Dinisvir 50
Dolutegravir Sodium
Film Coated Tablet 50 mg

1. NAME OF THE MEDICINAL PRODUCT
Dinisvir 50

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Dolutegravir Sodium 52.6 mg equivalent to Dolutegravir 50 mg.

3. PHARMACEUTICAL FORM
Dinisvir 50 Film-Coated tablet
Pink coloured, film-coated tablet, round biconvex, debossed with "I77" on one side, and plain on the other side.

4. CLINICAL PARTICULARS
4.1. Indication
Dolutegravir is indicated in combination other antiretroviral agents to treat human immunodeficiency virus (HIV) infection in adults and children over 12 years of age who have resistance to minimum of two treatments of antiretroviral agents [nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PI)], and have received one or two background therapy (darunavir, ritonavir, tenofovir, lopinavir, etravirine, and atazanavir).

4.2. Posology and Methode of Administration

Posology

Dolutegravir therapy should be initiated by a physician experienced in the management of HIV infection. Dinisvir 50 can be taken with or without food.

Methods of Administration
Adults

- **Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected)**

The recommended dose of Dolutegravir is 50 mg twice daily. The decision to use DOLUTEGRAVIR for such patients should be informed by the integrase resistance pattern.

Adolescents
In patients who have not previously been treated with an integrase inhibitor, (12 to less than 18 years of age and weighing greater than or equal to 40 kg) the recommended dose of DOLUTEGRAVIR is 50 mg once daily.

Children
There are insufficient safety and efficacy data available to recommend a dose for DOLUTEGRAVIR in children below age 12 or weighing less than 40 kg.

Elderly
There are limited data available on the use of dolutegravir in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients

Renal impairment
No dosage adjustment is required in patients with mild, moderate or severe (CrCl <30 mL/min, not on dialysis) renal impairment. No data are available in subjects receiving dialysis although differences in pharmacokinetics are not expected in this population.

Dolutegravir has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when Dolutegravir is co-administered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance.

Hepatic Impairment
No dosage adjusment is required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available in patients with severe hepatic impairment (Child-Pugh grade C).

4.3. Contraindications
Dolutegravir is contraindicated in combination with dofetilide or pilsicainide.

Dolutegravir is contraindicated in patients with known hypersensitivity to dolutegravir or to any of the excipients.

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

Hypersensitivity reactions

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Discontinue dolutegravir 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, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with dolutegravir or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Immune reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infection may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* (*P. carinii*) pneumonia. Any inflammatory symptoms should be evaluated and treatment

initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barre) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Liver biochemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients (see section 4.8).

Opportunistic infections

Patients should be advised that dolutegravir or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Trasmission of Infection

Patients should be advised that current antiretroviral therapy, including Dolutegravir, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Approriate precautions should continue to be taken.

Drug Interactions

Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. This includes co-administration with medicinal products that reduce dolutegravir exposure (e.g. magnesium/aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents, etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St. John's wort and certain antiepileptic medicinal products) (see section 4.5).

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control (see section 4.5). Metformin is eliminated renally and, therefore, it is of importance to monitor renal function when co-treated with dolutegravir. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment (stage 3a creatinine clearance [CrCl] 45– 59 mL/min) and a cautious approach is recommended. Reduction of the metformin dose should be highly considered.

Osteonecrosis

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

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

Effect of Dolutegravir on The Pharmacokinetics of Other Agents

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC50>50 μM) of the enzymes cytochrome P_{450} (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT1A1) or UGT2B7, or the transporter Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MRP2 or MRP4. *In vitro,* dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo,* dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, Dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters (e.g., reverse transcriptase and protease inhibitors, abacavir, zidovudine, maraviroc, opioid analgesics, antidepressants, statins, azole antifungals, proton pum inhibitors, antierectile dysfunction agents, aciclovir valaciclovir, sitagliptin, adefovir).

Dinisvir 50 dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, ritonavir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, boceprevir, telaprevir, daclastavir, and oral contraceptives containing norelgestimate and ethinyl estradiol.

In vitro, dolutegravir, inhibited the renal organic cation transporter 2 (OCT2) (IC50 = 1.93 μM) multidrug and toxin extrusion transporter (MATE) 1 (IC50 = 1.97 μM). However, dolutegravir had no notable effect on the in vivo pharmacokinetics of the OAT substrates tenofovir and para aminohippurate, and therefore has low propensity to cause drug interactions via inhibition of OAT transporters.

Effect of Other Agents on The Pharmacokinetics of Dolutegravir

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore drugs that induce those enzymes or transporters may theoretically decrease dolutegravir plasma concentration and reduce the therapeutic effect of Dolutegravir.

Co-administration of Dolutegravir and other drugs that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and.or Pgp may increase dolutegravir plasma concentration (see Table 1).

In vitro, dolutegravir is not a substrate of human organic anion transporting polypeptide (OATP) 1B1, OATP1 B3, or OCT1, therefore drugs that solely modulate these transporter are not expected to affect dolutegravir plasma concentration.

Efavirenz, etravirine, nevirapine, rifampicin, carbamazepine and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly, and require Dolutegravir dose adjusment to 50 mg twice daily. 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 dolutegravir dose adjusment is necessary when co-administered with etravirine, and either lopinavir/ritonavir, darunavir/ritonavir, or atazanavir/ritonavir. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjusment of Dolutegravir (see Table 1). A drug interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentration of dolutegravir. Tenofovir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, daclastavir, and omeprazole

had no or a minimal effect on dolutegravir pharmacokinetics, therefore no Dolutegravir dose adjusment is required when co-administered with these durgs.

Selected drug interactions are presented in Table 1. Recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 1: Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir or Concomitant Drug**	**Clinical Comment**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors: Etravirine (ETR) without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% C_T ↓ 88% ETR ↔	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI-resistant patients.
Protease Inhibitor: Lopinavir/ ritonavir + Etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% C_T ↑ 28% LPV ↔ RTV ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjusment is necessary.
Protease Inhibitor: Darunavir/ ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% C_T ↓ 36% DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjusment is necessary.
Non-nucleoside Reverse Transcriptase Inhibitors: Efavirenz (EFV)	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% C_T ↓ 75% EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of Dolutegravir is 50 mg twice daily when co-administered with efavirenz. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients.
Non-nucleoside Reverse Transcriptase	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration

Inhibitors: Nevirapine		due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of Dolutegravir is 50 mg twice daily when co-administered with nevirapine. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.
Protease Inhibitors: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% C_T ↑ 180% ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitors: Atazanavir/ ritonavir (ATV/RTV)	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% C_T ↑ 121% ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitors: Tipranavir/ ritonavir (TPV/RTV)	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% C_T ↓ 76% TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of Dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI-resistant patients.
Protease Inhibitors: Fosamprenavir/ ritonavir (FPV/RTV)	Dolutegravir ↓ AUC ↓ 35% C_{max} ↓ 24% C_T ↓ 49% FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based in limited data, did not result in decreased efficact in phase III studies. No dose adjusment is necessary in INI-naive patients. Alternative combinations that do not include fosamprenavir/ritonavir should be used where possible in INI-resistant patients.
Protease Inhibitors: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitors: Lopinavir/	Dolutegravir ↔ AUC ↓ 4% C_{max} ↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose

ritonavir (LPV+RTV)	C_T ↓ 6% LPV ↔ RTV ↔	adjustment is necessary.
Protease Inhibitors: Darunavir/ ritonavir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% C_T ↓ 38%	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent, No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors: Tenofovir	Dolutegravir ↔	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent, No dose adjustment is necessary.
Other agents		
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or pilsicainide co-administration with dolutegravir is contraindicated due to potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration.
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% C_T ↓ 73%	Carbamazepine decreased dolutegravir plasma concentration. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. Alternatives to carbamazepine should be used where possible for INI resistant patients.
Phenytoin Phenobarbital St. John's wort	Dolutegravir ↓	Co-administration with these metabolic inducers has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of these metabolic inducers in dolutegravir exposure is likely similar to carbamazepine. The recommended dose of Dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers . Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.
Oxcarbazepine	Dolutegravir ↓	This interaction has not been studied. Although an inducer of CYP3A4, based on data from other inducers, a clinically significant decrease in dolutegravir is not

		expected. No dose adjusment is necessary.
Antacids containing polyvalent cations (e.g. Mg, Al)	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% C_T ↓ 74%	Co-administrations of antacids containing polyvalent cations decreased dolutegravir plasma concentration. Dolutegravir is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C_T ↓ 39%	Dolutegravir is recommended to be administered 2 hours before or 6 hours after taking products containing calcium. If administered with food, Dolutegravir can be taken at the same time as calcium supplements.
Iron supplements	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_T ↓ 56%	Dolutegravir is recommended to be administered 2 hours before or 6 hours after taking products containing iron. If administered with food, Dolutegravir can be taken at the same time as iron supplements.
Metformin	Metformin ↑ When co-administered with dolutegravir 50 mg QD: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50 mg BID: Metformin AUC ↑ 145% C_{max} ↑ 111%	Co-administration of Dolutegravir increased metformin plasma concentration. A dose adjustment of metforming should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control.
Rifampicin	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% C_T ↓ 72%	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of Dolutegravir is 50 mg twice daily when co-administered with rifampicin. Alternatives to rifampicin should be used where possible for in INI-resistant patients.
Oral contraceptives (Ethinyl estradiol (EE) and Norelgestromin (NGMN))	Effect of dolutegravir: EE ↔ AUC ↑ 3% C_{max} ↓ 1% C_T ↑ 2%	Dolutegravir did not change ethinyl estradiol and norelgestromin plasma concentration to a clinically relevant extent. No dose adjusment of oral conctraceptives is necessary when co-administered with Dolutegravir.

	Effect of dolutegravir NGMN ↔ AUC ↓ 2% C_{max} ↔ 11% C_T ↓ 7%	
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2% C_{max} ↔ 0% C_T ↓ 1%	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjusment of methadone is necessary when co-administered with Dolutegravir.
Daclastavir	Effect of dolutegravir: AUC ↑ 33% C_{max} ↑ 29% C_T ↑ 45% Daclastavir ↔	Daclastavir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclastavir plasma concentration. No dose adjustment is necessary.

Abbreviations: ↑ = increase, ↓ decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; Cmax = maximum observed concentration, CT = concentration at the end of dosing interval.

4.6. Fertility, pregnancy, and lactation

Women of Childbearing Potential

Women of childbearing potential (WOCBP) should undergo pregnancy testing before initiation of dolutegravir. WOCBP who are taking dolutegravir should use effective contraception throughout treatment.

Fertility

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

Pregnancy

There are no adequate and well-controlled studies of DOLUTEGRAVIR in pregnant women. The effect of DOLUTEGRAVIR on human pregnancy is unknown. In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta. DOLUTEGRAVIR should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Lactation

Health expert recommend that where possible HIV infected women do not breast feed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.

It is excepted that dolutegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans

4.7. Effects on ability to drive and use machines

There have been no studies to investigate the effect of dolutegravir on driving performance or the ability to operate machines. The clinical status of the patient and the adverse reaction profile of dolutegravir should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8. Adverse Reactions

- Immune system disorders : hypersensitivity, immune reconstitution syndrome
- Psychiatric disorders : insomnia, abnormal dreams, depression, anxiety, suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)
- Nervous system disorders : headache, dizziness
- Gastrointestinal disorders : nausea, diarrhoea, vomiting, flatulence, upper abdominal pain, abdominal pain, abdominal discomfort
- Hepatobiliary disorders : hepatitis, acute hepatic failure
- Skin and subcutaneous tissue disorders : rash, pruritus
- Musculoskeletal and connective tissue disorders : arthalgia, myalgia
- General disorders and administration site conditions : fatigue
- Investigation : alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations, creatine phosphokinase (CPK) elevations.

4.9. Overdose
Symptoms and Signs
There is currently limited experience with overdosage in dolutegravir.

Limited experience of single higher doses (up to 250 mg in healthy subjects) revealed no specific symptoms or signs, apart from those listed as adverse reactions.

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

5. PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Dolutegravir Inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cyc

6. DRUG INFORMATION

6.1. List of exipients

Core tablet: mannitol, povidone, sodium starch glycolate, microcystaline cellulose and sodium stearyl fumarate.

Coating: Polyvinyl Alcohol, Titanium Dioxide, Macrogol/PEG, TALC, Iron Oxide Red.

6.2. Shelf life

24 months

6.3. Special precautions for storage

Do not store above 30°C. Store in the original container
USE WITHIN 180 DAYS AFTER PACKAGING OPENED

6.4. Nature and contents of container

30's Bottle Pack.

7. On Medical Prescription Only

8. Mfg. by

Macleods Pharmaceuticals Limited
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9. Market Authorization Holder

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"The Product has been produced under a license from the Medicine Patent Pool"
"Any other use is not authorized"
"The products are not authorized for supply to the Private Market"

Informasi Produk untuk Pasien
Dinisvir 50
Tablet Salut Selaput 50 mg

Baca keseluruhan brosur ini secara teliti sebelum Anda mulai menggunakan obat ini karena mengandung informasi penting untuk Anda.
- Simpan brosur ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada Dokter atau Apoteker.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan kepada orang lain. Hal ini bisa membahayakan mereka, meskipun tanda atau gejala penyakitnya sama dengan Anda.
- Jika Anda mengalami efek samping, konsultasikan dengan Dokter atau Apoteker Anda. Termasuk kemungkinan efek samping yang tidak tercantum dalam selebaran ini. Lihat bagian 4.

Apa saja yang ada dalam brosur ini:

1. Apa itu Dinisvir 50 dan Digunakan Untuk Apa
Dinisvir 50 mengandung zat aktif bernama dolutegravir, yang mana masuk ke dalam kelompok obat anti-retroviral yang disebut integrase inhibitors (INIs).
Dinisvir 50 digunakan untuk mengobati infeksi HIV (Human immunodeficiency Virus) pada orang dewasa, remaja dan anak-anak diatas 12 tahun dengan berat badan setidaknya 40 kg.
Dinisvir 50 tidak menyembuhkan infeksi HIV, hanya mengurangi jumlah virus pada tubuh Anda, dan menjaganya agar tetap rendah. Sebagai hasilnya, ini juga meningkatkan jumlah sel Cd4 dalam darah Anda. Sel Cd4 adalah jenis sel-sel darah putih yang penting dalam membantu tubuh Anda melawan infeksi.
Tidak semua orang memberikan respon yang sama terhadap pengobatan Dinisvir 50. Dokter Anda akan memantau keefektifan pengobatan Anda.
Dinisvir 50 selalu digunakan dalam kombinasi dengan obat anti-retroviral lainnya (terapi kombinasi). Untuk mengontrol infeksi HIV Anda dan mencegah penyakit Anda memburuk. Anda harus tetap menggunakan semua obat-obatan Anda, kecuali dokter memberi tahu Anda untuk berhenti menggunakannya.

2. Apa yang Perlu Anda ketahui Sebelum Menggunakan Dinisvir 50
Jangan gunakan Dinisvir 50:
- Jika Anda alergi terhadap dolutegravir atau bahan lain dari Dinisvir 50 (lihat di bagian 6).
- Jika Anda menggunakan obat lain yang disebut dofetilide (untuk mengobati kondisi jantung) atau pilsicainide.

→Jika Anda mengalami hal di atas, konsultasikan ke dokter Anda.

Perhatian dan Pencegahan
Perhatikan gejala penting ini
Beberapa orang yang menggunakan obat untuk infeksi HIV, dapat mengalami kondisi yang lebih serius, termasuk:
- Gejala infeksi dan radang
- Nyeri sendi, kekakuan dan masalah tulang

Anda perlu tahu tentang tanda dan gejala penting yang harus diwaspadai saat Anda menggunakan Dinisvir 50.
- **Baca informasi di bagian 4 dari leaflet ini.**

Lindungi orang lain
Infeksi HIV disebarkan melalui kontak seksual dengan seseorang yang memiliki infeksi, atau melalui transfer darah yang terinfeksi (misalnya, dengan berbagi jarum suntik). Anda masih bisa menularkan HIV saat minum obat ini, walaupun risikonya menurun dengan terapi anti-retroviral yang efektif. Diskusikan dengan Dokter Anda tentang tindakan pencegahan yang diperlukan untuk menghindari penularan terhadap orang lain.

Anak-anak
Jangan berikan obat ini kepada anak di bawah usia 12 tahun, dengan berat badan kurang dari 40 kg atau dengan infeksi HIV yang resisten terhadap obat-obatan lain yang mirip dengan Dinisvir 50. Penggunaan Dinisvir 50 pada anak di bawah 12 tahun atau berat badan kurang dari 40 kg belum diteliti.

Obat Lain dan Dinisvir 50
Beritahu dokter jika Anda sedang menggunakan, telah menggunakan, atau mungkin menggunakan obat lain, termasuk obat dengan atau tanpa resep dan obat tradisional atau suplemen.

Jangan gunakan Dinisvir 50 dengan obat dofetilide (untuk mengobati **kondisi jantung).**

Beberapa obat dapat mempengaruhi cara kerja Dinisvir 50, atau mungkin menimbulkan efek samping. Dinisvir 50 juga dapat mempengaruhi cara kerja beberapa obat.
Beritahu dokter Anda, jika Anda menggunakan obat sebagai berikut:
- **Metformin,** untuk mengobati diabetes
- Obat **antasida,** untuk mengobati **gangguan pencernaan** dan **rasa panas di dada**. **Jangan menggunakan antasida** selama 6 jam sebelum atau setidaknya 2 jam setelah Anda menggunakan Dinisvir 50 (lihat di bagian 3).
- Suplemen kalsium, suplemen zat besi, dan multivitamin. **Jangan menggunakan suplemen kalsium, suplemen zat besi atau multivitamin** selama 6 jam sebelum atau setidaknya 2 jam setelah Anda menggunakan Dinisvir 50 (lihat di bagian 3).
- Etravirine, efavirenz, fosamprenavir/ritonavir, nevirapine atau tipranavir/ritonavir, untuk mengobati **infeksi HIV**
- Rifampisin, untuk mengobati tuberculosis (TB) dan **infeksi bakteri** lainnya
- Fenitoin dan fenobarbital, untuk mengobati **epilepsi**
- Oxcarbazepine dan carbamazepine, untuk mengobati **epilepsi** atau **gangguan bipolar**
- **St. John's wort** (*Hypericum perforatum*), obat herbal untuk mengobati **depresi**

→ **Beritahu dokter atau apoteker** Anda jika Anda menggunakan obat tersebut**.** Dokter Anda akan menyesuaikan dosis Anda atau apabila perlu melakukan pemeriksaan tambahan.

Kehamilan
Jika Anda sedang hamil, curiga mungkin hamil atau berencana untuk memiliki bayi,
→**Konsultasikan dengan dokter Anda** tentang risiko dan keuntungan menggunakan Dinisvir 50.
Menggunakan Dinisvir 50 pada saat hamil atau selama dua belas minggu pertama kehamilan, mungkin dapat meningkatkan risiko cacat lahir, yang disebut neural tube defect, seperti spina bifida (malformed spinal cord). Jika Anda mungkin hamil pada saat menggunakan Dinisvir 50, Anda perlu menggunakan kontrasepsi (misalnya, kondom) dengan kontrasepsi lainnya termasuk oral (pit) atau hormonal (misalnya, implant, injeksi) untuk mencegah kehamilan.
Segera beritahu dokter Anda jika Anda hamil atau berencana hamil. Dokter Anda akan melakukan peninjauan pengobatan Anda. Jangan hentikan penggunaan Dinisvir 50 tanpa konsultasi dengan dokter Anda, karena ini dapat membahayakan Anda dan bayi Anda yang belum lahir.
Menyusui
Wanita yang positif HIV tidak boleh menyusui karena infeksi HIV dapat ditularkan kepada bayi melalui ASI. **Tidak diketahui** apakah kandungan Dinisvir 50 dapat masuk ASI Anda.
Jika Anda menyusui, atau berpikir untuk menyusui:
→**Segera konsultasikan dengan dokter Anda.**
Mengemudi dan Mengoperasikan Mesin
Dinisvir 50 dapat membuat Anda merasa pusing dan mengalami efek samping lain yang membuat Anda kurang waspada.
→Jangan mengemudi atau menggunakan mesin kecuali Anda yakin bahwa Anda tidak terpengaruh.

3. Cara menggunakan Dinisvir 50
Selalu gunakan obat ini sesuai saran dokter pada Anda. Konsultasikan dengan dokter atau apoteker jika Anda tidak yakin.
- Pada pasien yang belum pernah diobati (12-18 tahun dan beratnya lebih dari atau sama dengan 40 kg) dosis yang digunakan adalah satu tablet 50 mg **sekali sehari.**
- **Untuk pengobatan HIV yang resisten** terhadap obat lain yang serupa dengan Dinisvir 50, dosis Dinisvir 50 adalah satu tablet 50 mg **dua kali sehari.**

Dokter Anda akan menentukan dosis Dinisvir 50 yang tepat untuk Anda.

Telan tablet dengan cairan. Dinisvir 50 dapat digunakan dengan atau tanpa makanan. Ketika menggunakan Dinisvir 50 dua kali sehari, dokter Anda akan menyarankan untuk digunakan dengan makanan.
Dosis 50 mg harus diberikan sebagai tablet tunggal 50 mg, tidak boleh menggunakan 5 tablet 10 mg.

Anak dan Remaja
Anak dan remaja dengan berat setidaknya 40 kg dapat menggunakan dosis dewasa satu tablet (50 mg), sekali sehari. Dinisvir 50 tidak boleh digunakan pada anak-anak dan remaja dengan **infeksi HIV yang resisten** terhadap obat lain yang mirip dengan Dinisvir 50.

Obat Antasida
Antasida, untuk menurunkan asam lambung, pemakaian bersamaan dengan antasida dapat mengurangi penyerapan Dinisvir 50 ke dalam tubuh dan membuatnya kurang efektif.
Jangan menggunakan antasida selama 6 jam sebelum atau setidaknya 2 jam setelah Anda menggunakan Dinisvir 50. Obat penurun asam lambung lainnya seperti ranitidine dan omeprazole dapat dikonsumsi bersamaan dengan Dinisvir 50.
→Bicarakan dengan dokter Anda untuk saran lebih lanjut tentang penggunaan obat penurun asam lambung dengan Dinisvir 50.

Suplemen kalsium, suplemen zat besi atau multivitamin
Suplemen kalsium, suplemen zat besi atau multivitamin dapat menghentikan penyerapan Dinisvir 50 ke dalam tubuh Anda dan membuatnya kurang efektif.
Jangan menggunakan suplemen kalsium, suplemen zat besi atau multivitamin selama 6 jam sebelum atau setidaknya 2 jam setelah Anda menggunakan Dinisvir 50.
→Bicarakan dengan dokter Anda untuk saran lebih lanjut tentang penggunaan suplemen kalsium, suplemen zat besi atau multivitamin dengan Dinisvir 50.
Jika Anda diberikan terlalu banyak Dinisvir 50
Jika Anda menggunakan terlalu banyak tablet Dinisvir 50, **hubungi dokter atau apoteker Anda untuk saran.** Jika memungkinkan, tunjukkan kemasan Dinisvir 50 pada mereka.
Jika Anda lupa menggunakan Dinisvir 50
Jika Anda melewatkan satu dosis, Anda harus menggunakannya segera setelah Anda ingat. Tetapi jika penggunaan dosis Anda berikutnya adalah dalam waktu 4 jam, lewati saja dosis yang Anda lewatkan dan gunakan pada waktu selanjutnya.Kemudian lanjutkan perawatan Anda seperti sebelumnya.
→ Jangan menggunakan dosis ganda untuk mengganti dosis yang terlupakan.

Jika Anda berhenti menggunakan Dinisvir 50 tanpa saran dari dokter Anda
Gunakan Dinisvir 50 selama dokter sarankan. Jangan berhenti kecuali dokter menyarankan Anda untuk berhenti.
Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanya dokter atau apoteker Anda.

4. Efek Samping yang Mungkin Terjadi
Seperti semua obat-obatan lain, Dinisvir 50 dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya.

Reaksi alergi
Berikut adalah efek samping yang tidak umum terjadi saat menggunakan Dinisvir 50:
- Ruam kulit
- Deman
- Kekurangan energi (kelelahan)
- Pembengkakan, kadang-kadang pada wajah atau mulut (angioderma), menyebabkan sulit bernafas.
- Nyeri otot atau sendi

→ **Segera temui dokter.** Dokter Anda mungkin akan melakukan tes hati, ginjal atau darah Anda dan mungkin memberitahu Anda untuk berhenti menggunakan Dinisvir 50..

Efek samping yang sangat umum:
Dapat terjadi **lebih dari 1 dari 10 orang**
- Sakit kepala
- Diare
- Mual

Efek samping yang umum terjadi
Dapat terjadi hingga **1 dari 10 orang**:
- Ruam
- Gatal-gatal (pruritus)
- Mual
- Sakit perut
- Rasa tidak nyaman pada perut
- Insomnia
- Pusing
- Mimpi yang aneh
- Depresi (perasaan sedih dan tidak berharga)
- Rasa cemas dan gelisah
- Kekurangan energi (kelelahan)
- Perut kembung
- Peningkatan kadar enzim hati (ALT dan/atau AST)
- Peningkatan kadar enzim yang diproduksi di otot (*creatine phosphokinase)*

Efek samping yang tidak umum terjadi
Dapat terjadi hingga **1 dari 100 orang**:
- Peradangan hati (hepatitis)
- Percobaan bunuh diri dan/atau pikiran untuk bunuh diri (khususnya pada pasien yang pernah mengalami depresi atau masalah kesehatan mental sebelumnya)
- Nyeri sendi, nyeri otot, hipersensitivitas, *Immune reconstitution syndrome, arthralgia. myalgia*

Efek samping yang jarang terjadi:
Dapat terjadi hingga **1 dari 1000 orang**
- Gagal hati (termasuk tanda-tanda menguning pada kulit dan pada bagian putih mata atau air seni yang gelap).

Gejala infeksi dan peradangan
Orang dengan infeksi HIV (AIDS) memiliki sistem kekebalan tubuh yang lemah dan lebih mungkin berkembang menjadi infeksi serius (*opportunistic infections)*. Infeksi semacam itu mungkin tidak terdeteksi oleh sistem kekebalan tubuh yang lemah sebelum pengobatan dimulai. Setelah memulai pengobatan, sistem kekebalan menjadi lebih kuat dan dapat menyerang infeksi yang dapat menyebabkan gejala infeksi atau peradangan. Gejala yang terjadi biasanya termasuk **demam,** ditambah beberapa hal berikut :
- Sakit kepala
- Sakit perut
- Sulit bernafas

Dalam kasus yang jarang terjadi, ketika sistem kekebalan tubuh menjadi lebih kuat, virus juga dapat menyerang jaringan tubuh yang sehat (gangguan autoimun). Gejala-gejala autoimun dapat berkembang dalam waktu beberapa bulan setelah Anda mulai menggunakan obat untuk mengobati infeksi HIV Anda. Gejala tersebut termasuk:
- Palpitasi (detak jantung yang cepat atau tidak teratur) atau tremor
- Hiperaktif (kegelisahan dan gerakan yang berlebihan)
- Tubuh menjadi lemah dimulai pada tangan dan khaki lalu menyebar ke seluruh tubuh.

Jika Anda mengalami gejala infeksi dan peradangan atau jika Anda menyadari salah satu gejala di atas:
→**Segera beritahu dokter Anda.** Jangan menggunakan obat lain untuk infeksi tanpa saran dari dokter.
Nyeri sendi, kekakuan dan masalah tulang
Beberapa orang yang memakai terapi kombinasi untuk HIV mengalami osteonecrosis. Dengan kondisi ini, bagian jaringan tulang akan mati karena berkurangnya pasokan darah ke tulang. Orang lebih mungkin mendapatkan kondisi berikut:
- Jika menggunakan terapi kombinasi untuk waktu yang lama
- Jika menggunakan obat anti-inflamasi yang disebut kortikosteroid
- Jika meminum alkohol
- Jika sistem kekebalan tubuh sangat lemah
- Jika kelebihan berat badan.

Tanda-tanda osteonecrosis sebagai berikut:
- Kekakuan pada sendi
- Nyeri dan sakit pada persendian (terutama pada pinggul, lutut atau bahu)
- Kesulitan bergerak

Jika Anda menyadari salah satu gejala tersebut: → **Beritahu dokter Anda**.
Pelaporan efek samping
Jika Anda mengalami efek samping, harap konsultasikan ke dokter atau apoteker. Termasuk kemungkinan efek samping lain yang tidak tertulis dalam brosur ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi yang bermanfaat terhadap keamanan obat ini.

5. Cara Penyimpanan Dinisvir 50
Simpan obat jauh dari jangkauan anak-anak. Jangan menggunakan obat setelah tanggal kadaluwarsa yang tertulis pada karton dan botol. Jangan simpan pada suhu di atas 30°C. Simpan pada kemasan asli. Jangan membuang obat apapun melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana membuang obat yang tidak lagi diperlukan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lain
Apa kandungan Dinisvir 50
- Zat aktif Dinisvir 50 adalah Dolutegravir. Setiap tablet mengandung Dolutegravir Sodium setara dengan Dolutegravir 50 mg
- Kandungan lainnya adalah Mannitol, Microcrystalline cellulose, Povidone, Sodium starch glycolate, Sodium stearyl fumarate, Polyvinyl alcohol, Triacetin, Talc, Titanium Dioxide, Red Iron oxide

Apa yang terlihat dan isi kemasan
Dinisvir 50 memiliki bentuk berupa Tablet Salut Selaput, bulat, bewarna pink, biconvex, dengan cetakan "I77" pada sisi yang satu dan polos pada sisi yang lain.
Tablet salut selaput tersedia dalam botol berisi 30 tablet.
GUNAKAN DALAM 180 HARI SETELAH KEMASAN DIBUKA
HARUS DENGAN RESEP DOKTER
Dinisvir 50, Dus, 1 Botol Plastik @30 Tablet Salut Selaput, Reg. No.

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