are not significantly altered when co-administered with **REYDIN**. Zidovudine has no effect on the pharmacokinetics of **REYDIN**.

Table 3:

Medicine interaction: Changes in pharmacokinetic parameters for co-administered medicines in the presence of lamivudine.

Co-administered medicine	Dose of co-administered medicine (mg)	% Change of co-administered medicine pharmacokinetic parameters[1]		
		C_{max}	AUC	C_{min}
Trimethoprim/ Sulphametoxazole	160/800 mg	NS	↑ 40	NS
Zidovudine	150/300 mg twice daily	↑ 28	↑ 13	NS

1. Increase = ↑; NS = Not studied

Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

REYDIN may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. **REYDIN** is therefore not recommended to be used in combination with zalcitabine.

Administration of trimethoprim, a constituent of co-trimoxazole causes an increase in **REYDIN** plasma levels. Unless the patient has renal impairment, no dosage adjustment of **REYDIN** is necessary. **REYDIN** has no effect on the pharmacokinetics of co-trimoxazole.

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

The co-administration of **REYDIN** with etravirine (ETR) is not recommended unless the patient is also receiving concomitant atazanavir + ritonavir (ATV + RTV), lopinavir + ritonavir (LPV + RTV) or darunavir + ritonavir (DRV + RTV).

Dolutegravir:

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

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

Effects of REYDIN on the pharmacokinetics of other medicines:

In vitro, dolutegravir demonstrated no direct, or weak inhibition of the enzymes cytochrome P450, uridine diphosphate glucuronosyl transferase or the transporter Pgp. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4, *in vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Therefore, dolutegravir, as in **REYDIN**, is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or transporters [i.e. 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 agents (such as sildenafil, tadalafil, vardenafil), acyclovir, valaciclovir, sitagliptin, adefovir].

Dolutegravir, as in **REYDIN**, does not have any clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinyl oestradiol.

In vitro, dolutegravir inhibits the renal organic cation transporter 2 (OCT2). Based on this, **REYDIN** may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin).

Effects of other medicines on the pharmacokinetics of dolutegravir, as in REYDIN:

Dolutegravir, as in **REYDIN**, is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp and BCRP; therefore, medicines that induce those enzymes may theoretically decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir in **REYDIN**. Co-administration of **REYDIN** 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 reduces the plasma concentrations of dolutegravir significantly and requires dolutegravir dose adjustment of 50 mg twice daily. Etravirine also reduces 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 dose adjustment is necessary when co-administered with etravirine. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment. Caution is warranted, and clinical monitoring is recommended when these combinations are given in INI-resistant patients. A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no dose adjustment of dolutegravir is required when co-administered with these medicines.

Dolutegravir medicine interactions:

Concomitant medicine class: Medicine name	Effect on concentration of dolutegravir or concomitant medicine			
	Dolutegravir / concomitant medicine	AUC	C_{max}	C_T
HIV-1 antiviral agents				
Non-nucleoside reverse transcriptase inhibitor: Etravirine (ETR)	Dolutegravir ↑ ETR ↔	↓ 71 %	↓ 52 %	↓ 75 %
Non-nucleoside reverse transcriptase inhibitor: Efavirenz (EFV)	Dolutegravir ↓ EFV ↔	↓ 57 %	↓ 39 %	↓ 75 %
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	Dolutegravir ↓	NS	NS	NS
Protease inhibitor: Atazanavir (ATV)	Dolutegravir ↑ ATV ↔	↑ 91 %	↑ 49 %	↑ 180 %
Protease inhibitor: Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ ATV ↔ RTV ↔	↑ 62 %	↑ 33 %	↑ 121 %
Protease inhibitor: Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ TPV ↔ RTV ↔	↓ 59 %	↓ 47 %	↓ 76 %
Protease inhibitor: Fosamprenavir/ritonavir (FPV + RTV)	Dolutegravir ↓ FPV ↔ RTV ↔	↓ 35 %	↓ 24 %	↓ 49 %
Protease inhibitor: Nelfinavir	Dolutegravir ↔	NS	NS	NS
Protease inhibitor: Lopinavir/ritonavir (LPV + RTV)	Dolutegravir ↔ LPV ↔ RTV ↔	↔	↔	↔
Protease inhibitor: Darunavir/ritonavir (DRV/RTV)	Dolutegravir ↓ DRV ↔ RTV ↔	↓ 32 %	↓ 11 %	↓ 38 %
Nucleoside reverse transcriptase inhibitor: Tenofovir (TDV)	Dolutegravir ↔TDV ↔	NA	NA	NA
Protease inhibitor: Lopinavir/ritonavir + etravirine (LPV/RTV + ETR)	Dolutegravir ↔ LPV ↔ RTV ↔ ETR ↔	↑ 10 %	↑ 7 %	↑ 28 %
Other medicines				
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	NS	NS	NS
Oxcarbazepine Phenytoin Phenobarbitone Carbamazepine St. John's Wort	Dolutegravir ↓	NS	NS	NS
Antacids containing polyvalent cations (e.g. Mg, Al, or Ca)	Dolutegravir ↓	↓ 74 %	↓ 72 %	↓ 74 %
Calcium supplements	Dolutegravir ↓	↓ 39 %	↓ 37 %	↓ 39 %
Iron supplements	Dolutegravir ↓	↓ 54 %	↓ 57 %	↓ 56 %
Metformin	Metformin ↑	N/A	N/A	N/A
Rifampicin	Dolutegravir ↓	↓ 54 %	↓ 43 %	↓ 72 %
Oral contraceptives [ethinyl oestradiol (EE) and norgestromin (NGMN)]	EE ↔	↑ 3 %	↓ 1 %	↑ 2 %
	NGMN ↔	↓ 2%	↓ 11 %	↓ 7 %
Methadone	Methadone ↔	↓ 2 %	↔ 0 %	↓ 1 %

Abbreviations: ↑ = Increase; ↓ = Decrease; ↔ = No significant change; NA = Not applicable; NS = Not studied.

Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter. Dofetilide or pilsicainide co-administration with **REYDIN** is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentrations (see **"CONTRAINDICATIONS"**).

Co-administration of antacids containing polyvalent cations (e.g., Mg, Al, Fe or Ca) decreases dolutegravir plasma concentration. **REYDIN** should not be co-administered with polyvalent cation-containing antacids. **REYDIN** is recommended to be administered 2 hours before or 6 hours after these medicines.

Metformin concentrations may be increased by **REYDIN**. Metformin is contraindicated in patients taking **REYDIN** (see **"CONTRAINDICATIONS"**).

HUMAN REPRODUCTION:

Pregnancy:

REYDIN is contraindicated in human pregnancy and lactation. Neural tube defects have been noted in an observational study in humans, where dolutegravir-based regimens were used at the time of conception and early pregnancy (see **"CONTRAINDICATIONS"**).

Tenofovir, dolutegravir and lamivudine were shown to cross the placenta in reproductive toxicity studies in animals. Late onset neurological disorders, including seizures, have been observed in children who have been exposed to nucleoside analogues such as tenofovir and lamivudine (see **Mitochondrial dysfunction** under **"WARNINGS AND SPECIAL PRECAUTIONS"**).

REYDIN should not be prescribed in women who plan to become pregnant. Women of child-bearing age should not use **REYDIN** unless they are reliably using highly effective contraception. Treatment with **REYDIN** should not be initiated without a medically supervised negative pregnancy test. This test should be repeated at frequent intervals during treatment with **REYDIN**, and especially in the event that pregnancy is suspected.

Lactation:

Mothers breastfeeding their infants should not use **REYDIN**. Lamivudine is excreted in human milk at similar concentrations to those found in serum; tenofovir is excreted in breast milk and it is not known whether dolutegravir is excreted in human milk.

DOSAGE AND DIRECTIONS FOR USE:

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

Adults:

The dose of **REYDIN** is one tablet taken orally, once daily, without regard to food.

Paediatrics:

REYDIN is not recommended for use in patients younger than 18 years of age.

Dose adjustment for renal impairment:

Significantly increased exposure occurred when tenofovir, as in **REYDIN**, was administered to patients with moderate to severe renal impairment (see **"CONTRAINDICATIONS"**).
The pharmacokinetics of tenofovir, as in **REYDIN**, have not been evaluated in non-haemodialysis patients with creatinine clearance < 50 mL/min, therefore, no dosing recommendations is available for these patients. **REYDIN** is not suitable for use in patients with renal impairment with creatinine clearance less than 50 mL/min.

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

SIDE EFFECTS:

REYDIN can have side effects.

Dolutegravir:

Immune system disorders:
Less frequent: Hypersensitivity, immune reconstitution syndrome.

Psychiatric disorders:
Frequent: Insomnia.

Nervous system disorders:
Frequent: Headache, dizziness, abnormal dreams.

Gastrointestinal disorders:
Frequent: Nausea, diarrhoea.
Less frequent: Vomiting, flatulence, upper abdominal pain.
Frequency unknown: Abdominal pain, abdominal discomfort.

Hepatobiliary disorders:
Frequency not known: Hepatitis.

Skin and subcutaneous tissue disorders:
Frequent: Rash, pruritus.

Lamivudine:

The following side effects have been reported during therapy for HIV disease with **REYDIN** tablets alone and in combination with other antiretrovirals:

Blood and lymphatic system disorders:
Less frequent: Neutropenia, anaemia, thrombocytopenia.
Frequency unknown: Pure red cell aplasia.

Metabolism and nutrition disorders:
Frequent: Hyperlactataemia.
Less frequent: Lactic acidosis, lipodystrophy (redistribution / accumulation of body fat) (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Nervous system disorders:
Frequent: Headache, insomnia.
Frequency unknown: Peripheral neuropathy (or paraesthesia), late onset neurological disorders in children exposed *in utero*.

Gastrointestinal disorders:
Frequent: Nausea, vomiting, upper abdominal pain or cramps, diarrhoea.
Less frequent: Pancreatitis, elevations in serum amylase.

Hepatobiliary disorders:
Less frequent: Transient elevations in liver enzymes (AST, ALT).

Skin and subcutaneous tissue disorders:
Frequent: Rash, alopecia.

Musculoskeletal, connective tissue and bone disorders:
Frequent: Arthralgia, muscle disorders.
Less frequent: Rhabdomyolysis, decrease in bone mineral density, osteopenia, fractures.

General disorders and administration site conditions:
Frequent: Fatigue, malaise, fever.

Tenofovir:

Immune system disorders:
Less frequent: Allergic reactions.

Metabolism and nutrition disorders:
Frequency unknown: Hypophosphataemia, lactic acidosis.

Respiratory, thoracic and mediastinal disorders:
Frequency unknown: Dyspnoea.

Gastrointestinal disorders:
Frequent: Anorexia, dyspepsia, flatulence, abdominal pain.
Less frequent: Increased amylase, pancreatitis.

Hepatobiliary disorders:
Frequent: Increased liver enzymes, hepatitis.

Renal and urinary disorders:
Frequent: Renal insufficiency, increased creatinine, proximal renal tubulopathy, renal failure, acute tubular necrosis, nephrogenic diabetes insipidus, proteinuria.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

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 **REYDIN**. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As **REYDIN** is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Lamivudine:

Limited data are available on the consequences of ingestion of acute overdose 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 can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 mL/min. The elimination of tenofovir by peritoneal dialysis has not been studied.

IDENTIFICATION:

Blue coloured, capsule shaped, biconvex film-coated tablet, debossed with 'C' on one side and plain on other side.

PRESENTATION:

Containers of 28: **REYDIN** is packed in a 85 cc white HDPE bottle with 38 mm white non-child resistant cap containing 28 tablets and two silica gel bags of 2 g each, with or without a cardboard carton.

Containers of 30: **REYDIN** is packed in a 85 cc white HDPE bottle with 38 mm white non-child resistant cap containing 30 tablets and two silica gel bags of 2 g each, packed in a cardboard carton.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.
Keep the container tightly closed.
Keep in the original container until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

52/20.2.8/0451.450

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD
Building 9, Parc du Cap,
Mispel Street, Bellville,
7530, RSA

DATE OF PUBLICATION OF THIS PROFESSIONAL INFORMATION:

31 August 2018

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

Cipla

21073749

PATIENT INFORMATION LEAFLET

Information for the Patient about

REYDIN (Film-coated tablets)

SCHEDULING STATUS: S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM:

REYDIN containing dolutegravir 50 mg, lamivudine 300 mg and tenofovir disoproxil 300 mg (film-coated tablets).

Read all of this leaflet carefully before you start taking REYDIN:
- **Keep this leaflet, you may need to read it again.**
- **If you have further questions, please ask your doctor or pharmacist.**
- **REYDIN has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.**

WHAT REYDIN CONTAINS:

The active ingredients in **REYDIN** are dolutegravir (as dolutegravir sodium), lamivudine and tenofovir disoproxil (equivalent to tenofovir disoproxil fumarate).

The other ingredients are croscarmellose sodium, hydroxypropyl methyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose, opadry blue (containing polyvinyl alcohol, talc, titanium dioxide, indigo carmine, glycerol esters of fatty acids, sodium lauryl sulfate, brilliant blue aluminium lake), povidone, sodium starch glycolate.

Contains mannitol 145 mg (sugar).

WARNING:

TOO MUCH ACID IN THE BODY DUE TO LACTIC ACID AND SERIOUS ENLARGED, FATTY LIVER, INCLUDING CASES RESULTING IN DEATH, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES (MEDICINES USED FOR THE TREATMENT OF HIV) ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE "TAKE SPECIAL CARE WITH REYDIN"). REYDIN IS NOT INDICATED FOR TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. THE SAFETY AND EFFICACY OF REYDIN HAS NOT BEEN ESTABLISHED IN PATIENTS INFECTED WITH BOTH HBV AND HIV. SEVERE ACUTE WORSENING OF HEPATITIS B HAS BEEN REPORTED IN PATIENTS WHO ARE INFECTED WITH BOTH HBV AND HIV AND HAVE STOPPED TAKING THE COMBINATION TABLET. LIVER FUNCTION SHOULD BE MONITORED CLOSELY BY A HEALTHCARE PRACTITIONER FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO ARE INFECTED WITH BOTH HIV AND HBV AND WHO STOPPED TAKING THE COMBINATION TABLET. IF APPROPRIATE, MEDICINE TO TREAT HEPATITIS B MAY NEED TO BE PRESCRIBED (SEE "TAKE SPECIAL CARE WITH REYDIN").

WHAT REYDIN IS USED FOR:

REYDIN tablets are used to treat human immunodeficiency virus-1 (HIV-1) infected adults over 18 years of age.

BEFORE YOU TAKE REYDIN:

Do not take REYDIN:
- If you are hypersensitive (allergic) to dolutegravir, lamivudine or tenofovir disoproxil fumarate, or any of the ingredients in **REYDIN** (see **"WHAT REYDIN CONTAINS"**).
- If you have kidney failure.
- If you have liver disease.
- If you are pregnant or breastfeeding your baby.
- If you plan on becoming pregnant.
- If you are a woman of child bearing age and not using effective contraceptives to prevent falling pregnant.
- If you are also taking heart medication for irregular heartbeat containing dofetilide and pilsicainide.
- If you are taking metformin, for the treatment of type 2 diabetes.
- If you are taking chronic medication for hepatitis B infection, containing adefovir dipivoxil.
- If you are taking other anti-retroviral medicine containing didanosine.
- If you are younger than 18 years of age.

Take special care with REYDIN:

Tell your doctor:
- If you develop a rash, or show any general signs of allergy (rash, accompanied by fever, general feeling of being ill, tiredness, muscle or joint aches, sores, oral scrapes, eye infection, facial swelling, a serious liver infection or swelling of the skin).
- If you develop changes in body fat, since changes have been seen in some patients taking **REYDIN** and other anti-HIV medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms and face may also happen. The cause and long-term health effect of these conditions are not known at this time.
- If you show any symptoms of infection while you are taking **REYDIN**. People with advanced HIV infection (AIDS) have weak immune systems and are more likely to develop serious infections (opportunistic infections). When these people start with the treatment, they may find that old hidden infections (such as tuberculosis) flare up, causing signs and symptoms of inflammation (such as localised swelling, area appears red and hot, painful). These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections.
- If you have abnormal metabolic processes, such as increased cholesterol, glucose or lactate in the blood or are resistant to insulin. Your healthcare professional may perform regular blood tests to confirm normal metabolic processes.
- If you have liver problems, including hepatitis B virus (HBV) infection.
- If you show signs of liver injury.
- If you show symptoms such as nausea, vomiting, abdominal pain, non-specific general feeling of being ill, loss of appetite, weight loss, rapid and/or deep breathing, or muscle weakness.
- If you are female, very overweight (obese), or have been taking medicines used for the treatment of HIV for a long time, as you may be more likely to get lactic acidosis (build-up of lactic acid in the body) (see **"POSSIBLE SIDE EFFECTS"**).
- If you suffer from kidney disease.
- If you experience pain in the stomach, as this can be a symptom of pancreatitis (swelling of the pancreas) (see **"POSSIBLE SIDE EFFECTS"**).
- If you suffer from liver disease including hepatitis B or C, as the use of antiviral medicine can cause fatal unfavourable liver symptoms. Your doctor will monitor your liver enzymes as **REYDIN** can cause liver toxicity.
- If your child experiences symptoms of poor growth, loss of muscle coordination, muscle weakness, visual problems, hearing problems, learning disabilities, heart disease, liver disease, kidney disease, gastrointestinal disorders, respiratory disorders, nervous system problems (brain, spine and nerves), loss of voluntary body functions (such as breathing, bladder function, heartbeat and digestive processes) and dementia (loss of memory). It can be a sign of mitochondrial (part of the cell that creates energy) disorder. These findings should be considered for any child exposed to treatment, before being born.
- If you have had bone problems in the past. Your healthcare provider may need to do tests to check your bone mineral density or may prescribe medicines to help your bone mineral density.
- If you experience joint aches and pain, joint stiffness or difficulty in movement. You may suffer from osteonecrosis.
- If you are elderly and suffer from kidney or liver damage or failure.

REYDIN should not be used in children under the age of 18 years. Safety has not been established (see **"BEFORE YOU TAKE REYDIN"**).

REYDIN should be used with caution in the elderly (65 years and over), due to decreased liver and kidney function.

REYDIN should not be taken with other medicine containing any of the active ingredients, namely: dolutegravir, lamivudine or tenofovir disoproxil fumarate (see **"Taking other medicines with REYDIN"**).

REYDIN does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Therefore, it is important to continue to take appropriate precautions to prevent passing HIV to others.

Even if you are receiving treatment for HIV, you are still at risk of contracting other infections and other complications of the HIV infection. Therefore, you should remain under close observation by your doctor.

Pregnancy and breastfeeding:

Do not take **REYDIN** if you are pregnant or breastfeeding (see **"Do not take REYDIN"**). **REYDIN** could seriously harm your unborn child if you fall pregnant while on treatment or if you start taking **REYDIN** in the first few weeks of your pregnancy.

If you are pregnant or breastfeeding your baby, please consult your healthcare professional for advice before taking **REYDIN**. You should ensure that you always use effective contraception while you are taking **REYDIN**. Your healthcare professional can advise you on which contraceptives to take. Never stop taking **REYDIN** without first consulting your healthcare professional as your HIV condition may become worse.

If you are thinking about having a baby, do not stop using **REYDIN** and contraception before you have talked to your healthcare professional. If you think you are pregnant go to your healthcare professional to get a pregnancy test and to be advised on your future HIV treatment and on a pregnancy management plan.

Mothers should not breastfeed their infants while taking **REYDIN**.

If you are pregnant, planning on becoming pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking REYDIN.

Driving and using machinery:

REYDIN may cause dizziness, impaired concentration, and/or drowsiness. You should not drive or operate machinery until you are sure **REYDIN** does not affect your ability to drive or use machines.

Important information about some of the ingredients of REYDIN:

REYDIN contains mannitol and may have a laxative effect.

Taking other medicines with REYDIN:

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines).

If you are taking any of the following medicines, please inform your doctor before taking **REYDIN**:
- Other products that contain dolutegravir, lamivudine or tenofovir, either alone or as combined formulations. **REYDIN** should not be used with these medicines because they contain the same or similar active ingredients as **REYDIN**.
- Rifampicin, used for treatment of tuberculosis, can decrease blood concentrations of **REYDIN**.
- **REYDIN** can increase blood concentrations of metformin (for the treatment of type 2 diabetes), when used simultaneously.
- Other medicines used for the treatment of HIV infections that decrease **REYDIN** levels include efavirenz, nevirapine, ritonavir, tipranavir.
- **REYDIN** can increase levels of the following heart medicine for the treatment of irregular heartbeat – dofetilide and pilsicainide.
- **REYDIN** can increase blood concentration levels of isoniazid used for treatment of tuberculosis.
- Certain antacids can also decrease **REYDIN** levels, that contain for example magnesium, aluminium, iron or calcium.
- **REYDIN** must be taken 2 hours before or 6 hours after taking products containing magnesium, calcium, iron or aluminium.
- **REYDIN** may hinder the breakdown of zalcitabine, also used in the treatment of HIV infections.
- Taking **REYDIN** in combination with high doses of co-trimoxazole or trimethoprim (used for the treatment of bacterial infections) must be avoided if you have a kidney condition or disease.
- The use of **REYDIN** with etravirine for HIV infections is not recommended.
- Medicine that can cause toxicity of the kidneys, for example antibiotics e.g. vancomycin, aminoglycosides (gentamycin, amikacin, tobramycin, neomycin), antifungals (e.g. amphotericin B), antivirals (e.g. foscarnet, ganciclovir), antimicrobials (e.g. pentamidine).
- **REYDIN** increases the levels of atazanavir (also used for the treatment of HIV infection) and may need to be adjusted.
- Phenobarbitone, phenytoin, oxcarbazepine, carbamazepine and St. John's Wort decrease levels of **REYDIN**.
- **REYDIN** increases levels of abacavir used in the treatment of HIV and may need to be adjusted.
- **REYDIN** is not affected and does not influence the levels of emtricitabine, lopinavir and ritonavir used in the treatment of HIV.
- **REYDIN** is not affected and does not change levels of methadone, used in the treatment of opioid abuse.
- Combination medicines for treatment of HIV containing fosamprenavir and ritonavir, or darunavir and ritonavir decrease levels of **REYDIN**.
- Medicines used in the treatment of hepatitis B containing adefovir dipivoxil may increase levels of **REYDIN** in the blood, especially if you have kidney failure. Whereas medicines containing ribavirin used in the treatment of hepatitis B, is not affected and does not alter the levels of **REYDIN**.
- Medicines that contain didanosine. **REYDIN** may increase the amount of didanosine, used for the treatment of HIV, in your blood. You may need to be monitored more carefully if you are taking **REYDIN** and didanosine together. The dose of didanosine may also need to be reduced.

HOW TO TAKE REYDIN:

Do not share your medicine prescribed for you with any other person.

REYDIN therapy should be initiated by a healthcare professional experienced in the management of HIV infections.

Always take REYDIN exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The usual dose of **REYDIN** is one tablet taken orally, once daily, with or without food.

REYDIN can only be used by adults over the age of 18 years.

Your healthcare professional will tell you how long your treatment with **REYDIN** will last. Do not stop treatment early because this may worsen your condition and make your body resistant to the medicine.

If you have an impression that the effect of **REYDIN** is too strong or too weak tell your healthcare professional or pharmacist.

If you take medicine for tuberculosis containing rifampicin, please consult your healthcare professional (see **"Taking other medicines with REYDIN"**).

If you take more REYDIN than you should:

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to take REYDIN:

Do not take a double dose to make up for forgotten individual doses.

POSSIBLE SIDE EFFECTS:

REYDIN can have side effects.

Not all side effects reported for REYDIN are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, please consult your doctor, pharmacist or other healthcare professional for advice.

If you experience any of the following side effects, stop taking **REYDIN** and contact your healthcare professional immediately or go to the casualty department at your nearest hospital:
- Swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing.
- Rash or itching.
- Fainting.
- Yellowing of the skin and eyes, also called jaundice.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **REYDIN**. You may need urgent medical attention or hospitalisation.
- Hypersensitivity reactions:
  - Bronchospasm (sudden constriction of the muscles in the walls of the lungs).
  - Fast or irregular breathing.
  - Puffiness or swelling around the face.
  - Shortness of breath.
  - Sudden decrease in blood pressure.
- Swelling (inflammation) of the liver (hepatitis), that may include the following symptoms:
  - Fatigue.
  - Nausea and vomiting.
  - Stomach pain or discomfort, especially in the area of your liver on your right side, beneath your lower ribs.
  - Clay-coloured bowel movements.
  - Loss of appetite.
  - Low-grade fever.
  - Dark urine.
  - Joint pain.
  - Yellowing of the skin and eyes (jaundice).

These are all serious side effects. You may need urgent medical attention.

Tell your healthcare professional if you notice any of the following:
- Neutropenia (an abnormally low concentration of white blood cells). Symptoms include:
  - Fever.
  - Painful swallowing.
  - Gingival pain.
  - Skin abscesses.
  - Painful ears.
- Anaemia (when you have a low red blood cell count). Symptoms include:
  - Tiredness.
  - Unusually rapid heartbeat.
  - Shortness of breath.
  - Difficulty concentrating.
  - Dizziness.
  - Pale skin.
  - Leg cramps.
  - Sleeplessness.
- If you have a blood clotting problem, symptoms include:
  - Serious bleeding.
  - Purple, red or brown bruises.
- Patients who take **REYDIN** can develop a serious condition called lactic acidosis / hyperlactataemia (build-up of acid in the blood). Symptoms include:
  - You feel very weak or tired.
  - You have unusual (not normal) muscle pain.
  - You have trouble breathing.
  - You have stomach pain with nausea and vomiting.
  - You feel cold, especially in your arms and legs.
  - You feel dizzy or light-headed.
  - You have a fast or irregular heartbeat.
- You may be more likely to get lactic acidosis or liver problems if you are female, very overweight (obese), or have been taking **REYDIN**, for a long time.
- Red blood cell aplasia (decreased number of red blood cells). Symptoms include:
  - Fatigue.
  - Lethargy.
  - Decreased exercise tolerance.
  - Paleness.
- Lipodystrophy – abnormal distribution or loss of body fat in certain areas such as:
  - Increased waist or breast size.
  - Fat accumulation around neck, jaw or upper back (referred to as "moon face" or "buffalo hump").
  - Loss of fat under the skin, most visibly on the face (especially cheeks), arms and legs.
  - Prominent leg veins due to loss of fat under the skin.
- Thrombocytopenia [low levels of platelets (clotting agents in your blood)]. Symptoms include:
  - Bleeding in the skin that looks like tiny red or purple spots on the skin, called petechiae, or bruising.
  - Bleeding outside or inside your body including nosebleeds or bleeding gums.
  - Blood in your urine or bowel movement.
  - Heavy menstrual periods.
- Pancreatitis (swelling of the pancreas). Symptoms include:
  - Stomach pain.
  - Nausea.
  - Vomiting.
  - Abnormal urine tests.
- Rhabdomyolysis (breakdown of muscle fibres that leads to the release of muscle fibre contents into the bloodstream). Symptoms include:
  - Abnormal urine colour (dark, red, or cola coloured).
  - Decreased urine production.
  - General weakness.
  - Muscle stiffness or pain (myalgia).
  - Muscle tenderness.
  - Weakness of the affected muscles.
- Increased levels of amylase, an enzyme that is produced by the pancreas that help breaks down food in the intestines. Symptoms include:
  - Severe abdominal pain.
  - Loss of appetite.
  - Fever and nausea.
- Temporary increase in liver enzymes. Symptoms include:
  - Fatigue.
  - Nausea.
  - Anorexia.
  - Discomfort over the liver area (upper right quadrant of the body).
- Softening of bones and occasionally contributing to breaks.
- Kidney damage or failure that includes the following symptoms:
  - Weakness and shortness of breath.
  - Confusion.
  - Abnormal heart rhythm.
  - Loss of appetite.
  - High blood pressure.

Side effects with **REYDIN** that may occur at the beginning of the treatment. Tell your healthcare professional immediately:
- IRIS (immune reconstitution syndrome): This has been reported in patients treated with combination antiretroviral therapy, such as **REYDIN**. During the initial phase of combination antiretroviral treatment, the patient's immune system response may develop an allergic reaction to other infections, such as *Mycobacterium avium* infection (an infection that can produce severe illness in people with advanced AIDS), cytomegalovirus (a virus), *Pneumocystis jirovecii* pneumonia (or PCP – a severe infection found in people with HIV) or tuberculosis, which may necessitate further evaluation and treatment. Contact your doctor immediately if you experience any of the following, but not limited to the following effects: fever, cough, troubled breathing, blurred vision, painful swallowing, weakness and numbness in the legs, night sweats, weight loss, mouth ulcers or blisters.

The following side effects have frequently been reported. Contact your healthcare professional as soon as possible if you notice any of the following:
- Sleeplessness, headaches, dizziness, abnormal dreams.
- Diarrhoea, nausea, vomiting, upper abdominal pain, abdominal pain, abdominal discomfort, abdominal swelling, cramps, flatulence or wind, loss of appetite, indigestion.
- Rash, itching, hair loss.
- Tiredness, feeling of discomfort, fever, lack of energy.
- Increase in liver enzymes in the blood (ALT and AST), symptoms include tiredness.
- Muscle disorders, painful joints and muscles.
- Damage to or disease affecting nerves, which may harm sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected (peripheral neuropathy).

If you notice any side effects not mentioned in this leaflet, please inform your healthcare professional.

STORAGE AND DISPOSING OF REYDIN:

Store at or below 30 °C.
Keep the container tightly closed.
Keep in the original container until required for use.
Do not store in a bathroom.

STORE ALL MEDICINES OUT OF REACH AND SIGHT OF CHILDREN.

Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

PRESENTATION OF REYDIN:

Containers of 28: **REYDIN** is packed in a 85 cc white HDPE bottle with 38 mm white non-child resistant cap containing 28 tablets and two silica gel bags of 2 g each, with or without a cardboard carton.

Containers of 30: **REYDIN** is packed in a 85 cc white HDPE bottle with 38 mm white non-child resistant cap containing 30 tablets and two silica gel bags of 2 g each, packed in a cardboard carton.

IDENTIFICATION OF REYDIN:

Blue coloured, capsule shaped, biconvex film-coated tablet, debossed with 'C' on one side and plain on other side.

REGISTRATION NUMBER:

52/20.2.8/0451.450

NAME AND ADDRESS OF REGISTRATION HOLDER:

CIPLA MEDPRO (PTY) LTD
Building 9, Parc du Cap,
Mispel Street, Bellville,
7530, RSA

DATE OF PUBLICATION:

31 August 2018

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

Cipla

21073749

PASIËNTINLIGTINGSTUK

Inligting vir die Pasiënt oor

REYDIN (Filmbedekte tablette)

SKEDULERINGSTATUS: S4

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM:
REYDIN bevat dolutegravir 50 mg, lamivudien 300 mg en tenofovir disoproksiel 300 mg (filmbedekte tablette).

Lees hierdie hele inligtingstuk aandagtig voordat u begin om REYDIN te neem:
- **Hou hierdie inligtingstuk, dit mag nodig wees om dit later weer te lees.**
- **Indien u verdere vrae het, vra asseblief u dokter of apteker.**
- **REYDIN is vir u persoonlik voorgeskryf en u moenie u medisyne met ander mense deel nie. Dit mag skadelik wees vir hulle, selfs al het hulle dieselfde simptome as u.**

WAT REYDIN BEVAT:
Die aktiewe bestanddele in **REYDIN** is dolutegravir (as dolutegravir natrium), lamivudien en tenofovir disoproksiel (gelykstaande aan tenofovir disoproksielfumaraat).

Die ander bestanddele is natriumkroskarmellose, hidroksipropiel metielsellulose, magnesiumstearaat, mannitol, mikrokristallyne sellulose, opadry blou (wat polivinielalkohol, talk, titaandioksied, indigokarmyn, gliserolesters van vetsure, natriumlourielsulfaat en briljante blou aluminiumlak bevat), povidoon, natriumstyselglikolaat.

Bevat mannitol 145 mg (suiker).

WAARSKUWING:
OORMATIGE SUUR IN DIE LIGGAAM AS GEVOLG VAN MELKSUUR EN ERNSTIGE VERGROTE, VETTIGE LEWER, INSLUITEND NOODLOTTIGE GEVALLE, IS GEMELD MET DIE GEBRUIK VAN NUKLEOSIED ANALOË (MEDISYNE WAT GEBRUIK WORD VIR DIE BEHANDELING VAN MIV) ALLEEN OF IN KOMBINASIE MET ANDER ANTIRETROVIRALE MIDDELS (SIEN "NEEM SPESIALE SORG MET REYDIN"). REYDIN IS NIE AANGEDUI VIR BEHANDELING VAN CHRONIESE HEPATITIS B-VIRUS (HBV) INFEKSIE NIE. DIE VEILIGHEID EN EFFEKTIWITEIT VAN REYDIN IS NIE BEPAAL IN PASIËNTE WIE MET BEIDE HBV EN MIV GEÏNFEKTEER IS NIE. ERNSTIGE AKUTE VERERGERING VAN HEPATITIS B IS GEMELD IN PASIËNTE WIE MET BEIDE HBV EN MIV GEÏNFEKTEER IS EN OPGEHOU HET OM DIE KOMBINASIETABLET TE NEEM. LEWERFUNKSIE MOET NOUKEURIG GEMONITEER WORD DEUR 'N GESONDHEIDSORG PRAKTISYN VIR TEN MINSTE 'N PAAR MAANDE IN PASIËNTE WIE MET BEIDE MIV EN HBV GEÏNFEKTEER IS EN WIE OPGEHOU HET OM DIE KOMBINASIETABLET TE NEEM. INDIEN TOEPASLIK, SAL MEDISYNE OM HEPATITIS B TE BEHANDEL, VOORGESKRYF WORD (SIEN "NEEM SPESIALE SORG MET REYDIN").

WAARVOOR REYDIN GEBRUIK WORD:
REYDIN tablette word gebruik om volwassenes ouer as 18 jaar wie met menslike immuniteitsgebrekvirus-1 (MIV-1) geïnfekteer is, te behandel.

VOORDAT U REYDIN NEEM:
Moenie REYDIN neem nie:
- Indien u hipersensitief (allergies) is vir dolutegravir, lamivudien of tenofovir disoproksielfumaraat, of enige van die bestanddele van **REYDIN** (sien **"WAT REYDIN BEVAT"**).
- Indien u nierversaking het.
- Indien u lewersiekte het.
- Indien u swanger is of u baba borsvoed.
- Indien u beplan om swanger te raak.
- Indien u 'n vrou in u vrugbare jare is en nie effektiewe voorbehoedmiddels gebruik om te voorkom dat u swanger raak nie.
- Indien u gepaardgaande hartmedikasie vir onreëlmatige hartklop neem wat dofetilied en pilsikaïnied bevat.
- Indien u metformien vir die behandeling van tipe 2-diabetes neem.
- Indien u chroniese medikasie wat adefovir dipivoksiel bevat vir hepatitis B-infeksie neem.
- Indien u ander anti-retrovirale medisyne wat didanosien bevat neem.
- Indien u jonger as 18 jaar is.

Neem spesiale sorg met REYDIN:
Lig u dokter in:
- Indien u 'n uitslag ontwikkel, of enige van die algemene tekens van allergie toon (veluitslag met gepaardgaande koors, algemene gevoel van ongesteldheid, moegheid, knaende spier- of gewrigspyne, sere, mondseertjies, ooginfeksie, gesigswelling, 'n ernstige lewerinfeksie of swelling van die vel).
- Indien u veranderinge in liggaamsvet het, aangesien veranderinge waargeneem is in sommige pasiënte wie **REYDIN** en ander anti-MIV medisyne neem. Hierdie veranderinge kan meer vet in die boonste ruggedeelte by die nek (buffelskof), bors en romp insluit. Dit kan ook gebeur dat u vet van die bene, arms en gesig verloor. Dit is onbekend wat die oorsaak en langtermyn uitwerking hiervan op gesondheid is.
- Indien u enige simptome van infeksie toon terwyl u **REYDIN** neem. Mense met gevorderde MIV-infeksie (VIGS) het swak immuunstelsels en is meer geneig om ernstige infeksies (opportunistiese infeksies) te ontwikkel. Wanneer hierdie mense begin met die behandeling, mag hulle agterkom dat ou verborge infeksies (soos tuberkulose) opvlam, wat tekens en simptome van inflammasie veroorsaak (soos gelokaliseerde swelling, die area lyk rooi en is warm en pynlik). Hierdie simptome word waarskynlik veroorsaak deur die liggaam se immuunstelsel wat sterker word, met die gevolg dat die liggaam begin om hierdie infeksies te beveg.
- Indien u abnormale metaboliese prosesse het, soos verhoogde cholesterol, glukose of laktaat in die bloed, of weerstandig is teen insulien. U gesondheidsorgwerker mag gereelde bloedtoetse uitvoer om normale metaboliese prosesse te bevestig.
- Indien u lewerprobleme het, insluitend hepatitis B-virus (HBV) infeksie.
- Indien u tekens van lewerskade het.
- Indien u simptome soos naarheid, braking, buikpyn, nie-spesifieke algemene gevoel van ongesteldheid, aptytverlies, gewigsverlies, vinnige en/of diep asemhaling, of spierswakheid vertoon.
- Indien u vroulik of baie oorgewig (vetsugtig) is, of vir 'n lang tyd medisyne vir die behandeling van MIV geneem het, aangesien daar dan 'n groter kans is dat u laktaatasidose kan kry (opbou van melksuur in die liggaam) (sien **"MOONTLIKE NEWE-EFFEKTE"**).
- Indien u aan 'n niersiekte ly.
- Indien u pyn in u buik ervaar, aangesien dit 'n simptoom van pankreatitis kan wees (swelling van die pankreas) (sien **"MOONTLIKE NEWE-EFFEKTE"**).
- Indien u lewerprobleme het, insluitend hepatitis B of C, aangesien die gebruik van antivirale medisyne ongunstige lewersimptome kan veroorsaak, wat dodelik mag wees. U dokter sal u lewerensieme monitor aangesien **REYDIN** lewertoksisiteit kan veroorsaak.
- Indien u kind simptome soos swak groei, verlies van spierkoördinasie, spierswakheid, sigprobleme, gehoorprobleme, leergestremdheid, hartsiekte, lewersiekte, niersiekte, gastroïntestinale versteurings, asemhalingsversteurings, senuweestelselprobleme (brein, ruggraat en senuwees), verlies van willekeurige liggaamsfunksies (soos asemhaling, blaasfunksie, hartklop en verteringsprosesse) en demensie (geheueverlies) ervaar. Dit kan 'n teken van mitochondriale (die deel van die sel wat energie produseer) versteuring wees. Hierdie bevindings moet in gedagte gehou word vir enige kind wie voor geboorte aan behandeling blootgestel is.
- Indien u in die verlede probleme met u skeletbene gehad het. Dit mag nodig wees dat u professionele gesondheidsorgwerker toetse uitvoer om u beenmineraaldigtheid te bepaal of medisyne voorskryf om u beenmineraaldigtheid te verbeter.
- Indien u seer of pynlike gewrigte, gewrigstyfheid of moeisame beweging ervaar. U mag moontlik aan osteonekrose ly.
- Indien u bejaard is en aan nier- of lewerskade of -versaking ly.

REYDIN moenie gebruik word in kinders jonger as 18-jarige ouderdom nie. Veiligheid is nie bepaal nie (sien **"VOORDAT U REYDIN NEEM"**).

REYDIN moet versigtig gebruik word in bejaardes (65 jaar en ouer), weens verswakte lewer- en nierfunksie.

REYDIN moenie saam met ander medisyne wat enige van die aktiewe bestanddele bevat geneem word nie, naamlik: dolutegravir, lamivudien of tenofovir disoproksielfumaraat (sien **"Neem van ander medisyne saam met REYDIN"**).

REYDIN verminder nie die risiko om MIV aan ander oor te dra deur seksuele kontak of bloedbesmetting nie. Dit is gevolglik belangrik om aan te hou om gepaste voorsorgmaatreëls te neem om te voorkom dat MIV na ander oorgedra word.

Selfs al ontvang u behandeling vir MIV, is daar steeds die risiko dat u ander infeksies en ander komplikasies van die MIV-infeksie kan ervaar. Dit is dus nodig dat u onder toesig van u dokter bly.

Swangerskap en borsvoeding:
Moenie **REYDIN** neem indien u swanger is of borsvoed nie (sien **"Moenie REYDIN neem nie"**). **REYDIN** kan u ongebore kind ernstige skade aandoen indien u swanger raak terwyl u behandeling ontvang, of indien u **REYDIN** begin neem in die eerste paar weke van u swangerskap.

Indien u swanger is of u baba borsvoed, raadpleeg asseblief u professionele gesondheidsorgwerker voordat u **REYDIN** neem. U moet seker maak dat u altyd effektiewe voorbehoeding gebruik terwyl u **REYDIN** neem. U professionele gesondheidsorgwerker kan u raad gee oor watter voorbehoedmiddels om te gebruik. Moet nooit ophou om **REYDIN** te neem sonder om eers u professionele gesondheidsorgwerker te raadpleeg nie, aangesien u MIV-toestand erger kan raak.

Indien u dit oorweeg om swanger te raak, moenie ophou om **REYDIN** en voorbehoedmaatreëls te gebruik voordat u met u professionele gesondheidsorgwerker gepraat het nie. Indien u dink dat u swanger mag wees, moet u na u professionele gesondheidsorgwerker gaan vir 'n swangerskapstoets en vir advies rakende u toekomstige MIV-behandeling en 'n swangerskap bestuursplan.

Moeders moenie hulle kinders borsvoed terwyl hulle **REYDIN** neem nie.

Indien u swanger is, beplan om swanger te raak of u baba borsvoed, raadpleeg asseblief u dokter, apteker of ander professionele gesondheidsorgwerker vir advies voordat u REYDIN neem.

Bestuur en die gebruik van masjinerie:
REYDIN mag duiseligheid, belemmerde konsentrasie en/of lomerigheid veroorsaak. U moenie 'n voertuig bestuur of masjinerie hanteer totdat u seker is dat **REYDIN** nie u vermoë om te bestuur of om masjiene te hanteer beïnvloed nie.

Belangrike inligting oor sommige van die bestanddele van REYDIN:
REYDIN bevat mannitol en mag 'n lakserende uitwerking hê.

Neem van ander medisyne saam met REYDIN:

Stel altyd u professionele gesondheidsorgwerker in kennis indien u enige ander medisyne neem. (Dit sluit aanvullende of tradisionele medisyne in.)

Indien u enige van die volgende medisyne neem, moet u asseblief u dokter inlig voordat u **REYDIN** neem:
- Ander produkte wat dolutegravir, lamivudien of tenofovir bevat, alleen of as kombinasie formulerings. **REYDIN** moenie saam met hierdie medisyne gebruik word nie want dit bevat dieselfde, of soortgelyke, aktiewe bestanddele as **REYDIN**.
- Rifampisien, wat gebruik word vir die behandeling van tuberkulose, kan die bloedkonsentrasies van **REYDIN** verlaag.
- **REYDIN** kan die bloedkonsentrasies van metformien (vir die behandeling van tipe 2-diabetes) verhoog wanneer dit terselfdertyd gebruik word.
- Ander medisyne wat gebruik word vir die behandeling van MIV-infeksies, wat bloedvlakke van **REYDIN** verlaag, sluit in efavirens, nevirapien, ritonavir, tipranavir.
- **REYDIN** kan die bloedvlakke van die volgende hartmedisyne, vir die behandeling van onreëlmatige hartklop, verhoog – dofetilied en pilsikaïnied.
- **REYDIN** kan die bloedkonsentrasie vlakke van isoniasied, wat gebruik word vir die behandeling van tuberkulose, verhoog.
- Sekere teensuurmiddels wat byvoorbeeld magnesium, aluminium, yster of kalsium bevat, kan ook die vlakke van **REYDIN** verlaag.
- **REYDIN** moet 2 uur voor of 6 uur na produkte wat magnesium, kalsium, yster of aluminium bevat geneem word.
- **REYDIN** kan die afbraak van salsitabien, wat ook gebruik word vir die behandeling van MIV-infeksies, belemmer.
- Vermy die gebruik van **REYDIN** in kombinasie met hoë dosisse ko-trimoksasool of trimetoprim (gebruik vir die behandeling van bakteriële infeksies) indien u 'n niertoestand of -siekte het.
- Die gebruik van **REYDIN** saam met etravirien vir MIV-infeksies word nie aanbeveel nie.
- Medisyne wat toksies vir die niere kan wees, byvoorbeeld antibiotika soos vankomisien, aminoglikosiede (gentamisien, amikasien, tobramisien, neomisien), teenswammiddels (bv. amfoterisien B), antivirale middels (bv. foskarnet, gansiklovir), antimikrobiese middels (bv. pentamidien).
- **REYDIN** verhoog die vlakke van atasanavir (wat ook gebruik word vir die behandeling van MIV-infeksie) en dit mag nodig wees om die dosis aan te pas.
- Fenobarbitoon, fenitoïen, okskarbasepien, karbamasepien en Johanneskruid (St. John's Wort) verminder die vlakke van **REYDIN**.
- **REYDIN** verhoog die vlakke van abakavir, wat gebruik word vir die behandeling van MIV en dit mag nodig wees om die dosis aan te pas.
- **REYDIN** word nie geaffekteer nie en beïnvloed nie die vlakke van emtrisitabien, lopinavir en ritonavir wat gebruik word in die behandeling van MIV, nie.
- **REYDIN** word nie geaffekteer nie en verander nie die vlakke van metadoon, wat gebruik word vir die behandeling van opioïedmisbruik, nie.
- Kombinasie medisyne vir die behandeling van MIV wat fosamprenavir en ritonavir, of darunavir en ritonavir bevat, verminder die vlakke van **REYDIN**.
- Medisyne wat gebruik word vir die behandeling van hepatitis B wat adefovir dipivoksiel bevat, kan die bloedvlakke van **REYDIN** verhoog, veral indien u nierversaking het. Terwyl medisyne wat ribavirien bevat, wat gebruik word vir die behandeling van hepatitis B, nie geaffekteer word nie en nie die vlakke van **REYDIN** verander nie.
- Medisyne wat didanosien bevat. **REYDIN** mag die hoeveelheid didanosien, wat gebruik word vir die behandeling van MIV, in u bloed laat toeneem. Dit mag nodig wees dat u noukeuriger gemoniteer word indien u **REYDIN** en didanosien saam neem. Dit mag ook nodig wees om die dosis van didanosien te verlaag.

HOE OM REYDIN TE NEEM:
Moenie medisyne wat vir u voorgeskryf is met enige ander persoon deel nie.
REYDIN-terapie moet geïnisieer word deur 'n professionele gesondheidsorgwerker wat ervare is in die bestuur van MIV-infeksies.

Neem REYDIN altyd presies soos wat u dokter vir u voorgeskryf het. U moet met u dokter of apteker bevestig indien u onseker is.

Die gewone dosis **REYDIN** is een tablet mondeliks geneem, een keer daagliks, met of sonder kos.

REYDIN kan slegs deur volwassenes ouer as 18 jaar gebruik word.

U professionele gesondheidsorgwerker sal u inlig hoe lank u behandeling met **REYDIN** sal duur. Moenie die behandeling vroeg stop nie, aangesien dit u toestand kan vererger en u liggaam weerstandig teen die medisyne kan maak.

Indien u onder die indruk verkeer dat die effek van **REYDIN** te sterk of te swak is, vertel u professionele gesondheidsorgwerker of apteker.

Indien u medisyne vir tuberkulose neem wat rifampisien bevat, raadpleeg asseblief u professionele gesondheidsorgwerker (sien **"Neem van ander medisyne saam met REYDIN"**).

Indien u meer REYDIN geneem het as wat u behoort:
In die geval van oordosering, raadpleeg u dokter of apteker. Indien nie een van hulle beskikbaar is nie, kontak die naaste hospitaal of gifbeheersentrum.

Indien u vergeet om REYDIN te neem:
Moenie 'n dubbele dosis neem om te vergoed vir vergete individuele dosisse nie.

MOONTLIKE NEWE-EFFEKTE:
REYDIN kan newe-effekte hê.
Nie alle newe-effekte wat vir REYDIN gemeld is, word in hierdie inligtingstuk vervat nie. Indien u algemene gesondheid verswak of indien u enige ongunstige effekte ervaar terwyl u hierdie medisyne neem, raadpleeg asseblief u dokter, apteker of ander professionele gesondheidsorgwerker vir advies.

Indien u enige van die volgende newe-effekte ervaar, moet u ophou om **REYDIN** te neem en u professionele gesondheidsorgwerker onmiddellik kontak of na die ongevalle-afdeling by u naaste hospitaal gaan:
- Swelling van die hande, voete, enkels, gesig, lippe, mond of keel, wat dit moeilik kan maak om te sluk of asem te haal.
- Uitslag of gejeuk.
- Floutes.
- Vergeling van die vel en oë, wat ook geelsug genoem word.

Hierdie is almal baie ernstige newe-effekte. Indien u dit ervaar, mag u 'n ernstige allergiese reaksie op **REYDIN** gehad het. U mag dringende mediese sorg of hospitalisasie nodig hê.
- Hipersensitiwiteitsreaksies:
  - Bronchospasma (skielike sametrekking van die spiere in die wande van die longe).
  - Vinnige of onreëlmatige asemhaling.
  - Pofferigheid of swelling rondom die gesig.
  - Kortasemheid.
  - Skielike daling in bloeddruk.
- Swelling (inflammasie) van die lewer (hepatitis), wat die volgende simptome mag insluit:
  - Vermoeidheid.
  - Naarheid en braking.
  - Maagpyn of -ongemak, veral in die omgewing van u lewer aan die regterkant, agter u onderste ribbes.
  - Kleikleurige stoelgange.
  - Aptytverlies.
  - Laegraadse koors.
  - Donker urine.
  - Gewrigspyn.
  - Vergeling van die vel en oë (geelsug).

Hierdie is almal ernstige newe-effekte. U mag dringende mediese sorg nodig hê.

Stel u professionele gesondheidsorgwerker in kennis indien u enige van die volgende opmerk:
- Neutropenie ('n abnormale lae konsentrasie van witbloedselle). Simptome sluit in:
  - Koors.
  - Pyn met sluk.
  - Seer tandvleise.
  - Velabsesse.
  - Seer ore.
- Anemie (wanneer u 'n lae rooibloedseltelling het). Simptome sluit in:
  - Moegheid.
  - Buitengewoon vinnige hartklop.
  - Kortasemheid.
  - Sukkel om te konsentreer.
  - Duiseligheid.
  - Bleek vel.
  - Krampe in die bene.
  - Slaaploosheid.
- Indien u 'n probleem met bloedstolling het, sluit simptome in:
  - Ernstige bloeding.
  - Pers, rooi of bruin kneusplekke.
- Pasiënte wie **REYDIN** neem kan 'n ernstige toestand, naamlik laktaatasidose / hiperlaktatemie (opbou van suur in die bloed) ontwikkel. Simptome sluit in:
  - U voel baie swak of moeg.
  - U het ongewone (abnormale) spierpyn.
  - U sukkel om asem te haal.
  - U het maagpyn met gepaardgaande naarheid en braking.
  - U kry koud, veral u arms en bene.
  - U voel duiselig of lighoofdig.
  - U hart klop vinnig of onreëlmatig.
- U sal meer geneig wees om laktaatasidose of lewerprobleme te ontwikkel indien u vroulik is, erg oorgewig (vetsugtig) is, of **REYDIN** al vir 'n lang tyd neem.
- Rooibloedselaplasie (verminderde aantal rooibloedselle). Simptome sluit in:
  - Moegheid.
  - Lusteloosheid.
  - Verminderde oefentoleransie.
  - Bleekheid.
- Lipodistrofie – abnormale verspreiding of verlies van liggaamsvet in sekere areas soos:
  - Vergroting van middellyf- of borsgrootte.
  - Vetakkumulasie rondom nek, kakebeen of borug (wat na verwys word as "maagesig" of "buffelskof").
  - Verlies van vet onder die vel, meestal sigbaar op die gesig (veral wange), arms en bene.
  - Prominente beenare as gevolg van vetverlies onder die vel.
- Trombositopenie [lae vlakke van bloedplaatjies (stollingsagente in u bloed)]. Simptome sluit in:
  - Bloeding in die vel wat soos klein rooi- of pers kolle op die vel lyk, genaamd petegie, of kneusplekke.
  - Bloeding buite of binne u liggaam, insluitend neusbloeding of bloeiende tandvleis.
  - Bloed in u urine of ontlasting.
  - Swaar maandstonde.
- Pankreatitis (swelling van die pankreas). Simptome sluit in:
  - Maagpyn.
  - Naarheid.
  - Braking.
  - Abnormale urientoetse.
- Rabdomiolise (die afbraak van spiervesels wat aanleiding gee tot die vrystelling van spierveselinhoud in die bloedstroom). Simpome sluit in:
  - Abnormale kleur van die urine (donker, rooi, of kola-kleur).
  - Afname in urienvorming.
  - Algemene swakheid.
  - Spierstyfheid of -pyn (mialgie).
  - Spierteerheid.
  - Swakheid van die aangetaste spiere.
- Verhoogde amilasevlakke, 'n ensiem wat deur die pankreas geproduseer word wat help om voedsel in die ingewande af te breek. Simptome sluit in:
  - Erge buikpyn.
  - Aptytverlies.
  - Koors en naarheid.
- Tydelike toename in lewerensieme. Simptome sluit in:
  - Moegheid.
  - Naarheid.
  - Anoreksie.
  - Ongemak oor die lewerarea (boonste regterkantste kwadrant van die liggaam).
- Versagting van skeletbene, wat per geleentheid kan bydra tot beenbreuke.
- Nierskade of nierversaking wat die volgende simptome insluit:
  - Swakheid en kortasemheid.
  - Verwardheid.
  - Abnormale hartritme.
  - Aptytverlies.
  - Hoë bloeddruk.

Newe-effekte wat met aanvang van behandeling met **REYDIN** kan voorkom. Vertel onmiddellik vir u professionele gesondheidsorgwerker:
- IRIS (immuunheraktivering sindroom): Dit is gemeld in pasiënte wie met kombinasie antiretrovirale terapie, soos **REYDIN**, behandel word. Tydens die aanvangsfase van kombinasie antiretrovirale behandeling, mag die pasiënt se immuunstelsel respons 'n allergiese reaksie op ander infeksies ontwikkel, soos *Mycobacterium avium*-infeksie ('n infeksie wat ernstige siekte kan veroorsaak in mense met gevorderde VIGS), sitomegalovirus ('n virus), *Pneumocystis jirovecii* longontsteking (of PCP – 'n ernstige infeksie wat by mense met MIV voorkom) of tuberkulose, wat verdere evaluering en behandeling mag noodsaak. Kontak u dokter onmiddellik indien u enige van die volgende, maar nie beperk tot die volgende effekte, ervaar: koors, hoes, moeisame asemhaling, dowwe visie, pynlike sluk, swakheid en gevoelloosheid in die bene, nagswete, gewigsverlies, sere of blase in die mond.

Die volgende newe-effekte is dikwels gemeld. Kontak u professionele gesondheidsorgwerker so gou moontlik indien u enige van die volgende opmerk:
- Slaaploosheid, hoofpyne, duiseligheid, abnormale drome.
- Diarree, naarheid, braking, bobuikpyn, buikpyn, buikongemak, swelling van die buik, krampe, winderigheid, verlies aan aptyt, slegte spysvertering.
- Veluitslag, gejeuk, haarverlies.
- Moegheid, gevoel van ongemak, koors, gebrek aan energie.
- Styging in vlakke van lewerensieme (ALT en AST) in die bloed, simptome sluit moegheid in.
- Spiersteurings, pynlike gewrigte en spiere.
- Skade aan of siekte wat senuwees affekteer, wat sensasie, beweging, klier- of orgaanfunksie, of ander aspekte van gesondheid kan benadeel, afhangende van die tipe senuwee wat geaffekteer is (perifere neuropatie).

Indien u enige newe-effekte opmerk wat nie in hierdie inligtingstuk gelys word nie, lig asseblief u professionele gesondheidsorgwerker in.

BERGING EN WEGDOENING VAN REYDIN:
Berg teen of benede 30 °C.
Hou die houer dig geslote.
Berg in die oorspronklike houer tot benodig vir gebruik.
Moenie in die badkamer stoor nie.

BERG ALLE MEDISYNE BUITE BEREIK EN SIG VAN KINDERS.

Neem alle ongebruikte medisyne terug na u apteker.
Moenie ongebruikte medisyne in dreine of rioolstelsels (bv. toilette) weggooi nie.

AANBIEDING VAN REYDIN:

Houers van 28: **REYDIN** word verskaf in 'n 85 cc wit HDPE bottel met 38 mm wit nie-kinderbestande deksel, wat 28 tablette en twee silikajelsakkies van 2 g elk bevat, met of sonder 'n buitenste kartonhouer.

Houers van 30: **REYDIN** word verskaf in 'n 85 cc wit HDPE bottel met 38 mm wit nie-kinderbestande deksel, wat 30 tablette en twee silikajelsakkies van 2 g elk bevat, verpak in 'n buitenste kartonhouer.

IDENTIFIKASIE VAN REYDIN:
Blou, kapsulevormige, bikonvekse filmbedekte tablet, met 'C' aan die een kant ingepers en glad aan die ander kant.

REGISTRASIENOMMER:
52/20.2.8/0451.450

NAAM EN ADRES VAN DIE REGISTRASIEHOUER:
CIPLA MEDPRO (EDMS) BPK
Gebou 9, Parc du Cap,
Mispelstraat, Bellville,
7530, RSA

PUBLIKASIEDATUM:
31 Augustus 2018

Cipla

21073749

SKEDULERINGSTATUS: S4

EIENDOMSNAAM (EN DOSEERVORM):

REYDIN (Filmbedekte tablette)

SAMESTELLING:
Elke **REYDIN** filmbedekte tablet bevat:
Dolutegravir 50 mg (as dolutegravir natrium).
Lamivudien 300 mg.
Tenofovir disoproksiel 300 mg (gelykstaande aan tenofovir disoproksielfumaraat).

Onaktiewe bestanddele: natriumkroskarmellose, hidroksipropiel metielsellulose, magnesiumstearaat, mannitol, mikrokristallyne sellulose, opadry blou (wat polivinielalkohol, talk, titaandioksied, indigokarmyn, gliserolesters van vetsure, natriumlourielsulfaat en briljante blou aluminiumlak bevat), povidoon, natriumstyselglikolaat.

Bevat mannitol 145 mg (suiker).

WAARSKUWING:
LAKTAATASIDOSE EN ERGE HEPATOMEGALIE MET STEATOSE, INSLUITEND NOODLOTTIGE GEVALLE, IS GEMELD MET DIE GEBRUIK VAN NUKLEOSIED ANALOË ALLEEN OF IN KOMBINASIE MET ANDER ANTIRETROVIRALE MIDDELS (SIEN "WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"). REYDIN IS NIE AANGEDUI VIR DIE BEHANDELING VAN CHRONIESE HEPATITIS B-VIRUS (HBV) INFEKSIE NIE. DIE VEILIGHEID EN EFFEKTIWITEIT VAN REYDIN IS NIE BEPAAL IN PASIËNTE WIE TERSELFDERTYD MET HBV EN MIV GEÏNFEKTEER IS NIE. ERNSTIGE AKUTE OPFLIKKERING VAN HEPATITIS B IS GEMELD IN PASIËNTE WIE TERSELFDERTYD MET HBV EN MIV GEÏNFEKTEER IS EN OPGEHOU HET OM DIE KOMBINASIETABLET TE NEEM. LEWERFUNKSIE MOET NOUKEURIG GEMONITEER WORD, MET SOWEL KLINIESE AS LABORATORIUMOPVOLGE VIR TEN MINSTE 'N PAAR MAANDE, IN PASIËNTE WIE TERSELFDERTYD MET MIV EN HBV GEÏNFEKTEER IS EN DIE KOMBINASIETABLET GESTAAK HET. INDIEN TOEPASLIK, MAG DIT NODIG WEES OM ANTI-HEPATITIS B-TERAPIE TE BEGIN (SIEN "WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS").

FARMAKOLOGIESE KLASSIFIKASIE:
A 20.2.8 – Antimikrobiese (chemoterapeutiese) medisyne. Buiten antibiotika. Antivirale middels.

FARMAKOLOGIESE WERKING:
Farmakodinamiese eienskappe:
Dolutegravir:
Dolutegravir inhibeer MIV-integrase deur aan die aktiewe setels van die integrase te bind en die stringoordrag-stap van retrovirale deoksiribonukleïensuur (DNA) integrasie te blokkeer, wat noodsaaklik is vir die MIV-replikasiesiklus. *In vitro* dissosieer dolutegravir stadig vanaf die aktiewe setel van die wilde tipe integrase-DNA-kompleks ($t_{1/2}$ 71 uur).

Weerstandigheid in vitro:
Isolasie uit die wilde tipe MIV-1: Virusse wat hoogs weerstandig is teen dolutegravir is nie tydens MIV-1 passasie waargeneem nie. Tydens wilde tipe MIV-1 passasie in die teenwoordigheid van dolutegravir, is die integrase substitusies S153Y en S153F met ≤ 4,1-voudige veranderings (FC's) vir stam IIIB, of E92Q met FC = 3,1 en G193E met FC = 3,2 vir stam NL432, waargeneem. Addisionele passasie van wilde tipe subtipe B, C en A/G virusse in die teenwoordigheid van dolutegravir, het vir R263K, G118R en S153T geselekteer.

Anti-MIV aktiwiteit teen weerstandige stamme: Omgekeerde transkriptase inhibeerder (RTI)- en protease inhibeerder (PI)-weerstandige stamme: Dolutegravir het ekwivalente kragtigheid teen 2 nie-nukleosied (NN)-RTI-weerstandige, 3 nukleosied (N)-RTI-weerstandige en 2 PI-weerstandige MIV-1 mutante klone (1 drievoudig en 1 sesvoudig) vertoon in vergelyking met die wilde tipe stam.

Integrase inhibeerder-weerstandige MIV-1 stamme: Dolutegravir het anti-MIV aktiwiteit (vatbaarheid) met < 5-voudige verandering (FC) teen 27 van 28 integrase inhibeerder-weestandige mutante virusse met enkel substitusies, insluitend T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R en N155H getoon.

Integrase inhibeerder-weerstandige MIV-2 stamme: Setel-gerigte mutante MIV-2 virusse is gekonstrueer, gebaseer op proefpersone geïnfekteer met MIV-2 en behandel met raltegravir en wie virologiese mislukking getoon het. In die geheel was die MIV-2 FC's wat waargeneem is soortgelyk aan MIV-1 FC's wat vir soortgelyke roete mutasies waargeneem is.

Weerstandigheid in vivo:
Integrase inhibeerder-naïewe pasiënte: Geen integrase inhibeerder (INI)-weerstandige mutasies, of weerstand wat tydens behandeling te voorskyn kom teen die NRTI ruggraat terapie is met dolutegravir 50 mg een keer daagliks in behandeling-naïewe studies geïsoleer nie.

Effek op nierfunksie:
Die effek van dolutegravir op serum kreatinienopruiming (CrCl), glomerulêre filtrasietempo (GFR) met ioheksol as die peiler en effektiewe renale plasmavloei (ERPV) met para-aminohippuraat (PAH) as die peiler is geëvalueer. 'n Klein afname van 10 – 14 % in die gemiddelde serum kreatinienopruiming (CrCl) is binne die eerste week van behandeling met dolutegravir waargeneem. Dolutegravir het geen beduidende uitwerking op glomerulêre filtrasietempo (GFR) of die effektiewe renale plasmavloei (ERPV) nie. *In vitro* studies dui daarop dat die styging in kreatinien wat in kliniese studies waargeneem is, 'n gevolg van die nie-patologiese onderdrukking van die organiese katioontransporteerder 2 (OCT2) in die proksimale nierbuisies, wat die tubulêre sekresie van kreatinien bemiddel.

Lamivudien:
Lamivudien, 'n nukleosied omgekeerde transkriptase inhibeerder (NRTI), is 'n selektiewe inhibeerder van MIV-1 en MIV-2 replikasie *in vitro*. Lamivudien word intrasellulêr na die 5'-trifosfaat gemetaboliseer, wat 'n intrasellulêre halfleeftyd van 16 – 19 uur het. Lamivudien-5'-trifosfaat is 'n swak inhibeerder van die RNA- en DNA-afhanklike aktiwiteite van MIV omgekeerde transkriptase; dit werk deur die ketting van MIV omgekeerde transkripsie te termineer.

Verminderde *in vitro* sensitiwiteit vir lamivudien is gemeld vir MIV-isolate uit pasiënte wie lamivudienterapie ontvang het. Lamivudien-weerstandige MIV-1 mutante is kruisweerstandig vir didanosien en salsitabien. By sommige pasiënte wie met sidovudien plus didanosien of salsitabien behandel is, het isolate wat weerstandig is teen veelvuldige omgekeerde transkriptase inhibeerders, insluitende lamivudien, ontwikkel.

Lamivudien meng nie in met sellulêre deoksinukleotied metabolisme nie en het weinige effek op die soogdiersel en mitochondriale DNA-inhoud.

Tenofovir:
Tenofovir disoproksielfumaraat is 'n asikliese nukleosiedfosfonaat diëster-analoog van adenosienmonofosfaat en word *in vivo* na tenofovir omgeskakel. Dit is 'n nukleosied omgekeerde transkriptase inhibeerder.

Tenofovir word deur sellulêre ensieme gefosforileer om tenofovirdifosfaat te vorm. Tenofovirdifosfaat inhibeer die aktiwiteit van MIV-1 omgekeerde transkriptase deur met die natuurlike substraat deoksiadenosien-5'-trifosfaat te kompeteer en, na inbouing in DNA, deur terminasie van die DNA-ketting. Tenofovirdifosfaat inhibeer soogdier DNA-polimerase α, β, en mitochondriale DNA-polimerase γ swak.

Medisyneweerstandigheid:
MIV-1 isolate met verminderde vatbaarheid vir tenofovir is *in vitro* geselekteer en 'n K65R-mutasie in omgekeerde transkriptase is *in vitro* geselekteer en, by sommige pasiënte, met tenofovir in kombinasie met sekere antiretrovirale medisyne behandel. By behandeling-naïewe pasiënte wie met tenofovir + lamivudien + efavirens behandel is, het virale isolate van 17 % van pasiënte met virologiese mislukking verminderde vatbaarheid vir tenofovir getoon.

By behandeling-ervare pasiënte, het sommige van die pasiënte wie met tenofovir behandel is en waar virologiese mislukking deur week 96 voorgekom het, verminderde vatbaarheid vir tenofovir getoon. Genotipiese analise van die weerstandige isolate het 'n mutasie in die MIV-1 omgekeerde transkriptase geen getoon wat tot die K65R aminosuur substitusie lei.

Kruisweerstandigheid:
Kruisweerstandigheid tussen sekere omgekeerde transkriptase inhibeerders is bekend. Die K65R-mutasie kan ook deur abakavir, didanosien of salsitabien geselekteer word en lei tot verlaagde vatbaarheid vir hierdie medisyne plus lamivudien, emtrisitabien en tenofovir. Tenofovir disoproksielfumaraat moet vermy word in pasiënte met vorige antiretrovirale ervaring met stamme wat die K65R-mutasie huisves. Pasiënte met MIV-1 wat drie of meer timidien-analoog geassosieerde mutasies (TAMs) uitdruk wat óf die M41L óf L210W omgekeerde transkriptase mutasie ingesluit het, het verlaagde vatbaarheid vir tenofovir disoproksielfumaraat getoon.

Antivirale aktiwiteit:
Die *in vitro* antivirale aktiwiteit van tenofovir teen laboratorium- en kliniese isolate van MIV-1 is geassesseer in limfoblastoïede sellyne, primêre monosiet / makrofaagselle en perifere bloed limfosiete. Die IK_{50} (50 % inhibitoriese konsentrasie) waardes vir tenofovir was in die reikwydte van 0,04 μM – 8,5 μM. In medisyne kombinasiestudies van tenofovir met nukleosied omgekeerde transkriptase inhibeerders (abakavir, didanosien, lamivudien, stavudien, salsitabien, sidovudien), nie-nukleosied omgekeerde transkriptase inhibeerders (delavirdien, efavirens, nevirapien), en protease inhibeerders (amprenavir, indinavir, nelfinavir, ritonavir, sakinavir), is additiewe tot sinergistiese effekte waargeneem. Tenofovir het antivirale aktiwiteit *in vitro* teen MIV-1 klades A, B, C, D, E, F, G en O vertoon (IK_{50}-waardes het gewissel van 0,5 μM tot 2,2 μM). Die IK_{50}-waardes van tenofovir teen MIV-2 het gewissel van 1,6 μM tot 4,9 μM.

Farmakokinetiese eienskappe:
Dolutegravir:
Dolutegravir farmakokinetika is soortgelyk tussen gesonde en MIV-geïnfekteerde proefpersone. Die PK veranderlikheid van dolutegravir is laag tot matig. In Fase 1 studies in gesonde proefpersone, het tussen-proefpersoon CVb % vir AOK en C_{maks} oor studies gewissel van -20 tot 40 % en C_T van 30 tot 56 %. Die tussen-proefpersoon PK veranderlikheid van dolutegravir was hoër in MIV-geïnfekteerde proefpersone as gesonde proefpersone. Binne-proefpersoon veranderlikheid (CVw %) is laer as tussen-proefpersoon veranderlikheid.

Absorpsie:
Na orale toediening van dolutegravir, is piek plasmakonsentrasies 2 tot 3 uur na die dosering waargeneem. Met eenmaal daaglikse dosering word farmakokinetiese ewewigstoestand binne ongeveer 5 dae bereik met gemiddelde akkumulasie verhoudings vir AOK, C_{maks} en C_{24h} wat wissel van 1,2 tot 1,5.

Dolutegravir plasmakonsentrasies het op 'n minder as dosis-proporsionele wyse bo 50 mg toegeneem. Dolutegravir is 'n Pgp substraat *in vitro*. Die absolute biobeskikbaarheid van dolutegravir is nie vasgestel nie.

Dolutegravir mag met of sonder voedsel toegedien word. Voedsel het die mate van absorpsie verhoog en die tempo van absorpsie van dolutegravir vertraag. Biobeskikbaarheid van dolutegravir hang van die maaltyd inhoud af: lae-, matige- en hoë-vet maaltye verhoog die dolutegravir $AOK_{(0-\infty)}$ met 33 %, 41 % en 66 %, verhoog C_{maks} met 46 %, 52 % en 67 % en verleng T_{maks} tot 3, 4, en 5 uur vanaf 2 uur onder vastende toestande, onderskeidelik. Hierdie verhogings is nie klinies beduidend nie.

Verspreiding:
Dolutegravir is hoogs gebonde (groter as of gelyk aan 98,9 %) aan menslike plasmaproteïene gebaseer op *in vivo* data en binding is onafhanklik van plasmakonsentrasie van dolutegravir. Die oënskynlike volume van verspreiding (Vd/F) na 50 mg eenmaal daaglikse toediening word beraam as 17,4 L gebaseer op 'n populasie farmakokinetiese analise. Binding van dolutegravir aan plasmaproteïene is onafhanklik van die konsentrasie. Totale bloed en plasma geneesmiddelverwante radioaktiwiteit konsentrasie verhoudings was gemiddeld tussen 0,441 tot 0,535, wat minimale assosiasie van radioaktiwiteit met sellulêre komponente van die bloed aandui. Dit word beraam dat die vrye fraksie dolutegravir in plasma ongeveer 0,2 tot 1,1 % in gesonde proefpersone met matige hepatiese inkorting is, en 0,8 tot 1,0 % in persone met erge renale inkorting en 0,5 % by MIV-1-geïnfekteerde pasiënte. Dolutegravir is teenwoordig in serebrospinale vloeistof (SSV). In 12 behandeling-naïewe proefpersone op dolutegravir 50 mg daagliks plus abakavir/lamivudien, was die mediaan dolutegravir konsentrasie in SSV 13,2 ng/mL (reeks: 3,74 ng/mL tot 18,3 ng/mL) 2 tot 6 uur na-dosis na 16 weke van behandeling. Die kliniese belang van hierdie bevinding is nie vasgestel nie.

Metabolisme:
Dolutegravir word hoofsaaklik via UGT1A1 gemetaboliseer, met 'n bydrae van CYP3A. Dolutegravir is die vernaamste sirkulerende verbinding in plasma. Na 'n enkele orale dosering van [^{14}C] dolutegravir is 53 % van die totale orale dosis onveranderd in die feses uitgeskei. Dit is onbekend of dit geheel of gedeeltelik weens ongeabsorbeerde medisyne of biliêre ekskresie van die glukuronidaat konjugaat is, wat verder afgebreek kan word om die moederverbinding in die lumen van die derm te vorm. Een-en-dertig persent van die totale orale dosis word in die urine uitgeskei, en word verteenwoordig deur 'n eterglukuronied van dolutegravir (18,9 % van die totale dosis), N-dealkileringsmetaboliet (3,6 % van die totale dosis) en 'n metaboliet wat gevorm word deur oksidasie by die bensiel koolstofatoom (3,0 % van die totale dosis). Renale eliminasie van onveranderde geneesmiddel was laag (minder as 1 % van die dosis).

Eliminasie:
Dolutegravir het 'n terminale halfleeftyd van ~14 uur en 'n oënskynlike orale opruiming (CL/F) van 1,0 L per uur gebaseer op populasie farmakokinetiese analise.

Spesiale populasies:
Adolessente:
Die farmakokinetika van dolutegravir by 10 antiretrovirale behandeling-ervare MIV-1 geïnfekteerde adolessente (12 tot 18 jaar oud) het getoon dat dolutegravir 50 mg eenmaal daaglikse dosering tot 'n dolutegravir blootstelling gelei het wat vergelykbaar is met dit wat waargeneem is by volwassenes wie dolutegravir 50 mg eenmaal daagliks ontvang het.

Adolessent farmakokinetiese parameters:

Ouderdom / gewig	Dolutegravir dosis	Geometriese gemiddeld van beramings van dolutegravir farmakokinetiese parameters (CV %)		
		$AOK_{(0-24)}$ μg.h/mL	C_{maks} μg/mL	C_{24} μg/mL
12 tot < 18 jaar ≥ 40 kg[a]	50 mg een keer daagliks[a]	46 (43)	3,49 (38)	0,90 (59)

[a]Een proefpersoon wie 37 kg weeg het 35 mg een keer per dag ontvang.

Bejaardes:
Populasie farmakokinetiese analise van dolutegravir met data van MIV-1 geïnfekteerde volwassenes het getoon dat daar geen klinies relevante effek van ouderdom op dolutegravir blootstelling is nie. Farmakokinetiese data vir dolutegravir in proefpersone > 65-jarige ouderdom is beperk.

Renale inkorting:
Renale opruiming van die onveranderde medisyne is 'n mindere weg van eliminasie vir dolutegravir. 'n Studie van die farmakokinetika van dolutegravir is uitgevoer in proefpersone met erge renale inkorting (CLcr < 30 mL/min). Geen klinies belangrike farmakokinetiese verskille is tussen persone met erge renale inkorting (CLcr < 30 mL/min) en ooreenstemmende gesonde persone waargeneem nie. AOK, C_{maks} en C_{24} van dolutegravir is met 40 %, 23 % en 43 % onderskeidelik verlaag, in vergelyking met ooreenstemmende gesonde persone. Geen dosisaanpassing is nodig vir pasiënte met ingekorte nierfunksie nie. Dolutegravir is nie in pasiënte op dialise bestudeer nie, alhoewel verskille in blootstelling nie verwag word nie.

Hepatiese inkorting:
Dolutegravir word hoofsaaklik deur die lewer gemetaboliseer en geëlimineer. In 'n studie wat 8 proefpersone met matige hepatiese inkorting (Child-Pugh kategorie B telling 7 tot 9) met 8 ooreenstemmende gesonde volwasse kontrolepersone vergelyk het, was die dolutegravir blootstelling na 'n 50 mg enkeldosis soortgelyk tussen die twee groepe. Geen dosisaanpassing is nodig vir pasiënte met geringe tot matige hepatiese inkorting nie. Die effek van erge hepatiese inkorting op die farmakokinetika van dolutegravir is nie bestudeer nie.

Polimorfismes in metaboliserende ensieme:
Daar is geen bewyse dat algemene polimorfismes in metaboliserende ensieme die farmakokinetika van dolutegravir tot 'n klinies beduidende mate wysig nie. In 'n meta-analise wat farmakogenomika monsters versamel in kliniese studies in gesonde proefpersone gebruik het, het persone met UGT1A1 (n = 7) genotipes, wat swak dolutegravir metabolisme oordra, 'n 32 % laer opruiming van dolutegravir en 46 % hoër AOK gehad vergeleke met persone met genotipes wat geassosieer word met normale metabolisme via UGT1A1 (n = 41). Polimorfismes in CYP3A4, CYP3A5 en NR1I2 word nie met verskille in die farmakokinetika van dolutegravir geassosieer nie.

Gesamentlike infeksie met hepatitis B of C:
Populasie farmakokinetiese analise toon dat gesamentlike infeksie met hepatitis C-virus geen klinies relevante effek op die blootstelling aan dolutegravir het nie. Daar is beperkte data vir pasiënte met hepatitis B gesamentlike infeksie.

Lamivudien:
Absorpsie:
Ná orale toediening word lamivudien vinnig geabsorbeer en ekstensief versprei. Absolute biobeskikbaarheid in 12 volwasse proefpersone was 86 % ± 16 % (gemiddeld ± SD) vir die 150 mg tablet en 87 % ± 13 % vir die orale oplossing. Ná orale toediening van 2 mg/kg twee keer per dag aan 9 volwassenes met MIV-1, was die piek serum lamivudienkonsentrasie (C_{maks}) 1,5 ± 0,5 μg/mL (gemiddeld ± SD). Die area onder die plasmakonsentrasie teenoor tyd kurwe (AOK) en C_{maks} het toegeneem in verhouding met die orale dosis oor die reeks van 0,25 tot 10 mg/kg. Die akkumulasie verhouding van lamivudien by MIV-1 positiewe asimptomatiese volwassenes met normale nierfunksie was 1,50 na 15 dae van orale toediening van 2 mg/kg twee keer per dag. Die gemiddelde tyd (T_{maks}) tot maksimum serumkonsentrasie (C_{maks}) is ongeveer 'n uur.

Effek van voedsel op orale absorpsie:
Lamivudien tablette en orale oplossing kan met of sonder voedsel toegedien word. 'n 25 mg lamivudien navorsingsdoseervorm is oraal toegedien aan 12 asimptomatiese, MIV-1-geïnfekteerde proefpersone by 2 geleenthede, een keer in die vastende toestand en een keer met voedsel (1,099 kcal, 75 g vet, 34 g proteïen, 72 g koolhidrate). Absorpsie van lamivudien was stadiger met voedsel (T_{maks}: 3,2 ± 1,3 uur) in vergelyking met die vastende toestand (T_{maks}: 0,9 ± 0,3 uur); C_{maks} met voedsel was 40 % ± 23 % (gemiddeld ± SD) laer as in die vastende toestand. Daar was geen beduidende verskil in sistemiese blootstelling (AOK_{∞}) met voedsel of in die vastende toestand nie.

Verspreiding:
Die skynbare volume van verspreiding na IV toediening van lamivudien aan 20 proefpersone was 1,3 ± 0,4 L/kg, wat daarop dui dat lamivudien in ekstravaskulêre ruimtes versprei word. Volume van verspreiding was onafhanklik van dosis en het nie met liggaamsgewig verband gehou nie.

Binding van lamivudien aan menslike plasmaproteïene is laag (minder as 36 %). *In vitro* studies het getoon dat die hoeveelheid lamivudien wat geassosieer is met eritrosiete tussen 53 % en 57 % gewissel het oor die konsentrasiereeks van 0,1 tot 100 μg/mL en onafhanklik was van konsentrasie.

Metabolisme:
Metabolisme van lamivudien is 'n mindere roete van eliminasie. In die mens is die enigste bekende metaboliet van lamivudien die trans-sulfoksied metaboliet (ongeveer 5 % van 'n orale dosis na 12 uur). Serumkonsentrasies van hierdie metaboliet is nie bepaal nie. Lamivudien word nie beduidend deur CYP450 ensieme gemetaboliseer nie.

Eliminasie:
Die meerderheid lamivudien word onveranderd in urine geëlimineer deur aktiewe organiese kationiese sekresie. In 9 gesonde proefpersone wat 'n enkele 300 mg orale dosis lamivudien ontvang het, was renale opruiming 199,7 ± 56,9 mL/min (gemiddeld ± SD). In 20 MIV-1 geïnfekteerde proefpersone wat 'n enkele IV dosis ontvang het, was renale opruiming 280,4 ± 75,2 mL/min (gemiddeld ± SD), wat 71 % ± 16 % (gemiddeld ± SD) van totale opruiming van lamivudien verteenwoordig.

In meeste enkeldosis proewe in MIV-1 geïnfekteerde persone, HBV-geïnfekteerde persone of gesonde proefpersone met serum monsterneming vir 24 uur na dosering, het die waargenome gemiddelde eliminasie halfleeftyd (t½) van 5 tot 7 uur gewissel. In MIV-1 geïnfekteerde persone was totale opruiming 398,5 ± 69,1 mL/min (gemiddeld ± SD). Orale opruiming en eliminasie halfleeftyd was onafhanklik van dosis en liggaamsgewig oor 'n mondelinge doseringsreeks van 0,25 tot 10 mg/kg.

Geen dosisaanpassing is nodig wanneer dit saam met voedsel toegedien word nie, aangesien lamivudien biobeskikbaarheid onveranderd bly, alhoewel 'n vertraging in T_{maks} en verlaging in C_{maks} waargeneem is. Lamivudien vertoon lineêre farmakokinetika oor die terapeutiese dosisreikwydte en vertoon beperkte binding aan albumien, die belangrikste plasmaproteïen. Eliminasie van lamivudien sal deur ingekorte nierfunksie beïnvloed word.

Gepaardgaande toediening met sidovudien lei tot 'n 13 % toename in sidovudien blootstelling en 'n 28 % toename in piek plasmavlakke. Geen dosisaanpassings is nodig nie, aangesien daar nie gereken word dat dit pasiëntveiligheid beïnvloed nie. Die waarskynlikheid van ongunstige interaksies tussen geneesmiddels en lamivudien is laag weens die beperkte metabolisme en plasmaproteïenbinding en feitlik volledige renale opruiming.

'n Interaksie met trimetoprim, 'n bestanddeel van ko-trimoksasool, veroorsaak 'n 40 % toename in lamivudien blootstelling teen terapeutiese dosisse. Dit vereis nie 'n aanpassing in dosering nie, tensy die pasiënt ook renale inkorting het. Die toediening van ko-trimoksasool met die 3TC/sidovudien kombinasie in pasiënte met renale inkorting moet versigtig geassesseer word. Daar is beperkte data wat dui dat lamivudien die sentrale senuweestelsel penetreer en die serebrospinale vog (SSV) bereik. Die gemiddelde verhouding van SSV / serum lamivudien konsentrasie 2 – 4 uur na orale toediening is ongeveer 0,12. Die volle mate van penetrasie of die verband wat dit met kliniese effektiwiteit het, is onbekend.

Spesiale bevolkings:
Farmakokinetika in kinders:
Oor die algemeen is die farmakokinetika van lamivudien in pediatriese pasiënte soortgelyk aan volwassenes. Die absolute biobeskikbaarheid (ongeveer 55 – 65 %) is egter verminder in pediatriese pasiënte jonger as 12 jaar. Daarbenewens was die sistemiese opruimingswaardes groter by jonger pediatriese pasiënte en verminder met ouderdom en bereik volwasse waardes rondom 12-jarige ouderdom. Onlangse bevindinge dui dat blootstelling in kinders 2 tot < 6 jaar oud met ongeveer 30 % verminder kan word in vergelyking met ander farmakokinetiese data vir pasiënte < 3 maande oud. By neonate wat een week oud was, was lamivudien mondelinge opruiming verminder in vergelyking met pediatriese pasiënte en is waarskynlik weens onvolwasse nierfunksie en veranderlike absorpsie.

Farmakokinetika tydens swangerskap:
Ná orale toediening was die farmakokinetika van lamivudien in laat-swangerskap soortgelyk aan nie-swanger volwassenes. Toediening van lamivudien in diere toksisiteitstudies teen baie hoë dosisse was nie geassosieer met enige groot orgaan-toksisiteit nie. Die klinies relevante effekte wat waargeneem word, was 'n afname in rooibloedseltelling en neutropenie. Lamivudien was nie mutagenies in bakteriële toetse nie, maar het, soos baie nukleosied analoë, aktiwiteit getoon in 'n *in vitro* sitogeniese toets.

Lamivudien was nie genotoksies *in vivo* teen dosisse wat plasma konsentrasies ongeveer 30 – 40 keer hoër as die verwagte kliniese plasmavlakke, gegee het nie. Aangesien die *in vitro* mutagene aktiwiteit van lamivudien nie in *in vivo* toetse bevestig kon word nie, word die gevolgtrekking gemaak dat lamivudien nie 'n genotoksiese gevaar vir pasiënte wie behandeling ondergaan, inhou nie. Daar is tans geen inligting oor die tumorigene risiko in diere nie, en derhalwe moet enige potensiële risiko vir mense opgeweeg word teen die verwagte voordele van behandeling.

Tenofovir disoproksielfumaraat:
Die farmakokinetika van tenofovir disoproksielfumaraat is in gesonde vrywilligers en individue wat met MIV-1 geïnfekteer is, geëvalueer. Die famakokinetiese eienskappe van tenofovir is soortgelyk by hierdie populasies.

Absorpsie:
Tenofovir disoproksielfumaraat is 'n wateroplosbare diëster voorganger-geneesmiddel van die aktiewe bestanddeel tenofovir. Die orale biobeskikbaarheid van tenofovir vanaf tenofovir disoproksielfumaraat by vastende pasiënte is ongeveer 25 %. Ná orale toediening van 'n enkele 300 mg dosis van tenofovir disoproksielfumaraat aan MIV-1 geïnfekteerde proefpersone in die vastende toestand, is maksimum serumkonsentrasies (C_{maks}) binne 1,0 ± 0,4 uur (gemiddeld ± SD) bereik, en C_{maks} en AOK-waardes was 0,30 ± 0,09 μg/mL en 2,29 ± 0,69 μg•hr/mL, onderskeidelik. Die farmakokinetika van tenofovir is dosis-proporsioneel oor 'n doseringsreikwydte van 75 tot 600 mg en word nie deur herhaalde dosering beïnvloed nie.

In 'n enkel-dosis bioekwivalensie studie wat onder nie-vastende toestande uitgevoer was (dosis toegedien met 113,4 g appelsous) in gesonde volwasse vrywilligers, was die gemiddelde C_{maks} van tenofovir 26 % laer vir die orale poeier relatief tot die tabletformulering. Gemiddelde AOK van tenofovir was soortgelyk tussen die orale poeier- en tabletformulerings.

Effek van voedsel op orale absorpsie:
Toediening van tenofovir na 'n hoë-vet maaltyd (~700 tot 1000 kcal, bevattende 40 % tot 50 % vet) verhoog die orale biobeskikbaarheid, met 'n toename in tenofovir $AOK_{0-\infty}$ van ongeveer 40 % en 'n toename in C_{maks} van ongeveer 14 %. Vergeleke met toediening onder vastende toestande, het toediening van tenofovir met 'n ligte maaltyd egter nie 'n beduidende effek op die famakokinetika van tenofovir gehad nie. Voedsel vertraag die tyd tot tenofovir C_{maks} met ongeveer 1 uur. C_{maks} en AOK van tenofovir is 0,33 ± 0,12 μg/mL en 3,32 ± 1,37 μg•hr/mL na veelvoudige dosisse van tenofovir disoproksiel 300 mg een keer daagliks met voedsel, wanneer die maaltyd inhoud nie beheer was nie.

Verspreiding:
In vitro binding van tenofovir aan menslike plasmaproteïene is minder as 0,7 % en 7,2 %, onderskeidelik, oor die tenofovir konsentrasiereikwydte van 0,01 – 25 μg/mL. Die volume van verspreiding by ewewigstoestand is 1,3 ± 0,6 L/kg en 1,2 ± 0,4 L/kg ná intraveneuse toediening van 1,0 mg/kg en 3,0 mg/kg tenofovir.

Metabolisme:
In vitro studies dui aan dat nie tenofovir disoproksiel of tenofovir substrate van CYP450-ensieme is nie. Ná IV-toediening van tenofovir word ongeveer 70 – 80 % van die dosis in die urine herwin as onveranderde tenofovir, binne 72 uur na dosering. Na orale toediening van 'n enkele dosis tenofovir is die terminale eliminasie halfleeftyd van tenofovir ongeveer 17 uur. Na veelvoudige orale dosisse tenofovir 300 mg een keer daagliks (onder gevoede toestande), word 32 ± 10 % van die toegediende dosis oor 24 uur in die urine herwin.

Eliminasie:
Tenofovir word deur 'n kombinasie van glomerulêre filtrasie en aktiewe tubulêre sekresie geëlimineer. Daar mag kompetisie vir eliminasie wees met ander verbindings wat ook deur die niere uitgeskei word.

Spesiale populasies:
Pediatriese en bejaarde pasiënte:
Farmakokinetiese studies is nie in kinders (< 18 jaar) of bejaardes (> 65 jaar) uitgevoer nie.

Hepatiese inkorting:
Die farmakokinetiese eienskappe van tenofovir na 'n enkele 300 mg dosis is geëvalueer in nie-MIV-geïnfekteerde pasiënte met matige tot ernstige hepatiese inkorting. Daar was geen wesenlike veranderinge in die farmakokinetika van tenofovir in pasiënte met hepatiese inkorting in vergelyking met nie-ingekorte pasiënte nie. Dit is nie nodig om die dosering van tenofovir te verander in pasiënte met ingekorte lewerfunksie nie.

Renale inkorting:
Die farmakokinetiese eienskappe van tenofovir is gewysig in pasiënte met renale inkorting. In pasiënte met kreatinienopruiming < 50 mL/min of met eindstadium niersiekte (ESNS) wat dialise benodig, is C_{maks} en $AOK_{0-\infty}$ van tenofovir verhoog. Dit word aanbeveel dat die doseringsinterval vir tenofovir aangepas word in pasiënte met kreatinienopruiming < 50 mL/min of in pasiënte met ESNS wie dialise benodig (sien **"DOSIS EN GEBRUIKSAANWYSINGS"**). Tenofovir word effektief deur hemodialise verwyder, met 'n ekstraksie koëffisiënt van ongeveer 54 %. Ná 'n enkele 300 mg dosis tenofovir het 'n vier-uur hemodialise sessie ongeveer 10 % van die toegediende tenofovir dosis verwyder.

INDIKASIES:
REYDIN is aangedui vir die behandeling van MIV-1-infeksie in volwassenes van 18 jaar en ouer.

KONTRA-INDIKASIES:
REYDIN is teenaangedui in:
- Pasiënte met bekende hipersensitiwiteit vir dolutegravir, lamivudien, tenofovir disoproksielfumaraat of enige van die bestanddele van **REYDIN**.
- Onbeheerde nierversaking (sien **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**).
- Swangerskap en laktasie (sien **"MENSLIKE REPRODUKSIE"**).
- Vroue in hulle vrugbare jare wie nie hoogs effektiewe voorbehoeding gebruik nie.
- Gepaardgaande gebruik met adefovir dipivoksiel.
- Gepaardgaande toediening met dofetilied en pilsikaïnied.
- Gepaardgaande toediening met didanosien.
- Gepaardgaande toediening with metformien.
- Pasiënte jonger as 18-jarige ouderdom.
- Matige en erge hepatiese inkorting.

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS:
Veiligheid en effektiwiteit van die individuele aktiewe bestanddele in verskeie antiretrovirale kombinasie regimens met soortgelyke doserings as bevat in **REYDIN** is vasgestel in kliniese studies vir die behandeling van MIV-pasiënte. Veiligheid en effektiwiteit van die vaste-geneesmiddel kombinasie, soos in **REYDIN**, vir die behandeling van MIV is egter nie in kliniese studies bepaal nie. Die volledige professionele inligting van die ander medisyne wat in kombinasie gebruik word, moet geraadpleeg word voordat terapie begin word.

Metaboliese abnormaliteite:
Kombinasie antiretrovirale terapie, insluitende **REYDIN**, is met metaboliese abnormaliteite soos hipertrigliseridemie, hipercholesterolemie, insulien weerstandigheid, hiperglisemie en hiperlaktatemie geassosieer.

Lipodistrofie:
Kombinasie antiretrovirale terapie, insluitende **REYDIN**, is ook met die herverspreiding / akkumulasie van liggaamsvet, insluitende sentrale obesiteit, dorsoservikale vetvergroting (buffelskof), perifere uittering, uittering van die gesig en borsvergroting by MIV-pasiënte geassosieer.

'n Hoër risiko vir lipodistrofie is geassosieer met individuele faktore soos hoër ouderdom, en met medisyne-verwante faktore soos 'n langer duur van antiretrovirale behandeling en geassosieerde metaboliese steurings. Kliniese ondersoeke behoort evaluasie vir fisieke tekens van vet herverspreiding in te sluit. Vastende serumlipiede en bloedglukosevlakke moet gemoniteer word. Lipiedversteurings moet klinies toepaslik hanteer word. Pasiënte met tekens van lipodistrofie moet deeglik vir kardiovaskulêre risiko geassesseer word.

Immuunheraktivering inflammatoriese sindroom:
Immuunheraktivering inflammatoriese sindroom (IRIS) is 'n immunopatologiese respons weens die vinnige herstel van patogeen-spesifieke immuunresponse op voorafbestaande antigene gekombineer met immuundisregulering, wat kort na aanvang van behandeling met kombinasie antiretrovirale terapie (cART) voorkom. So 'n reaksie presenteer tipies deur paradoksale agteruitgang van opportunistiese infeksies wat behandel word of deur ontbloting van 'n asimptomatiese opportunistiese siekte, dikwels met 'n atipiese inflammatoriese presentering. IRIS ontwikkel gewoonlik binne die eerste drie maande na aanvang van ART en kom meer dikwels voor in pasiënte met 'n lae CD4-telling. Algemene voorbeelde van IRIS reaksies op opportunistiese siektes is tuberkulose, atipiese mikobakteriële infeksies, sitomegalovirus retinitis, *Pneumocystis jirovecii* en kriptokokkale meningitis.

Toepaslike behandeling van die opportunistiese siekte moet ingestel of volgehou word en ART moet voortgesit word. Inflammatoriese manifestasies neem gewoonlik na 'n paar weke af. Erge gevalle mag op glukokortikoïede reageer, maar daar is slegs beperkte bewyse hiervan in pasiënte met tuberkulose IRIS. Outoïmmuunversteurings (soos Graves se siekte, Guillain-Barre-sindroom, polimiositis) is ook as IRIS reaksies gemeld; die aangemelde tyd tot aanvang is egter meer veranderlik en hierdie voorvalle kan baie maande na aanvang van behandeling voorkom.

Osteonekrose:
Alhoewel gereken word dat die etiologie multifaktoriaal is (insluitend gebruik van kortikosteroïede, alkoholgebruik, erge immuunonderdrukking, hoër liggaamsmassa indeks), is gevalle van osteonekrose gemeld, veral in pasiënte met gevorderde MIV-siekte en/of langtermyn blootstelling aan kombinasie antiretrovirale terapie (cART), insluitende die komponente van **REYDIN**. Pasiënte moet aangeraai word om mediese advies te verkry indien hulle seer of pynlike gewrigte, gewrigstyfheid of moeilike beweging ervaar.

Opportunistiese infeksies:
Pasiënte wie **REYDIN** ontvang kan steeds opportunistiese infeksies en ander komplikasies van MIV-infeksie ontwikkel, en moet gevolglik onder noukeurige kliniese waarneming deur dokters wat ervare is in die behandeling van pasiënte met MIV-geassosieerde siekte, bly.

Die risiko vir MIV oordrag na ander:
Pasiënte moet ingelig word dat behandeling met **REYDIN** nie bewys is om die risiko vir oordrag van MIV aan ander deur seksuele kontak of bloedkontaminasie te voorkom nie. Toepaslike voorsorgmaatreëls moet steeds getref word.

Laktaatasidose / erge hepatomegalie met steatose:
Laktaatasidose, gewoonlik geassosieer met hepatiese steatose, insluitend noodlottige gevalle, is met die gebruik van nukleosied analoë, soos in **REYDIN**, gemeld. Vroeë simptome (simptomatiese hiperlaktatemie) sluit benigne simptome van die verteringstelsel (naarheid, braking en abdominale pyn), nie-spesifieke malaise, aptytverlies, gewigsverlies, respiratoriese simptome (vinnige en/of diep asemhaling) of neurologiese simptome (insluitende motoriese swakheid) in. Laktaatasidose het 'n hoë sterftesyfer en mag met pankreatitis, lewerversaking of nierversaking gepaardgaan.

Laktaatasidose kom gewoonlik na 'n paar of verskeie maande van behandeling voor. Behandeling met nukleosied analoë moet gestaak word in die opset van simptomatiese hiperlaktatemie en metaboliese- / laktaatasidose, progressiewe hepatomegalie, of aminotransferase vlakke wat vinnig styg.

Verdagte biochemiese kenmerke sluit matig verhoogde transaminasevlakke, verhoogde laktaatdehidrogenase (LDH) en/of kreatienkinase in. In pasiënte met verdagte simptome of biochemie, moet die veneuse laktaatvlak (normaal < 2 mmol/L) gemeet en soos volg opgetree word:
- Laktaat 2 – 5 mmol/L: monitor gereeld en wees op die uitkyk vir kliniese tekens.
- Laktaat 5 – 10 mmol/L sonder simptome: monitor noukeurig.
- Laktaat 5 – 10 mmol/L met simptome: STOP alle terapie. Sluit ander oorsake uit (bv. sepsis, uremie, diabetiese ketoasidose, tirotoksikose, limfoom).
- Laktaat > 10 mmol/L: STOP alle terapie (80 % mortaliteit in gevallestudies).

Bogenoemde laktaatwaardes is nie noodwendig van toepassing op pediatriese pasiënte nie.

Diagnose van laktaatasidose word bevestig deur metaboliese asidose met 'n vergrote anioongaping en verhoogde laktaatvlak aan te dui. Terapie moet gestaak word by enige asidotiese pasiënt met 'n verhoogde laktaatvlak.

Laktaatasidose en erge hepatomegalie met steatose, insluitend noodlottige gevalle, is met die gebruik van **REYDIN** alleen of in kombinasie, in die behandeling van MIV-infeksie gemeld. Die meeste van hierdie gevalle het by vroue voorgekom. Sorg moet geneem word wanneer **REYDIN** aan pasiënte met bekende risikofaktore vir lewersiekte toegedien word.

Behandeling met **REYDIN** moet onderbreek word in enige pasiënt wie kliniese- of laboratoriumbevindings ontwikkel wat op laktaatasidose of hepatotoksisiteit mag dui. Sorg moet geneem word wanneer nukleosied analoë, soos in **REYDIN**, aan enige pasiënt (veral vetsugtige vroue) met hepatomegalie, hepatitis of ander bekende risikofaktore vir lewersiekte en hepatiese steatose (insluitende sekere medisyne en alkohol) toegedien word. Pasiënte met gepaardgaande hepatitis C-infeksie en wie behandel word met alfa-interferon en ribavirien mag veral 'n risiko hê. Pasiënte met 'n verhoogde risiko moet noukeurig opgevolg word. Gevalle is egter ook gemeld in pasiënte met geen bekende risikofaktore nie.

Pasiënte met 'n verhoogde risiko moet noukeurig opgevolg word. Daar is geen studieresultate wat die effek van **REYDIN** op die kliniese progressie van MIV-1 demonstreer nie.

Mitochondriale disfunksie:
Daar is *in vitro* en *in vivo* getoon dat nukleosied- en nukleotied analoë, soos bevat in **REYDIN**, 'n variërende graad van skade aan mitochondria aanrig. Daar was verslae van mitochondriale disfunksie by MIV-negatiewe babas wat *in utero* en/of nageboortelik aan nukleosied analoë blootgestel is. Die belangrikste ongunstige effekte wat gemeld is, is hematologiese versteurings (anemie, neutropenie) en metaboliese versteurings (hiperlaktatemie, hiperlipidemie). Hierdie effekte is gewoonlik van verbygaande aard. Sommige laat-aanvang neurologiese versteurings is gemeld (hipertonie, konvulsies, abnormale gedrag). Dit is onbekend of hierdie neurologiese versteurings verbygaande of permanent is. Enige fetus wat *in utero* aan nukleosied- en nukleotied analoë blootgestel is, insluitend MIV-negatiewe kinders, moet klinies en met laboratoriumtoetse opgevolg word en moet ten volle ondersoek word vir moontlike mitochondriale disfunksie in geval van relevante tekens of simptome.

Pankreatitis:
Pankreatitis is by sommige pasiënte waargeneem wie lamivudien, soos in **REYDIN**, ontvang. Dit is nie duidelik of dit weens lamivudien of die onderliggende MIV-siekte is nie. Pankreatitis moet oorweeg word wanneer 'n pasiënt buikpyn, naarheid, braking of verhoogde biochemiese merkers ontwikkel. Staak behandeling met **REYDIN** totdat 'n diagnose van pankreatitis uitgesluit is.

Pasiënte met matige tot erge renale inkorting:
In pasiënte met matige tot erge renale inkorting, is die terminale halfleeftyd van **REYDIN** verleng weens die verminderde opruiming. Die dosis van **REYDIN** moet gevolglik aangepas word (sien **"DOSIS EN GEBRUIKSAANWYSINGS"**).

Lewersiekte:
Behandeling met **REYDIN** kan tot hepatomegalie weens nie-alkoholiese vettige lewersiekte (hepatiese steatose) lei. Die veiligheid en effektiwiteit van **REYDIN** is nie in pasiënte met beduidende onderliggende lewerversteurings bepaal nie. Pasiënte met voorafbestaande lewerdisfunksie, insluitend chroniese aktiewe hepatitis, het 'n verhoogde frekwensie van lewerfunksie abnormaliteite gedurende kombinasie antiretrovirale terapie en moet volgens standaardpraktyk gemoniteer word. Indien daar bewyse is dat die lewersiekte vererger in sulke pasiënte, moet dit oorweeg word om die behandeling tydelik of permanent te staak.

Renale inkorting:
REYDIN is 'n kombinasie medisyne en die dosis van die individuele komponente kan nie gewysig word nie. Tenofovir en lamivudien word hoofsaaklik deur die niere uitgeskei. **REYDIN** word nie aanbeveel vir pasiënte met kreatinienopruiming < 50 mL/min of vir pasiënte wie hemodialise benodig nie. Renale inkorting, insluitende gevalle van akute nierversaking en Fanconi se sindroom (renale tubulêre skade met erge hipofosfatemie), is met die gebruik van tenofovir disoproksielfumaraat in kliniese praktyk gemeld. Noukeurige monitering van nierfunksie (serumkreatinien en serumfosfaat) word dus aanbeveel voordat **REYDIN** geneem word.

Nierfunksie:
Aangesien **REYDIN** hoofsaaklik deur die niere uitgeskei word, mag gesamentlike toediening van **REYDIN** met medisyne wat nierfunksie verlaag of kompeteer vir aktiewe tubulêre sekresie die serum konsentrasies van **REYDIN** verhoog en/of die konsentrasies van ander medisyne wat deur die niere uitgeskei word, verhoog. Sommige voorbeelde sluit in, maar is nie beperk tot adefovir dipivoksiel, sidofovir, asiklovir, valasiklovir, gansiklovir en valgansiklovir.

Renale veiligheid met tenofovir is slegs tot 'n baie beperkte mate in volwasse pasiënte met ingekorte nierfunksie (kreatinienopruiming < 80 mL/min) bestudeer.

Monitering van nierfunksie:
Dit word aanbeveel dat nierfunksie (kreatinienopruiming en serumfosfaat) geassesseer word in alle pasiënte voordat terapie met tenofovir disoproksielfumaraat begin word en dat dit ook elke vier weke tydens die eerste jaar van behandeling met tenofovir disoproksielfumaraat gemoniteer word, en daarna elke drie maande. In pasiënte wie 'n risiko vir ingekorte nierfunksie het, insluitend pasiënte wie vantevore renale voorvalle ondervind het terwyl adefovir dipivoksiel geneem is, moet dit oorweeg word om nierfunksie meer gereeld te monitor.

Gepaardgaande toediening en risiko vir renale toksisiteit:
Die gebruik van tenofovir disoproksielfumaraat moet vermy word met gepaardgaande of onlangse gebruik van 'n nefrotoksiese medisyne (bv. aminoglikosiede, amfoterisien B, foskarnet, gansiklovir, pentamidien, vankomisien, sidofovir of interleukien-2). Indien dit onvermydelik is om tenofovir disoproksielfumaraat en nefrotoksiese medisyne gesamentlik te gebruik, behoort nierfunksie weekliks gemoniteer te word.

Tenofovir disoproksielfumaraat is nie klinies geëvalueer in pasiënte wie medisyne ontvang wat deur dieselfde renale weg uitgeskei word nie, insluitende die transportproteïene menslike organiese anioon transporteerder (hOAT) 1 en 3 of MRP 4 (bv. sidofovir, 'n medisyne wat bekend is dat dit nefrotoksies is). Hierdie renale transportproteïene mag verantwoordelik wees vir tubulêre sekresie en deels vir die renale eliminasie van tenofovir en sidofovir. Die farmakokinetika van hierdie medisyne wat deur dieselfde renale weg uitgeskei word, insluitende transportproteïene hOAT 1 en 3 of MRP 4, mag gevolglik gewysig word indien dit gesamentlik toegedien word. Tensy dit regtig nodig is, word gepaardgaande gebruik van hierdie medisyne wat deur dieselfde renale weg uitgeskei word nie aanbeveel nie, maar indien dit onvermydelik is, moet nierfunksie weekliks gemoniteer word.

REYDIN moet vermy word met gepaardgaande of onlangse gebruik van 'n nefrotoksiese medisyne. Pasiënte met 'n risiko vir, of met 'n geskiedenis van nierdisfunksie en pasiënte wie nefrotoksiese middels terselfdertyd ontvang moet noukeurig vir veranderinge in serumvlakke van kreatinien en fosfor gemoniteer word.

K65R-mutasie:
REYDIN moet vermy word in antiretrovirale behandeling-ervare pasiënte wie MIV-1 het wat die K65R-mutasie huisves.

Beenmineraaldigtheid:
Afnames in beenmineraaldigtheid van die werwels en veranderinge in been-biomerkers vanaf die basislyn is beduidend groter met tenofovir disoproksielfumaraat, soos bevat in **REYDIN**. Afnames in beenmineraaldigtheid van die heup is beduidend groter. Klinies relevante beenfrakture is gemeld. Indien been-abnormaliteite vermoed word, moet toepaslike konsultasie verkry word. Beenmonitering moet oorweeg word vir MIV-geïnfekteerde pasiënte wie 'n geskiedenis van patologiese beenbreuk of 'n risiko vir osteopenie het.

REYDIN mag 'n verlaging in beenmineraaldigtheid veroorsaak. Dit is tans onbekend wat die effek van tenofovir disoproksielfumaraat geassosieerde veranderinge in beenmineraaldigtheid op langtermyn beengesondheid en toekomstige risiko vir frakture is.

Dit moet oorweeg word om beenmineraaldigtheid te monitor in MIV-geïnfekteerde pasiënte met 'n geskiedenis van patologiese beenfraktuur of met 'n risiko vir osteopenie. Alhoewel die uitwerking van aanvulling met kalsium en vitamien D nie bestudeer is nie, mag sodanige aanvulling vir alle pasiënte voordelig wees. Indien abnormaliteite van die been vermoed word, moet toepaslike konsultasie verkry word.

Beenabnormaliteite (wat ongereeld bydra tot frakture) kan met proksimale renale tubulopatie geassosieer word.

Pasiënte met MIV en hepatitis B- of C-virus gesamentlike infeksie:
REYDIN word nie aangedui vir die behandeling van HBV-infeksie nie. Die veiligheid en effektiwiteit van **REYDIN** is nie bepaal vir die behandeling van pasiënte met gesamentlike HBV en MIV-infeksie nie.

Pasiënte met chroniese hepatitis B of C wie antiretrovirale terapie ontvang, het 'n hoër risiko vir ernstige en potensieel noodlottige hepatiese ongunstige reaksies. Mediese praktisyns moet na huidige MIV-behandelingsriglyne verwys vir die optimale bestuur van MIV-infeksie in pasiënte wie gesamentlik met hepatitis B-virus (HBV) geïnfekteer is. In geval van gelyktydige antivirale terapie vir hepatitis B of C, verwys asseblief ook na die betrokke professionele inligting vir hierdie medisyne.

Pasiënte met chroniese hepatitis B of C wat met **REYDIN** behandel word, het 'n hoër risiko vir ernstige en potensieel noodlottige hepatiese ongunstige reaksies. Dokters moet verwys na huidige MIV-behandelingsriglyne vir die optimale bestuur van MIV-infeksie in pasiënte wie gesamentlik met hepatitis B-virus (HBV) geïnfekteer is.

Verergering van hepatitis:
Opflikkerings tydens behandeling:
Spontane opflikkerings van chroniese hepatitis B is relatief algemeen en word gekenmerk deur verbygaande stygings in serum ALT. Nadat antivirale terapie begin is, mag serum ALT in sommige pasiënte toeneem. In pasiënte met gekompenseerde lewersiekte, gaan hierdie stygings in serum ALT gewoonlik nie gepaard met 'n styging in serum bilirubien konsentrasies of hepatiese dekompensasie nie. Pasiënte met sirrose mag 'n groter risiko vir hepatiese dekompensasie hê na opflikkering van hepatitis en moet gevolglik noukeurig gemoniteer word tydens terapie.

Opflikkerings na staking van behandeling:
Akute opflikkerings van hepatitis is in pasiënte gemeld na staking van hepatitis B-terapie. Opflikkerings na-behandeling gaan gewoonlik gepaard met 'n toename in HBV DNA, en dit blyk dat die meerderheid selfbeperkend is. Hewige opflikkerings, insluitende sterfgevalle, is egter gemeld. Lewerfunksie moet met herhaalde intervalle gemoniteer word met sowel kliniese as laboratoriumopvolge vir ten minste 6 maande na staking van hepatitis B-terapie. Indien toepaslik, kan dit nodig wees om hepatitis B-terapie te hervat. In pasiënte met gevorderde lewersiekte of sirrose word staking van behandeling nie aanbeveel nie aangesien opflikkerings van hepatitis na-behandeling lewerdekompensasie kan veroorsaak. Lewer opflikkerings is veral ernstig en soms dodelik in pasiënte met gedekompenseerde lewersiekte.

Hipersensitiwiteitsreaksies:
Hipersensitiwiteitsreaksies is gemeld met integrase inhibeerders, insluitend dolutegravir en is gekenmerk deur veluitslag, konstitusiebevindinge en soms orgaandisfunksie, insluitend lewerskade. Staak **REYDIN** en ander verdagte middels onmiddellik indien tekens of simptome van hipersensitiwiteitsreaksies ontwikkel (insluitend maar nie beperk tot ernstige uitslag of uitslag met gepaardgaande koors, algemene malaise, moegheid, spier- of gewrigspyne, blase, orale letsels, konjunktivitis, gesigedeem, hepatitis, eosinofilie, angioedeem). Kliniese status, insluitende lewer aminotransferases, moet gemoniteer word en toepaslike terapie geïnisieer word. Vertraagde staking van behandeling met **REYDIN**, of ander verdagte middels, na die aanvang van hipersensitiwiteit kan tot 'n lewensdreigende reaksie lei.

Gebruik in pediatriese pasiënte:
Veiligheid en effektiwiteit in pediatriese pasiënte en pasiënte < 18-jarige ouderdom is nie bepaal nie.

Gebruik in bejaarde pasiënte:
Kliniese studies het nie 'n voldoende aantal proefpersone van 65 jaar en ouer ingesluit om te bepaal of hulle anders as jonger persone reageer nie.

Effek op die vermoë om te bestuur en masjiene te gebruik:
REYDIN kan duiseligheid, belemmerde konsentrasie en/of lomerigheid veroorsaak en kan die vermoë om te bestuur en masjiene te gebruik affekteer. Pasiënte moet seker maak dat hulle nie 'n voertuig bestuur of masjiene gebruik voordat hulle weet hoe **REYDIN** hul affekteer nie.

INTERAKSIES:
Die waarskynlikheid van interaksies is laag weens die beperkte metabolisme en plasmaproteïenbinding, en feitlik volledige renale opruiming. Plasmavlakke van sidovudien word nie beduidend gewysig wanneer dit saam met lamivudien toegedien word nie. Sidovudien het geen effek op die farmakokinetika van lamivudien nie. Lamivudien mag die intrasellulêre fosforilasie van salsitabien inhibeer wanneer die twee medisyne gelyktydig gebruik word. Lamivudien word dus nie aanbeveel om in kombinasie met salsitabien gebruik te word nie. Toediening van trimetoprim, 'n bestanddeel van ko-trimoksasool, veroorsaak 'n styging in die plasmavlakke van lamivudien. Tensy die pasiënt ingekorte nierfunksie het, is dit egter nie nodig om die dosis van lamivudien aan te pas nie. Lamivudien het geen effek op die farmakokinetika van ko-trimoksasool nie. Die moontlikheid van interaksies met ander medisyne wat gesamentlik toegedien word moet oorweeg word, veral wanneer dit hoofsaaklik deur die niere uitgeskei word.

Geen medisyne interaksiestudies is met **REYDIN** uitgevoer nie. Aangesien **REYDIN** tenofovir disoproksielfumaraat en lamivudien bevat, mag enige interaksies wat met hierdie individuele medisyne geïdentifiseer is ook met **REYDIN** voorkom. Belangrike inligting oor medisyne interaksies vir **REYDIN** word in Tabelle 1, 2 en 3 opgesom. Die medisyne interaksies wat beskryf word is gebaseer op studies wat met tenofovir disoproksielfumaraat of lamivudien as individuele medisyne uitgevoer is, of is potensiële medisyne interaksies. Alhoewel die tabelle moontlik beduidende interaksies bevat, is dit nie allesomvattend nie. Gebaseer op die resultate van *in vitro* eksperimente en die eliminasieroete van tenofovir wat bekend is, is die potensiaal vir CYP450-bemiddelde interaksies wat tenofovir behels met ander medisyne, laag.

'n Interaksie met trimetoprim, 'n bestanddeel van ko-trimoksasool, veroorsaak 'n 40 % toename in lamivudien blootstelling teen terapeutiese dosisse. Dit vereis nie 'n aanpassing in dosering nie, tensy die pasiënt ook renale inkorting het. Toediening van ko-trimoksasool saam met die lamivudien/sidovudien kombinasie in pasiënte met ingekorte nierfunksie moet versigtig geassesseer word.

Tenofovir:
Medisyne wat renaal geëlimineer word:
Tenofovir, soos in **REYDIN**, word hoofsaalik deur die niere uitgeskei deur 'n kombinasie van glomerulêre filtrasie en aktiewe tubulêre sekresie. Gepaardgaande toediening van **REYDIN** saam met medisyne wat deur aktiewe tubulêre sekresie geëlimineer word, mag serumkonsentrasies van óf tenofovir óf die gepaardgaande medisyne verhoog weens kompetisie vir hierdie roete van eliminasie. Medisyne wat nierfunksie verminder mag ook serumkonsentrasies van tenofovir, soos in **REYDIN**, verhoog.

Tenofovir is geëvalueer in gesonde vrywilligers in kombinasie met abakavir, adefovir dipivoksiel, atasanavir, didanosien, efavirens, emtrisitabien, indinavir, lamivudien, lopinavir/ritonavir, metadoon, orale voorbehoedmiddels en ribavirien. Tabelle 1 en 2 som die farmakokinetiese effekte van medisyne wat gelyktydig toegedien word op tenofovir farmakokinetika, en effekte van tenofovir op die farmakokinetika van medisyne wat gelyktydig toegedien word, op.

Wanneer dit saam met veelvoudige dosisse tenofovir toegedien word, het die C_{maks} en AOK van didanosien 400 mg beduidend toegeneem. Die meganisme van hierdie interaksie is onbekend. Wanneer didanosien 250 mg enteries-bedekte kapsules saam met tenofovir toegedien word, was sistemiese blootstellings aan didanosien soortgelyk aan daardie wat met die 400 mg enteries-bedekte kapsules alleen onder vastende toestande, gesien is.

Tabel 1:
Medisyne interaksies: Veranderinge in farmakokinetiese parameters vir tenofovir[1] in die teenwoordigheid van medisyne wat gesamentlik toegedien word:

Medisyne wat gesamentlik toegedien word	Dosis van medisyne wat gesamentlik toegedien word (mg)	N	% Verandering van tenofovir farmakokinetiese parameters[2] (90 % VI)		
			C_{maks}	AOK	C_{min}
Abakavir	300 een keer	8	↔	↔	NC
Adefovir dipivoksiel	10 een keer	22	↔	↔	↔
Atasanavir	400 een keer daagliks x 14 dae	33	↑ 14 (↑ 8 tot ↑ 20)	↑ 24 (↑ 21 tot ↑ 28)	↑ 22 (↑ 15 tot ↑ 30)
Didanosien (enteries-bedek)	400 een keer	25	↔	↔	↔
Didanosien (gebuffer)	250 of 400 een keer daagliks x 7 dae	14	↔	↔	↔
Efavirens	600 een keer daagliks x 14 dae	29	↔	↔	↔
Emtrisitabien	200 een keer daagliks x 7 dae	17	↔	↔	↔
Indinavir	800 drie keer daagliks x 7 dae	13	↑ 14 (↓ 3 tot ↑33)	↔	↔
Lamivudien	150 twee keer daagliks x 7 dae	15	↔	↔	↔
Lopinavir/ Ritonavir	400/100 twee keer daagliks x 14 dae	24	↔	↑ 32 (↑ 25 tot ↑ 38)	↑ 51 (↑ 37 tot ↑ 66)

Pasiënte het tenofovir DF 300 mg een keer daagliks ontvang
1. Toename = ↑; Afname = ↓; Geen effek = ↔; NC = Nie bereken nie

Na herhaalde dosering aan MIV-negatiewe proefpersone wat of chroniese metadoon instandhoudingsterapie, orale voorbehoedmiddels, of enkeldosisse ribavirien ontvang het, was die farmakokinetika van tenofovir by ewewigstoestande soortgelyk aan dit wat in vorige studies waargeneem is, wat dui op 'n gebrek aan klinies beduidende medisyne interaksies tussen hierdie medisyne en tenofovir disoproksielfumaraat.

Tabel 2:
Medisyne interaksies: Veranderinge in farmakokinetiese parameters vir medisyne wat gesamentlik toegedien word in die teenwoordigheid van tenofovir:

Medisyne wat gesamentlik toegedien word	Dosis van medisyne wat gesamentlik toegedien word (mg)	N	% Verandering van die medisyne wat gesamentlik toegedien word se farmakokinetiese parameters[1]		
			C_{maks}	AOK	C_{min}
Abakavir	300 een keer	8	↑ 122 (↑ 1 tot ↑ 26)	↔	NA
Adefovir dipivoksiel	10 een keer	22	↔	↔	NA
Efavirens	600 mg een keer daagliks x 14 dae	30	↔	↔	↔
Emtrisitabien	200 mg een keer daagliks x 7 dae	17	↔	↔	↔
Indinavir	800 mg drie keer daagliks x 7 dae	12	↑ 14 (↓ 3 tot ↑33)	↔	↔
Lamivudien	150 mg twee keer daagliks x 7 dae	15	↔	↔	↔
Lopinavir/ Ritonavir	400/100 mg twee keer daagliks x 14 dae	21	↔	↔	↔
Metadoon[2]	40 – 110 een keer daagliks x 14 dae[3]	13	↔	↔	↔
Orale voorbehoedmiddels[4]	Etinielestradiol/ norgestimaat (Ortho-Tricyclen®) Een keer daagliks x 7 dae	20	↔	↔	↔
Ribavirien	600 een keer	22	↔	↔	NA
Ritonavir	Lopinavir/ritonavir 400/100 twee keer daagliks x 14 dae	24	↔	↔	↔
Atasanavir[5]	400 een keer daagliks x 14 dae	29	↔	↔	↔
Atasanavir[5]	Atazanavir/ritonavir 300/100 een keer daagliks x 42 dae	10	↑ 28 (↑ 50 tot ↑ 5)	↑ 25 (↑ 42 tot ↑ 3)	↑ 23[6] (↑ 46 tot ↑ 10)

Toename = ↑; Afname = ↓; Geen effek = ↔; NA = Nie van toepassing nie
1. R-(aktief), S- en totale metadoon blootstellings was ekwivalent wanneer dit alleen gedoseer is of met tenofovir as tenofovir disoproksielfumaraat 300 mg.
2. Individuele proefpersone is op hul stabiele metadoon dosis instand gehou. Geen farmakodinamiese wysigings (opiaattoksisiteit of tekens of simptome van onttrekking) is gemeld nie.
3. Etinielestradiol en 17-deasetielnorgestimaat (die farmakologies aktiewe metaboliet) blootstellings was ekwivalent wanneer dit alleen gedoseer is of saam met tenofovir as tenofovir disoproksielfumaraat 300 mg.
4. Reyataz VSA voorskrywersinligting (Bristol-Meyers Squibb).
5. In MIV-geïnfekteerde pasiënte het byvoeging van tenofovir disoproksielfumaraat by atasanavir 300 mg plus ritonavir 100 mg, gelei tot AOK en C_{min}-waardes van atasanavir wat 2,3- en 4-voudig onderskeidelik hoër was as die waardes wat waargeneem is vir atasanavir 400 mg wanneer dit alleen toegedien is.

Lamivudien:
Die waarskynlikheid van metaboliese interaksies is laag weens beperkte metabolisme en plasmaproteïenbinding en feitlik volledige renale opruiming.

Plasmavlakke van sidovudien word nie beduidend verander wanneer dit gepaardgaande met **REYDIN** toegedien word nie. Sidovudien het geen effek op die farmakokinetika van **REYDIN** nie.

Tabel 3:
Medisyne interaksie: Veranderinge in farmakokinetiese parameters vir medisyne wat gesamentlik toegedien word in die teenwoordigheid van lamivudien.

Medisyne wat gesamentlik toegedien word	Dosis van medisyne wat gesamentlik toegedien word (mg)	% Verandering van die medisyne wat gesamentlik toegedien word se farmakokinetiese parameters[1]		
		C_{maks}	AOK	C_{min}
Trimetopriem/ Sulfametoksasool	160/800 mg	NS	↑ 40	NS
Sidovudien	150/300 mg twee keer daagliks	↑ 28	↑ 13	NS

Toename = ↑; NS = Nie bestudeer nie

Gepaardgaande toediening met sidovudien veroorsaak 'n 13 % toename in sidovudien blootstelling en 'n 28 % styging in piek plasmavlakke. Geen dosisaanpassings is nodig nie, aangesien daar nie gereken word dat dit pasiëntveiligheid beïnvloed nie.

REYDIN mag die intrasellulêre fosforilasie van salsitabien inhibeer wanneer die twee medisyne terselfdertyd gebruik word. **REYDIN** word gevolglik nie vir gebruik in kombinasie met salsitabien aanbeveel nie.

Toediening van trimetopriem, 'n bestanddeel van ko-trimoksasool, veroorsaak 'n styging in die plasmavlakke van **REYDIN**. Tensy die pasiënt se nierfunksie ingekort is, is dit nie nodig om die dosis van **REYDIN** aan te pas nie. **REYDIN** het geen effek op die farmakokinetika van ko-trimoksasool nie.

Die moontlikheid van interaksies met ander medisyne wat gepaardgaande toegedien word moet oorweeg word, veral wanneer die belangrikste roete van eliminasie renaal is.

Gesamentlike toediening van **REYDIN** met etravirien (ETR) word nie aanbeveel nie, behalwe as die pasiënt ook gelyktydig atasanavir + ritonavir (ATV + RTV), lopinavir + ritonavir (LPV + RTV) of darunavir + ritonavir (DRV + RTV) ontvang.

Dolutegravir:
Rifampisien verlaag die bloedvlakke van dolutegravir. 'n Aanvullende dosis dolutegravir moet aan pasiënte wie **REYDIN** neem gegee word.

Daar is bewyse dat dolutegravir, soos bevat in **REYDIN**, die konsentrasie van isoniasied verhoog.

Effek van REYDIN op die farmakokinetika van ander middels:
In vitro het dolutegravir geen direkte, of swak inhibisie van die ensieme sitochroom P450, uridiendifosfaat glukuronosieltransferase of die transporteerder Pgp gedemonstreer nie. *In vitro* het dolutegravir nie CYP1A2, CYP2B6 of CYP3A4 geïnduseer nie, *in vivo* het dolutegravir nie 'n effek op midasolaam, 'n CYP3A4-peiler, gehad nie. Gevolglik word nie verwag dat dolutegravir, soos in **REYDIN**, die farmakokinetika van medisyne wat substrate is van hierdie ensieme of transporteerders [d.i. omgekeerde transkriptase- en protease inhibeerders, opioïedanalgetika, antidepressante, statiene, asool-antiswammiddels (soos flukonasool, itrakonasool, klotrimasool), protonpomp inhibeerders (soos esomeprasool, lansoprasool, omeprasool), anti-erektiele disfunksie medisyne (soos sildenafil, tadalafil, vardenafil), asiklovir, valasiklovir, sitagliptin, adefovir] sal affekteer nie.

Dolutegravir, soos in **REYDIN**, het nie enige klinies relevante effek op die farmakokinetika van die volgende nie: tenofovir, metadoon, efavirens, lopinavir, atasanavir, darunavir, etravirien, fosamprenavir, rilpivirien, telaprevir en orale voorbehoedmiddels wat norgestimaat en etinielestradiol bevat.

In vitro inhibeer dolutegravir die renale organiese katioon transporteerder 2 (OCT2). Gebaseer hierop mag **REYDIN** die plasmakonsentrasies van medisyne waarvan die ekskresie van OCT2 afhanklik is (dofetilied, metformien), verhoog.

Effek van ander medisyne op die farmakokinetika van dolutegravir, soos in REYDIN:
Dolutegravir, soos in **REYDIN**, word hoofsaaklik via metabolisme deur UGT1A1 uitgeskei. Dolutegravir is ook 'n substraat van UGT1A3, UGT1A9, CYP3A4, Pgp en BCRP; medisyne wat daardie ensieme induseer mag gevolglik teoreties plasmakonsentrasies van dolutegravir verlaag en die terapeutiese effek van dolutegravir in **REYDIN** verminder. Gepaardgaande toediening van **REYDIN** en ander medisyne wat UGT1A1, UGT1A3, UGT1A9, CYP3A4, en/of Pgp inhibeer mag die plasmakonsentrasie van dolutegravir verhoog.

Efavirens, nevirapien, rifampisien en tipranavir in kombinasie met ritonavir verminder elk die plasmakonsentrasies van dolutegravir beduidend en vereis 'n dolutegravir dosisaanpassing van 50 mg twee keer daagliks. Etravirien verlaag ook plasmakonsentrasies, maar die effek van etravirien is verlig deur gelyktydige toediening van die CYP3A4 inhibeerders lopinavir/ritonavir, darunavir/ritonavir en word verwag om deur atasanavir/ritonavir verlig te word. Geen dosisaanpassing is dus nodig wanneer dit gesamentlik met etravirien toegedien word nie. 'n Ander induseerder, fosamprenavir, in kombinasie met ritonavir het die plasmakonsentrasies van dolutegravir verlaag maar 'n dosisaanpassing is nie nodig nie. Versigtigheid is nodig, en kliniese monitering word aanbeveel wanneer hierdie kombinasies aan INI-weerstandige pasiënte gegee word. 'n Medisyne interaksiestudie met die UGT1A1-inhibeerder, atasanavir, het nie gelei tot 'n klinies betekenisvolle styging in die plasmakonsentrasies van dolutegravir nie. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirien, bosepravir, telaprevir, prednisoon, rifabutien en omeprasool het geen of 'n minimale effek op dolutegravir farmakokinetika gehad, gevolglik is geen dosisaanpassing van dolutegravir nodig wanneer hierdie medisyne gesamentlik toegedien word nie.

Dolutegravir medisyne interaksies:

Gepaardgaande medisyne klas: Medisyne naam	Effek op konsentrasie van dolutegravir of gepaardgaande medisyne			
	Dolutegravir / gepaardgaande medisyne	AOK	C_{maks}	C_T
MIV-1 antivirale middels				
Nie-nukleosied omgekeerde transkriptase inhibeerder: Etravirien (ETR)	Dolutegravir ↑ ETR ↔	↓ 71 %	↓ 52 %	↓ 75 %
Nie-nukleosied omgekeerde transkriptase inhibeerder: Efavirens (EFV)	Dolutegravir ↓ EFV ↔	↓ 57 %	↓ 39 %	↓ 75 %
Nie-nukleosied omgekeerde transkriptase inhibeerder: Nevirapien	Dolutegravir ↓	NS	NS	NS
Protease inhibeerder: Atasanavir (ATV)	Dolutegravir ↑ ATV ↔	↑ 91 %	↑ 49 %	↑ 180 %
Protease inhibeerder: Atasanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ ATV ↔ RTV ↔	↑ 62 %	↑ 33 %	↑ 121 %
Protease inhibeerder: Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ TPV ↔ RTV ↔	↓ 59 %	↓ 47 %	↓ 76 %
Protease inhibeerder: Fosamprenavir/ritonavir (FPV + RTV)	Dolutegravir ↓ FPV ↔ RTV ↔	↓ 35 %	↓ 24 %	↓ 49 %
Protease inhibeerder: Nelfinavir	Dolutegravir ↔	NS	NS	NS
Protease inhibeerder: Lopinavir/ritonavir (LPV + RTV)	Dolutegravir ↔ LPV ↔ RTV ↔	↔	↔	↔
Protease inhibeerder: Darunavir/ritonavir (DRV/RTV)	Dolutegravir ↓ DRV ↔ RTV ↔	↓ 32 %	↓ 11 %	↓ 38 %
Nukleosied omgekeerde transkriptase inhibeerder: Tenofovir (TDV)	Dolutegravir ↔ TDV ↔	NA	NA	NA
Protease inhibeerder: Lopinavir/ritonavir + etravirien (LPV/RTV + ETR)	Dolutegravir ↔ LPV ↔ RTV ↔ ETR ↔	↑ 10 %	↑ 7 %	↑ 28 %
Ander medisyne				
Dofetilied Pilsikaïnied	Dofetilied ↑ Pilsikaïnied ↑	NS	NS	NS
Okskarbasepien Fenitoïen Fenobarbitoon Karbamasepien Johanneskruid (St. John's Wort)	Dolutegravir ↓	NS	NS	NS
Teensuurmiddels wat polivalente katione bevat (bv. Mg, Al of Ca)	Dolutegravir ↓	↓ 74 %	↓ 72 %	↓ 74 %
Kalsiumaanvullings	Dolutegravir ↓	↓ 39 %	↓ 37 %	↓ 39 %
Ysteraanvullings	Dolutegravir ↓	↓ 54 %	↓ 57 %	↓ 56 %
Metformien	Metformien ↑	N/A	N/A	N/A
Rifampisien	Dolutegravir ↓	↓ 54 %	↓ 43 %	↓ 72 %
Orale voorbehoedmiddels [etinielestradiol (EE) en norgestromien (NGMN)]	EE ↔	↑ 3 %	↓ 1 %	↑ 2 %
	NGMN ↔	↓ 2%	↓ 11 %	↓ 7 %
Metadoon	Metadoon ↔	↓ 2 %	↔ 0 %	↓ 1 %

Afkortings: ↑ = Toename; ↓ = Afname; ↔ = Geen beduidende verandering nie; NA = Nie van toepassing nie; NS = Nie bestudeer nie.

Gepaardgaande toediening van dolutegravir het die potensiaal om die plasmakonsentrasies van dofetilied of pilsikaïnied te verhoog via onderdrukking van OCT2-transporteerder. Gepaardgaande toediening van dofetilied of pilsikaïnied met **REYDIN** is teenaangedui weens die potensiële lewensdreigende toksisiteit wat deur hoë dofetilied- of pilsikaïniedkonsentrasies veroorsaak word (sien **"KONTRA-INDIKASIES"**).

Gepaardgaande toediening van teensuurmiddels wat polivalente katione bevat (bv. Mg, Al, Fe of Ca) verlaag die plasmakonsentrasie van dolutegravir. **REYDIN** moenie gesamentlik met teensuurmiddels wat polivalente katione bevat toegedien word nie. Dit word aanbeveel dat **REYDIN** 2 uur voor of 6 uur na hierdie medisyne toegedien word.

Die konsentrasie van metformien mag verhoog word deur **REYDIN**. Metformien word teenaangedui in pasiënte wie **REYDIN** neem (sien **"KONTRA-INDIKASIES"**).

MENSLIKE REPRODUKSIE:
Swangerskap:
REYDIN is teenaangedui tydens swangerskap en laktasie in die mens. Neurale buisdefekte is gemeld in 'n waarnemingstudie in mense, waar regimens gebaseer op dolutegravir gebruik is ten tye van bevrugting en vroeë swangerskap (sien **"KONTRA-INDIKASIES"**).

In reproduktiewe toksisiteitstudies in diere is getoon dat tenofovir, dolutegravir en lamivudien die plasenta kruis. Laat-aanvang neurologiese afwykings, insluitend toevalle, is waargeneem in kinders wie aan nukleosied analoë soos tenofovir en lamivudien blootgestel is (sien **Mitochondriale disfunksie** onder **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**).

REYDIN moenie voorgeskryf word aan vroue wie beplan om swanger te raak nie. Vroue in hulle vrugbare jare, moenie **REYDIN** neem nie, behalwe as hulle hoogs effektiewe voorbehoeding getrou gebruik. Behandeling met **REYDIN** moenie geïnisieer word sonder dat 'n negatiewe swangerskaptoets onder mediese toesig verkry is nie. Hierdie toets moet met gereelde tussenposes tydens behandeling met **REYDIN** herhaal word, en veral indien swangerskap vermoed word.

Laktasie:
Moeders wat hulle babas borsvoed moenie **REYDIN** gebruik nie. Lamivudien word in moedersmelk uitgeskei teen konsentrasies soortgelyk aan die in die serum; tenofovir word in borsmelk uitgeskei en dit is onbekend of dolutegravir in moedersmelk uitgeskei word.

DOSIS EN GEBRUIKSAANWYSINGS:
Terapie moet geïnisieer word deur 'n mediese praktisyn wat ervare is in die bestuur van MIV-infeksie.

Volwassenes:
Die dosis vir **REYDIN** is een tablet oraal geneem, een keer daagliks, met of sonder voedsel.

Pediatriese pasiënte:
REYDIN word nie aanbeveel vir gebruik in pasiënte jonger as 18-jarige ouderdom nie.

Dosisaanpassing vir renale inkorting:
Beduidende verhoogde blootstelling het voorgekom wanneer tenofovir, soos in **REYDIN**, toegedien is aan pasiënte met matige tot erge renale inkorting (sien **"KONTRA-INDIKASIES"**).

Die farmakokinetika van tenofovir, soos in **REYDIN**, is nie geëvalueer in nie-hemodialise pasiënte met kreatinien opruiming < 50 mL/min nie, gevolglik kan geen aanbevelings vir dosisaanpassings in hierdie pasiënte gemaak word nie. **REYDIN** is nie geskik vir gebruik in pasiënte met renale inkorting met kreatinien opruiming van minder as 50 mL/min nie.

Rifampisien verlaag die bloedvlakke van dolutegravir. 'n Aanvullende dosis dolutegravir moet aan pasiënte wie **REYDIN** neem, gegee word.

NEWE-EFFEKTE:
REYDIN kan newe-effekte hê.

Dolutegravir:
Immuunstelsel versteurings:
Minder dikwels: Hipersensitiwiteit, immuunheraktivering sindroom.

Psigiatriese versteurings:
Dikwels: Slaaploosheid.

Senuweestelsel versteurings:
Dikwels: Hoofpyn, duiseligheid, abnormale drome.

Gastroïntestinale versteurings:
Dikwels: Naarheid, diarree.
Minder dikwels: Braking, winderigheid, bobuikpyn.
Frekwensie onbekend: Abdominale pyn, abdominale ongemak.

Hepatobiliêre versteurings:
Frekwensie onbekend: Hepatitis.

Vel- en subkutane weefselversteurings:
Dikwels: Uitslag, pruritus.

Lamivudien:
Die volgende newe-effekte is gemeld tydens terapie vir MIV-siekte met **REYDIN** tablette alleen en in kombinasie met ander antiretrovirale middels:

Bloed- en limfstelsel versteurings:
Minder dikwels: Neutropenie, anemie, trombositopenie.
Frekwensie onbekend: Suiwer rooisel aplasie.

Metabolisme- en voedingsversteurings:
Dikwels: Hiperlaktatemie.
Minder dikwels: Laktaatasidose, lipodistrofie (herverspreiding / akkumulasie van liggaamsvet) (sien **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**).

Senuweestelsel versteurings:
Dikwels: Hoofpyn, slaaploosheid.
Frekwensie onbekend: Perifere neuropatie (of parestesie), laat-aanvang neurologiese versteurings in kinders wat *in utero* blootgestel is.

Gastroïntestinale versteurings:
Dikwels: Naarheid, braking, bobuikpyn of -krampe, diarree.
Minder dikwels: Pankreatitis, stygings in serum amilase.

Hepatobiliêre versteurings:
Minder dikwels: Verbygaande verhogings van lewerensieme (AST, ALT).

Vel- en subkutane weefselversteurings:
Dikwels: Uitslag, alopesie.

Muskuloskeletale-, bindweefsel- en skeletbeen versteurings:
Dikwels: Artralgie, spiersteurings.
Minder dikwels: Rabdomiolise, daling in beenmineraaldigtheid, osteopenie, frakture.

Algemene versteurings en toestande by die toedieningsplek:
Dikwels: Uitputting, malaise, koors.

Tenofovir:
Immuunstelsel versteurings:
Minder dikwels: Allergiese reaksies.

Metabolisme- en voedingsversteurings:
Frekwensie onbekend: Hipofosfatemie, laktaatasidose.

Respiratoriese-, torakale- en mediastinale versteurings:
Frekwensie onbekend: Dispnee.

Gastroïntestinale versteurings:
Dikwels: Anoreksie, dispepsie, winderigheid, abdominale pyn.
Minder dikwels: Styging in amilase, pankreatitis.

Hepatobiliêre versteurings:
Dikwels: Styging in lewerensieme, hepatitis.

Nier- en urienwegversteurings:
Dikwels: Renale ontoereikendheid, verhoogde kreatinien, proksimale renale tubulopatie, nierversaking, akute tubulêre nekrose, nefrogeniese diabetes insipidus, proteïenurie.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VIR DIE BEHANDELING DAARVAN:
Indien oordosering plaasvind moet die pasiënt gemoniteer word vir tekens van toksisiteit, en standaard ondersteunende behandeling soos nodig toegepas word.

Dolutegravir:
Bestuur volgens wat klinies aangedui word of soos aanbeveel deur die nasionale gifsentrum, indien beskikbaar. Daar is geen spesifieke behandeling vir 'n oordosis van **REYDIN** nie. Indien oordosering plaasvind moet die pasiënt ondersteunende terapie ontvang met gepaste monitering soos nodig. Aangesien **REYDIN** hoogs gebonde aan plasmaproteïene is, is dit onwaarskynlik dat dit beduidend deur dialise verwyder sal word.

Lamivudien:
Beperkte data is beskikbaar oor die gevolge van inname van 'n akute oordosis in mense. Indien oordosering plaasvind, moet die pasiënt gemoniteer word en palliatiewe ondersteunende behandeling soos nodig gegee word.

Tenofovir disoproksielfumaraat:
Indien oordosering voorkom moet die pasiënt gemoniteer word vir tekens van toksisiteit en palliatiewe ondersteunende behandeling moet soos nodig gegee word. Tenofovir kan deur hemodialise verwyder word; die mediaan opruiming van tenofovir via hemodialise is 134 mL/min. Die eliminasie van tenofovir deur peritoneale dialise is nie bestudeer nie.

IDENTIFIKASIE:
Blou, kapsulevormige, bikonvekse filmbedekte tablet, met 'C' aan die een kant ingepers en glad aan die ander kant.

AANBIEDING:

Houers van 28: **REYDIN** word verskaf in 'n 85 cc wit HDPE bottel met 38 mm wit nie-kinderbestande deksel, wat 28 tablette en twee silikajelsakkies van 2 g elk bevat, met of sonder 'n buitenste kartonhouer.

Houers van 30: **REYDIN** word verskaf in 'n 85 cc wit HDPE bottel met 38 mm wit nie-kinderbestande deksel, wat 30 tablette en twee silikajelsakkies van 2 g elk bevat, verpak in 'n buitenste kartonhouer.

BERGINGSINSTRUKSIES:
Berg teen of benede 30 °C.
Hou die houer dig geslote.
Berg in die oorspronklike houer tot benodig vir gebruik.

HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER:
52/20.2.8/0451.450

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT:
CIPLA MEDPRO (EDMS) BPK
Gebou 9, Parc du Cap,
Mispelstraat, Bellville,
7530, RSA

PUBLIKASIEDATUM VAN HIERDIE PROFESSIONELE INLIGTING:
31 Augustus 2018

Cipla

21073749