ABRIDGED SUMMARY OF PRODUCT CHARACTERISTICS Please refer to the Summary of Product Characteristics for a complete information on the use of this product. **NAME OF THE MEDICINAL PRODUCT** Dovato 50 mg/300 mg film-coated tablets; EU/1/19/1370/001; EU/1/19/1370/002 Pharmacotherapeutic group: Antivirals for systemic use, antivirals for treatment of HIV infections, combinations. ATC code: J05AR25 **QUALITATIVE AND QUANTITATIVE COMPOSITION** Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir and 300 mg lamivudine. For the full list of excipients, see section 6.1 of the complete SPC **Therapeutic indications** Dovato is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine (see section 5.1 of the complete SPC). **Posology and method of administration** Dovato should be prescribed by physicians experienced in the management of HIV infection. Posology *Adults and adolescents (above 12 years of age weighing at least 40 kg).* The recommended dose of Dovato in adults and adolescents is one 50 mg/300 mg tablet once daily. *Dose adjustments* A separate preparation of dolutegravir is available where a dose adjustment is indicated due to drug-drug interactions (e.g. rifampicin, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, St. John's wart, etravirine (without boosted protease inhibitors), efavirenz, nevirapine, or tipranavir/ritonavir, see sections Special warnings and precautions for use and 4.5 of the complete SPC). In these cases the physician should refer to the individual product information for dolutegravir. *Missed doses* If the patient misses a dose of Dovato, the patient should take Dovato as soon as possible, providing the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and simply resume the usual dosing schedule. *Elderly* There are limited data available on the use of Dovato in patients aged 65 years and over. No dose adjustment is necessary (see section 5.2 of the complete SPC). *Renal impairment* Dovato is not recommended for use in patients with a creatinine clearance < 30 mL/min (see section 5.2 of the complete SPC). No dose adjustment is required in patients with mild or moderate renal impairment. However, the lamivudine exposure is significantly increased in patients with a creatinine clearance < 50 mL/min (see section Special warnings and precautions for use). *Hepatic impairment* No dosage adjustment 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); therefore Dovato should be used with caution in these patients (see section 5.2 of the complete SPC). *Paediatric population* The safety and efficacy of Dovato in children aged less than 12 years or weighing less than 40 kg have not been established. No data are available. Method of administration Oral use. Dovato can be taken with or without food (see section 5.2 of the complete SPC). **Contraindications** Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 of the complete SPC Co-administration with medicinal products with narrow therapeutic windows, that are substrates of organic cation transporter (OCT) 2, including but not limited to fampridine (also known as dalfampridine; see section 4.5 of the complete SPC). **Special warnings and precautions for use** Hypersensitivity reactions Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dovato and other suspect medicinal products should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with Dovato or other suspect active substances after the onset of hypersensitivity may result in a life-threatening allergic reaction. Weight and metabolic parameters An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids and weight, there is in some cases evidence for a treatment effect. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate. Liver disease Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products. Dovato includes lamivudine, which is active against hepatitis B. Dolutegravir lacks such activity. Lamivudine monotherapy is generally not considered an adequate treatment for hepatitis B, since the risk for hepatitis B resistance development is high. If Dovato is used in patients co-infected with hepatitis B an additional antiviral is therefore generally needed. Reference should be made to treatment guidelines. If Dovato is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis. 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. Immune Reactivation Syndrome In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are *Cytomegalovirus retinitis*, generalised and/ or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia (often referred to as PCP). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment. Liver chemistry 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. (See 'Liver disease' earlier in this section and also see section "Undesirable effects"). Mitochondrial dysfunction following exposure *in utero* Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues, these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), and metabolic disorders (hyperlactatemia, hyperlipasemia). These reactions have often been transitory. Some late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown aetiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV. 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. Opportunistic infections Patients should be advised that dolutegravir, lamivudine 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. Administration in subjects with moderate renal impairment Patients with a creatinine clearance between 30 and 49 mL/min receiving Dovato may experience a 1.6-to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL/min. There are no safety data from randomized, controlled trials comparing Dovato to the individual components in patients with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of haematologic toxicities (neutropenia and anaemia), although discontinuations due to neutropenia or anaemia each occurred in <1% of subjects. Other lamivudine-related adverse events (such as gastro-intestinal and hepatic disorders) may occur. Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive Dovato should be monitored for lamivudine-related adverse events, notably haematologic toxicities. If new or worsening neutropenia or anaemia develop, a dose adjustment of lamivudine, per lamivudine prescribing information, is indicated, which cannot be achieved with Dovato. Dovato should be discontinued and the individual components should be used to construct the treatment regimen. Drug interactions The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, St. John's wort, etravirine (without boosted protease inhibitors), efavirenz, nevirapine, or tipranavir/ritonavir (see section 4.5 of the complete SPC). Dovato should not be co-administered with polyvalent cation-containing antacids. Polyvalent cation-containing antacids are recommended to be taken 2 hours after or 6 hours before Dovato (see section 4.5 of the complete SPC). When taken with food, Dovato and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. If Dovato is administered under fasting conditions, supplements or multivitamins containing calcium, iron or magnesium are recommended to be taken 2 hours after or 6 hours before Dovato (see section 4.5 of the complete SPC). Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of Dovato with metformin, to maintain glycaemic control (see section 4.5 of the complete SPC). Metformin is eliminated renally and, therefore, it is of importance to monitor renal function when co-treated with Dovato. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment (stage 3a creatinine clearance 45– 59 mL/min) and a cautious approach is recommended. Reduction of the metformin dose should be highly considered. The combination of Dovato with cladribine is not recommended (see section 4.5 of the complete SPC). Dovato should not be taken with any other medicinal product containing dolutegravir, lamivudine or emtricitabine, except where a dose adjustment of dolutegravir is indicated due to drug-drug interactions (see section 4.5 of the complete SPC). **Undesirable effects** Summary of the safety profile The most frequently reported adverse reactions are headache (3%), diarrhoea (2%), nausea (2%) and insomnia (2%). The most severe adverse reaction reported with dolutegravir was a hypersensitivity reaction that included rash and severe liver effects (see section Special warnings and precautions for use). Tabulated list of adverse reactions The adverse reactions from clinical study and post-marketing experience are listed in Table 2 by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). **Table 2: Tabulated summary of adverse reactions to Dovato based on clinical study and post-marketing experience with Dovato and its individual components**

Frequency	Adverse reaction
Blood and lymphatic systems disorders:	
Uncommon:	neutropenia, anaemia, thrombocytopenia
Very rare:	pure red cell aplasia
Immune system disorders:	
Uncommon:	hypersensitivity (see section Special warnings and precautions for use), immune reconstitution syndrome (see section Special warnings and precautions for use)
Metabolism and nutrition disorders:	
Very rare:	lactic acidosis
Psychiatric disorders:	
Common:	depression, anxiety, insomnia, abnormal dreams
Uncommon:	suicidal ideation*, suicide attempt*, panic attack *particularly in patients with a pre-existing history of depression or psychiatric illness.
Rare:	completed suicide* *particularly in patients with a pre-existing history of depression or psychiatric illness.
Nervous system disorders:	
Very common:	headache
Common:	dizziness, somnolence
Very rare:	peripheral neuropathy, paraesthesia
Gastrointestinal disorders:	
Very common:	nausea, diarrhoea
Common:	vomiting, flatulence, abdominal pain/ discomfort
Rare:	pancreatitis
Hepatobiliary disorders:	
Common:	alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations
Uncommon:	hepatitis
Rare:	acute hepatic failure[1], increased bilirubin[2]
Skin and subcutaneous tissue disorders:	
Common:	rash, pruritus, alopecia
Rare:	angioedema
Musculoskeletal and connective tissue disorders:	
Common:	arthralgia, muscle disorders (including myalgia)
Rare:	rhabdomyolysis
General disorders and administration site conditions:	
Common:	fatigue
Investigations:	
Common:	creatine phosphokinase (CPK) elevations, weight increased
Rare:	amylase elevations

[1] This adverse reaction was identified through post-marketing surveillance for dolutegravir in combination with other ARVs. The frequency category of rare was estimated based on post-marketing reports. [2] In combination with increased transaminases.

Description of selected adverse reactions *Changes in laboratory biochemistries* Dolutegravir has been associated with an increase in serum creatinine occuring in the first week of treatment when administered with other antiretroviral medicinal products. Increases in serum creatinine occurred within the first four weeks of treatment with dolutegravir plus lamivudine and remained stable through 48 weeks. In the pooled GEMINI studies a mean change from baseline of 10.3 µmol/L (range: 36.3 µmol/L to 55.7 µmol/L) was observed after 48 weeks of treatment. These changes are linked to the inhibiting effect of dolutegravir on renal tubular transporters of creatinine. The changes are not considered to be clinically relevant and do not reflect a change in glomerular filtration rate. *Co-infection with Hepatitis B or C* In the Phase III studies for the dolutegravir single agent, patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see section Special warnings and precautions for use). *Metabolic parameters* Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section Special warnings and precautions for use). *Osteonecrosis* Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section Special warnings and precautions for use). *Immune response syndrome* In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section Special warnings and precautions for use). Paediatric population There are no clinical study data on the effects of Dovato in the paediatric population. Individual components have been investigated in adolescents (12 to 17 years). Based on limited available data with the dolutegravir single entity or lamivudine single entity used in combination with other antiretroviral agents to treat adolescents (12 to 17 years), there were no additional types of adverse reactions beyond those observed in the adult population. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: **Belgium** Federal Agency for Medicines and Health Products Division Vigilance Boîte Postale 97 1000 Brussels Madou Website: www.notifieruneffetindesirable.be e-mail: adr@afmps.be **Luxembourg** Centre Régional de Pharmacovigilance de Nancy Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) CHRU de Nancy – Hôpitaux de Brabois Rue du Morvan 54 511 Vandoeuvre Les Nancy Cedex Tél.: (+33) 3 83 65 60 85 / 87 e-mail : crpv@chru-nancy.fr ou Direction de la Santé Division de la Pharmacie et des Médicaments 20, rue de Bitbourg L-1273 Luxembourg-Hamm Tél.: (+352) 2478 5592 e-mail: pharmacovigilance@ms.etat.lu Link pour le formulaire : https://guichet.public.lu/fr/entreprises/sectoriel/sante/medecins/notification-effets-indesirables-medicaments.html **MARKETING AUTHORISATION HOLDER** ViiV Healthcare BV, Van Asch van Wijckstraat 55H, 3811 LP Amersfoort, Netherlands **DATE OF APPROVAL OF THE TEXT** 1st September 2022 (version 10) **DELIVERY STATUS** Medicinal product subject to medical prescription

References: 1. Montaner JS et al. J Acquir Immune Defic Syndr. 2010;55 Suppl 1:5. 2. Eisinger RW et al. JAMA. 2019;321(5):451–452. 3. Cahn P et al. AIDS. 2022;36(1):39-48. 4. Osiyemi O et al. Clin. Infect. Dis. 2022; ciac036. 5. Llibre JM et al. Clin. Infect. Dis. 2022; ciac130. 6. Dovato Summary of Product Characteristics.

DTG 50 mg + 3TC 300 mg used in the GEMINI studies.
HIV = human immunodeficiency virus (type 1); TDF = tenofovir disoproxil fumarate; TAF = tenofovir alafenamide; ABC = abacavir

Dovato dolutegravir/lamivudine

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