1. NAME OF THE MEDICINAL PRODUCT

Odefsey®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of emtricitabine, rilpivirine hydrochloride equivalent to 25 mg of rilpivirine and tenofovir alafenamide fumarate equivalent to 25 mg of tenofovir alafenamide.

Excipients with known effect

Each tablet contains 189.8 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Grey, capsule-shaped, film-coated tablet, debossed with “GSI” on one side of the tablet and “255” on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Odefsey is indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus-1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine and with a viral load ≤ 100,000 HIV-1 RNA copies/mL (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

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

Posology

One tablet to be taken once daily with food (see section 5.2).

If the patient misses a dose of Odefsey within 12 hours of the time it is usually taken, the patient should take Odefsey with food as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Odefsey by more than 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 4 hours of taking Odefsey another tablet should be taken with food. If a patient vomits more than 4 hours after taking Odefsey they do not need to take another dose of Odefsey until the next regularly scheduled dose.

Elderly
No dose adjustment of Odefsey is required in elderly patients (see section 5.2).

Renal impairment
No dose adjustment of Odefsey is required in adults or in adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ≥ 30 mL/min. Odefsey should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment (see section 5.2).

No dose adjustment of Odefsey is required in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis; however, Odefsey should, generally, be avoided but may be used with caution in these patients if the potential benefits are considered to outweigh the potential risks (see sections 4.4 and 5.2). On days of haemodialysis, Odefsey should be administered after completion of haemodialysis treatment.

Odefsey should be avoided in patients with estimated CrCl ≥ 15 mL/min and < 30 mL/min, or< 15 mL/min who are not on chronic haemodialysis, as the safety of Odefsey has not been established in these populations.

No data are available to make dose recommendations in children less than 18 years with end stage renal disease.
Hepatic impairment
No dose adjustment of Odefsey is required in patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic impairment. Odefsey should be used with caution in patients with moderate hepatic impairment. Odefsey has not been studied in patients with severe hepatic impairment (Child Pugh Class C); therefore, Odefsey is not recommended for use in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Odefsey in children younger than 12 years of age, or weighing < 35 kg, have not yet been established. No data are available.

Method of administration

Oral use.

Odefsey should be taken orally, once daily with food (see section 5.2). It is recommended that the film-coated tablet is not chewed, crushed or split due to the bitter taste.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Odefsey should not be co-administered with medicinal products that can result in significant decreases in rilpivirine plasma concentrations (due to cytochrome P450 [CYP]3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of Odefsey (see section 4.5), including:

- carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- rifabutin, rifampicin, rifapentine
- omeprazole, esomeprazole, dexlansoprazole, lansoprazole, pantoprazole, rabeprazole
- dexamethasone (oral and parenteral doses), except as a single dose treatment

- St. John's wort (*Hypericum perforatum*)

4.4 Special warnings and precautions for use

Virologic failure and development of resistance

There are insufficient data to justify the use in patients with prior NNRTI failure. Resistance testing and/or historical resistance data should guide the use of Odefsey (see section 5.1).

In the pooled efficacy analysis from the two Phase 3 clinical studies in adults (C209 [ECHO] and C215 [THRIVE]) through 96 weeks, patients treated with emtricitabine/tenofovir disoproxil fumarate + rilpivirine with a baseline viral load > 100,000 HIV-1 RNA copies/mL had a greater risk of virologic failure (17.6% with rilpivirine *versus* 7.6% with efavirenz) compared to patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/mL (5.9% with rilpivirine *versus* 2.4% with efavirenz). The virologic failure rate in patients treated with emtricitabine/tenofovir disoproxil fumarate + rilpivirine at Week 48 and Week 96 was 9.5% and 11.5% respectively, and 4.2% and 5.1% in the emtricitabine/tenofovir disoproxil fumarate + efavirenz arm. The difference in the rate of new virologic failures from the Week 48 to Week 96 analysis between rilpivirine and efavirenz arms was not statistically significant. Patients with a baseline viral load > 100,000 HIV-1 RNA copies/mL who experienced virologic failure exhibited a higher rate of treatment emergent resistance to the NNRTI class. More patients who failed virologically on rilpivirine than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance (see section 5.1).

Findings in adolescents (12 to less than 18 years of age) in Study C213 were generally in line with these data (for details see section 5.1).

Only adolescents deemed likely to have good adherence to antiretroviral therapy should be treated with rilpivirine, as suboptimal adherence can lead to development of resistance and the loss of future treatment options.

Cardiovascular

At supratherapeutic doses (75 mg once daily and 300 mg once daily), rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG) (see sections 4.5 and 4.9). Rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. Odefsey should be used with caution when co-administered with medicinal products with a known risk of Torsade de Pointes.

Patients co-infected with HIV and hepatitis B or C virus

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

The safety and efficacy of Odefsey in patients co-infected with HIV-1 and hepatitis C virus (HCV) have not been established.

Tenofovir alafenamide is active against hepatitis B virus (HBV). Discontinuation of Odefsey therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Odefsey should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Liver disease

The safety and efficacy of Odefsey in patients with significant underlying liver disorders have not been established.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) 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.

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, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction following exposure *in utero*

Nucleos(t)ide 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 postnatally 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 events have often been transitory. 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 nucleos(t)ide analogues, who present 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.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of 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 include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. 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.

Opportunistic infections

Patients receiving Odefsey may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

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 CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Nephrotoxicity

Post-marketing cases of renal impairment, including acute renal failure and proximal renal tubulopathy have been reported with tenofovir alafenamide-containing products. A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).
It is recommended that renal function is assessed in all patients prior to, or when initiating, therapy with Odefsey and that it is also monitored during therapy in all patients as clinically appropriate. In patients who develop clinically significant decreases in renal function, or evidence of proximal renal tubulopathy, discontinuation of Odefsey should be considered.

Patients with end stage renal disease on chronic haemodialysis

Odefsey should generally be avoided but may be used with caution in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis if the potential benefits outweigh the potential risks (see section 4.2). In a study of emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat as a fixed-dose combination tablet (E/C/F/TAF) in HIV-1 infected adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis, efficacy was maintained through 48 weeks but emtricitabine exposure was significantly higher than in patients with normal renal function. Although there were no new safety issues identified, the implications of increased emtricitabine exposure remain uncertain (see sections 4.8 and 5.2).

Pregnancy

Lower exposures of rilpivirine were observed when rilpivirine 25 mg once daily was taken during pregnancy. In the Phase 3 studies (C209 and C215), lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure, therefore viral load should be monitored closely (see sections 4.6, 5.1 and 5.2). Alternatively, switching to another antiretroviral regimen could be considered.

Co-administration of other medicinal products

Some medicinal products should not be co-administered with Odefsey (see sections 4.3 and 4.5).

Odefsey should not be co-administered with other antiretroviral medicinal products (see section 4.5).

Odefsey should not be co-administered with other medicinal products containing tenofovir alafenamide, lamivudine, tenofovir disoproxil or adefovir dipivoxil (see section 4.5).

Excipients

Odefsey contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Odefsey is indicated for use as a complete regimen for the treatment of HIV-1 infection and should not be co-administered with other antiretroviral medicinal products. Therefore, information regarding drug-drug interactions with other antiretroviral medicinal products is not provided. Interaction studies have only been performed in adults.

Emtricitabine

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low. Co-administration of emtricitabine with medicinal products that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the co-administered medicinal product. Medicinal products that decrease renal function may increase concentrations of emtricitabine.

Rilpivirine

Rilpivirine is primarily metabolised by CYP3A. Medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine (see section 5.2). Rilpivirine inhibits P-glycoprotein (P-gp) *in vitro* (50% inhibitory concentration [IC_{50}] is 9.2 μM). In a clinical study, rilpivirine did not significantly affect the pharmacokinetics of digoxin. Additionally, in a clinical drug-drug interaction study with tenofovir alafenamide, which is more sensitive to intestinal P-gp inhibition, rilpivirine did not affect tenofovir alafenamide exposures when administered concurrently, indicating that rilpivirine is not a P-gp inhibitor *in vivo*.

Rilpivirine is an *in-vitro* inhibitor of the transporter MATE-2K with an IC_{50} of < 2.7 nM. The clinical implications of this finding are currently unknown.

Tenofovir alafenamide

Tenofovir alafenamide is transported by P-gp and breast cancer resistance protein (BCRP). Medicinal products that affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption (see Table 1). Medicinal products that induce P-gp activity (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital) are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentration of tenofovir alafenamide, which may lead to loss of therapeutic effect of Odefsey and development of resistance. Co-administration of Odefsey with other medicinal products that inhibit P-gp and BCRP activity (e.g., ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole, ciclosporin) is expected to increase the absorption and plasma concentration of tenofovir alafenamide. Based on data from an *in-vitro* study, co-administration of tenofovir alafenamide and xanthine oxidase inhibitors (e.g., febuxostat) is not expected to increase systemic exposure to tenofovir *in vivo*.

Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 *in vitro*. Tenofovir alafenamide is not an inhibitor or inducer of CYP3A *in vivo*. Tenofovir alafenamide is a substrate of organic anion transporting polypeptide (OATP) 1B1 and OATP1B3

in vitro. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and OATP1B3.

Concomitant use contraindicated

Co-administration of Odefsey and medicinal products that induce CYP3A has been observed to decrease the plasma concentrations of rilpivirine which could potentially lead to loss of virologic response to Odefsey (see section 4.3) and possible resistance to rilpivirine and to the NNRTI class.

Co-administration of Odefsey with proton pump inhibitors has been observed to decrease the plasma concentrations of rilpivirine (due to an increase in gastric pH) which could potentially lead to loss of virologic response to Odefsey (see section 4.3) and possible resistance to rilpivirine and to the NNRTI class.

Concomitant use where caution is recommended

CYP enzyme inhibitors
Co-administration of Odefsey with medicinal products that inhibit CYP3A enzyme activity has been observed to increase rilpivirine plasma concentrations.

QT prolonging medicinal products
Odefsey should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes (see section 4.4).

Other interactions

Tenofovir alafenamide is not an inhibitor of human uridine diphosphate glucuronosyltransferase (UGT) 1A1 *in vitro*. It is not known whether emtricitabine, or tenofovir alafenamide are inhibitors of other UGT enzymes. Emtricitabine did not inhibit the glucuronidation reaction of a non-specific UGT substrate *in vitro*.

Interactions between Odefsey or its individual component(s) and co-administered medicinal products are listed in Table 1 below (increase is indicated as "↑", decrease as "↓" and no change as "↔").

Table 1: Interactions between Odefsey or its individual component(s) and other medicinal products

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Odefsey
ANTI-INFECTIVES		
Antifungals		
Ketoconazole (400 mg once daily)/ Rilpivirine[1]	Ketoconazole: AUC: ↓ 24% C_{min}: ↓ 66% C_{max}: ↔ Rilpivirine: AUC: ↑ 49% C_{min}: ↑ 76% C_{max}: ↑ 30% Inhibition of CYP3A *Expected:* Tenofovir alafenamide: AUC: ↑ C_{max}: ↑ Inhibition of P-gp Interaction not studied with tenofovir alafenamide. Co-administration of ketoconazole is expected to increase plasma concentrations of tenofovir alafenamide (inhibition of P-gp).	Co-administration is not recommended.
Fluconazole Itraconazole Posaconazole Voriconazole	Interaction not studied with any of the components of Odefsey. Co-administration of these antifungal agents is expected to increase plasma concentrations of rilpivirine (inhibition of CYP3A) and tenofovir alafenamide (inhibition of P-gp).	Co-administration is not recommended.
Antimycobacterials		
Rifampicin/ Rilpivirine	Rifampicin: AUC: ↔ C_{min}: N/A C_{max}: ↔ 25-desacetyl-rifampicin: AUC: ↓ 9% C_{min}: N/A C_{max}: ↔ Rilpivirine: AUC: ↓ 80% C_{min}: ↓ 89% C_{max}: ↓ 69% Induction of CYP3A *Expected:*	Co-administration is contraindicated.

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Odefsey
	Tenofovir alafenamide: AUC: ↓ C_{max}: ↓ Induction of P-gp Interaction not studied with tenofovir alafenamide. Co-administration is likely to cause significant decreases in the plasma concentrations of tenofovir alafenamide (induction of P-gp).	
Rifapentine	Interaction not studied with any of the components of Odefsey. Co-administration is likely to cause significant decreases in the plasma concentrations of rilpivirine (induction of CYP3A) and tenofovir alafenamide (induction of P-gp).	Co-administration is contraindicated.
Rifabutin (300 mg once daily)/ Rilpivirine[1]	Rifabutin: AUC: ↔ C_{min}: ↔ C_{max}: ↔ 25-O-desacetyl-rifabutin: AUC: ↔ C_{min}: ↔ C_{max}: ↔	Co-administration is contraindicated.
Rifabutin (300 mg once daily)/ Rilpivirine	Rilpivirine: AUC: ↓ 42% C_{min}: ↓ 48% C_{max}: ↓ 31% Induction of CYP3A *Expected:* Tenofovir alafenamide: AUC: ↓ C_{max}: ↓ Induction of P-gp Interaction not studied with tenofovir alafenamide. Co-administration is likely to cause significant decreases in the plasma concentrations of tenofovir alafenamide (induction of P-gp).	
Macrolide antibiotics		
Clarithromycin Erythromycin	Interaction not studied with any of the components of Odefsey. The combination of Odefsey with these macrolide antibiotics may cause an increase in the plasma concentrations of rilpivirine	Co-administration is not recommended.

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Odefsey
	(inhibition of CYP3A) and tenofovir alafenamide (inhibition of P-gp).	
Antiviral agents		
Ledipasvir/Sofosbuvir (90 mg/400 mg once daily)/ Rilpivirine	Ledipasvir: AUC: ↑ 2% C_{min}: ↑ 2% C_{max}: ↑ 1% Sofosbuvir: AUC: ↑ 5% C_{max}: ↓ 4% Sofosbuvir metabolite GS-331007: AUC: ↑ 8% C_{min}: ↑ 10% C_{max}: ↑ 8% Rilpivirine: AUC: ↓ 5% C_{min}: ↓ 7% C_{max}: ↓ 3%	No dose adjustment is required.
Ledipasvir/Sofosbuvir (90 mg/400 mg once daily)/ Tenofovir alafenamide	Tenofovir alafenamide: AUC: ↑ 32% C_{max}: ↑ 3%	
Sofosbuvir/Velpatasvir (400 mg/100 mg once daily)/ Rilpivirine[2]	Sofosbuvir: AUC: ↔ C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Velpatasvir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Rilpivirine: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment is required.

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Odefsey
Sofosbuvir/Velpatasvir/Voxilaprevir (400 mg/100 mg/100 mg + 100 mg once daily)[3]/ Emtricitabine/Rilpivirine/Tenofovir alafenamide (200 mg/25 mg/25 mg once daily)	Sofosbuvir: AUC: ↔ C_{min}: N/A C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ C_{min}: N/A C_{max}: ↔ Velpatasvir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Voxilaprevir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Emtricitabine: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Rilpivirine: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Tenofovir alafenamide: AUC: ↑ 52% C_{min}: N/A C_{max}: ↑ 32%	No dose adjustment is required.
Sofosbuvir (400 mg once daily)/ Rilpivirine (25 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↑ 21% Sofosbuvir metabolite GS-331007: AUC: ↔ C_{max}: ↔ Rilpivirine: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment is required.

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Odefsey
ANTICONVULSANTS		
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Interaction not studied with any of the components of Odefsey. Co-administration may cause significant decreases in the plasma concentrations of rilpivirine (induction of CYP3A) and tenofovir alafenamide (induction of P-gp).	Co-administration is contraindicated.
GLUCOCORTICOIDS		
Dexamethasone (systemic, except for single dose use)	Interaction not studied with any of the components of Odefsey. Significant dose dependent decreases in rilpivirine plasma concentrations are expected (induction of CYP3A).	Co-administration is contraindicated.
PROTON PUMP INHIBITORS		
Omeprazole (20 mg once daily)/ Rilpivirine[1]	Omeprazole: AUC: ↓ 14% C_{min}: N/A C_{max}: ↓ 14% Rilpivirine: AUC: ↓ 40% C_{min}: ↓ 33% C_{max}: ↓ 40% Reduced absorption, increase in gastric pH	Co-administration is contraindicated.
Lansoprazole Rabeprazole Pantoprazole Esomeprazole Dexlansoprazole	Interaction not studied with any of the components of Odefsey. Significant decreases in rilpivirine plasma concentrations are expected (reduced absorption, increase in gastric pH).	Co-administration is contraindicated.
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)	Interaction not studied with any of the components of Odefsey. Co-administration may cause significant decreases in the plasma concentrations of rilpivirine (induction of CYP3A) and tenofovir alafenamide (induction of P-gp).	Co-administration is contraindicated.

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Odefsey
H_2-RECEPTOR ANTAGONISTS		
Famotidine (40 mg single dose taken 12 hours before rilpivirine)/ Rilpivirine[1]	Rilpivirine: AUC: ↓ 9% C_{min}: N/A C_{max}: ↔	Only H_2-receptor antagonists that can be dosed once daily should be used. A strict dosing schedule with intake of the H_2-receptor antagonists at least 12 hours before or at least 4 hours after Odefsey should be used.
Famotidine (40 mg single dose taken 2 hours before rilpivirine)/ Rilpivirine[1]	Rilpivirine: AUC: ↓ 76% C_{min}: N/A C_{max}: ↓ 85% Reduced absorption, increase in gastric pH	
Famotidine (40 mg single dose taken 4 hours after rilpivirine)/ Rilpivirine[1]	Rilpivirine: AUC: ↑ 13% C_{min}: N/A C_{max}: ↑ 21%	
Cimetidine Nizatidine Ranitidine	Interaction not studied with any of the components of Odefsey. Co-administration may cause significant decreases in rilpivirine plasma concentrations (reduced absorption, increase in gastric pH).	
ANTACIDS		
Antacids (e.g., aluminium or magnesium hydroxide, calcium carbonate)	Interaction not studied with any of the components of Odefsey. Co-administration may cause significant decreases in rilpivirine plasma concentrations (reduced absorption, increase in gastric pH).	Antacids should only be administered either at least 2 hours before or at least 4 hours after Odefsey.
ORAL CONTRACEPTIVES		
Ethinylestradiol (0.035 mg once daily)/ Rilpivirine	Ethinylestradiol: AUC: ↔ C_{min}: ↔ C_{max}: ↑ 17%	No dose adjustment is required.
Norethindrone (1 mg once daily)/ Rilpivirine	Norethindrone: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Rilpivirine: AUC: ↔* C_{min}: ↔* C_{max}: ↔* *based on historic controls	

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Odefsey
Norgestimate (0.180/0.215/0.250 mg once daily)/ Ethinylestradiol (0.025 mg once daily)/ Emtricitabine/Tenofovir alafenamide (200/25 mg once daily)	Norelgestromin: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Norgestrel: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Ethinylestradiol: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment is required.
NARCOTIC ANALGESICS		
Methadone (60-100 mg once daily, individualised dose)/ Rilpivirine	R(-) methadone: AUC: ↓ 16% C_{min}: ↓ 22% C_{max}: ↓ 14% S(+) methadone: AUC: ↓ 16% C_{min}: ↓ 21% C_{max}: ↓ 13% Rilpivirine: AUC: ↔* C_{min}: ↔* C_{max}: ↔* *based on historic controls	No dose adjustments are required. Clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
ANALGESICS		
Paracetamol (500 mg single dose)/ Rilpivirine[1]	Paracetamol: AUC: ↔ C_{min}: N/A C_{max}: ↔ Rilpivirine: AUC: ↔ C_{min}: ↑ 26% C_{max}: ↔	No dose adjustment is required.
ANTIARRHYTHMICS		
Digoxin/ Rilpivirine	Digoxin: AUC: ↔ C_{min}: N/A C_{max}: ↔	No dose adjustment is required.
ANTICOAGULANTS		
Dabigatran etexilate	Interaction not studied with any of the components of Odefsey. A risk for increases in dabigatran plasma concentrations cannot be excluded (inhibition of intestinal P-gp).	Co-administration should be used with caution.

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Odefsey
IMMUNOSUPPRESSANTS		
Ciclosporin	Interaction not studied with any of the components of Odefsey. Co-administration of ciclosporin is expected to increase plasma concentrations of rilpivirine (inhibition of CYP3A) and tenofovir alafenamide (inhibition of P-gp).	Co-administration is not recommended.
ANTIDIABETICS		
Metformin (850 mg single dose)/ Rilpivirine	Metformin: AUC: ↔ C_{min}: N/A C_{max}: ↔	No dose adjustment is required.
HMG CO-A REDUCTASE INHIBITORS		
Atorvastatin (40 mg once daily)/ Rilpivirine[1]	Atorvastatin: AUC: ↔ C_{min}: ↓ 15% C_{max}: ↑ 35% Rilpivirine: AUC: ↔ C_{min}: ↔ C_{max}: ↓ 9%	No dose adjustment is required.
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS		
Sildenafil (50 mg single dose)/ Rilpivirine[1]	Sildenafil: AUC: ↔ C_{min}: N/A C_{max}: ↔ Rilpivirine: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment is required.
Vardenafil Tadalafil	Interaction not studied with any of the components of Odefsey. These are medicinal products within class where similar interactions could be predicted.	No dose adjustment is required.
HYPNOTICS/SEDATIVES		
Midazolam (2.5 mg, orally, single dose)/ Tenofovir alafenamide Midazolam (1 mg, intravenously, single dose)/ Tenofovir alafenamide	Midazolam: AUC: ↑ 12% C_{min}: N/A C_{max}: ↑ 2% Midazolam: AUC: ↑ 8% C_{min}: N/A C_{max}: ↓ 1%	No dose adjustment is required.

N/A = not applicable

[1] This interaction study has been performed with a dose higher than the recommended dose for rilpivirine hydrochloride assessing the maximal effect on the co-administered medicinal product. The dosing recommendation is applicable to the recommended dose of rilpivirine of 25 mg once daily.

[2] Study conducted with emtricitabine/rilpivirine/tenofovir disoproxil fumarate fixed-dose combination tablet.
[3] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Studies conducted with other medicinal products

Based on drug-drug interaction studies conducted with the components of Odefsey, no clinically significant interactions are expected when Odefsey is combined with the following medicinal products: buprenorphine, naloxone and norbuprenorphine.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

The use of Odefsey should be accompanied by the use of effective contraception.

Pregnancy

There are no adequate and well-controlled studies of Odefsey or its components in pregnant women.

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of tenofovir alafenamide in pregnant women A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformative or foetal/neonatal toxicity of rilpivirine (see sections 4.4, 5.1 and 5.2). Lower exposures of rilpivirine were observed during pregnancy; therefore viral load should be monitored closely. A large amount of data on pregnant women (more than 1,000 exposed outcomes) indicate no malformative nor foetal/neonatal toxicity associated with emtricitabine.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3) with the components of Odefsey.

Odefsey should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

Emtricitabine is excreted in human milk. It is not known whether rilpivirine or tenofovir alafenamide are excreted in human milk. In animal studies it has been shown that tenofovir is excreted in milk. Rilpivirine is excreted in the milk of rats.

There is insufficient information on the effects of all the components of Odefsey in newborns/infants.

Because of the potential for adverse reactions in breastfed infants, women should be instructed not to breast-feed if they are receiving Odefsey.
In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants.

Fertility

No human data on the effect of Odefsey on fertility are available. Animal studies do not indicate harmful effects of emtricitabine, rilpivirine hydrochloride or tenofovir alafenamide on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Odefsey may have minor influence on the ability to drive and use machines. Patients should be informed that fatigue, dizziness and somnolence have been reported during treatment with the components of Odefsey (see section 4.8). This should be considered when assessing a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions in clinical studies of treatment-naïve patients taking emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat were nausea (11%), diarrhoea (7%), and headache (6%). The most frequently reported adverse reactions in clinical studies of treatment-naïve patients taking rilpivirine hydrochloride in combination with emtricitabine + tenofovir disoproxil fumarate were nausea (9%), dizziness (8%), abnormal dreams (8%), headache (6%), diarrhoea (5%) and insomnia (5%).

Tabulated summary of adverse reactions

Assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies in which patients received emtricitabine + tenofovir alafenamide given with elvitegravir + cobicistat as a fixed-dose combination tablet, pooled data from patients who received rilpivirine 25 mg once daily in combination with other antiretroviral medicinal products in the controlled studies TMC278-C209 and TMC278-C215, patients who received Odefsey in Studies GS-US-366-1216 and GS-US-366-1160, and post-marketing experience.

The adverse reactions in Table 2 are listed by system organ class and highest frequency observed. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1,000 to < 1/100).

Table 2: Tabulated list of adverse reactions

Frequency	Adverse reaction
Blood and lymphatic system disorders	
Common:	decreased white blood cell count[1], decreased haemoglobin[1], decreased platelet count[1]
Uncommon:	anaemia[2]
Immune system disorders	
Uncommon:	immune reactivation syndrome[1]
Metabolism and nutrition disorders	
Very common:	increased total cholesterol (fasted)[1], increased LDL-cholesterol (fasted)[1]
Common:	decreased appetite[1], increased triglycerides (fasted)[1]
Psychiatric disorders	
Very common:	insomnia[1]
Common:	depression[1], abnormal dreams[1, 3], sleep disorders[1], depressed mood[1]
Nervous system disorders	
Very common:	headache[1, 3], dizziness[1, 3]
Common:	somnolence[1]

Frequency	Adverse reaction
Gastrointestinal disorders	
Very common:	nausea[1, 3], increased pancreatic amylase[1]
Common:	abdominal pain[1, 3], vomiting[1, 3], increased lipase[1], abdominal discomfort[1], dry mouth[1], flatulence[3], diarrhoea[3]
Uncommon:	dyspepsia[3]
Hepatobiliary disorders	
Very common:	increased transaminases (AST and/or ALT)[1]
Common:	increased bilirubin[1]
Skin and subcutaneous tissue disorders	
Common:	rash[1, 3]
Uncommon:	severe skin reactions with systemic symptoms[4], angioedema[5, 6], pruritus[3], urticaria[6]
Musculoskeletal and connective tissue disorders	
Uncommon:	arthralgia[3]
General disorders and administration site conditions	
Common:	fatigue[1, 3]

[1] Adverse reactions identified from rilpivirine clinical studies.

[2] This adverse reaction was not observed in the Phase 3 studies of emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat or in the Phase 3 studies with Odefsey but identified from clinical studies or post-marketing experience of emtricitabine when used with other antiretrovirals.

[3] Adverse reactions identified from clinical studies of emtricitabine + tenofovir alafenamide containing products.

[4] Adverse reaction identified through post-marketing surveillance of emtricitabine/rilpivirine/tenofovir disoproxil fumarate

[5] Adverse reaction identified through post-marketing surveillance for emtricitabine-containing products.

[6] Adverse reaction identified through post-marketing surveillance for tenofovir alafenamide-containing products.

Laboratory abnormalities

Changes in serum creatinine for rilpivirine-containing regimens
The pooled data from the Phase 3 TMC278-C209 and TMC278-C215 studies of treatment-naïve patients also demonstrate that serum creatinine increased and estimated glomerular filtration rate (eGFR) decreased over 96 weeks of treatment with rilpivirine. Most of this increase in creatinine and decrease in eGFR occurred within the first four weeks of treatment. Over 96 weeks of treatment with rilpivirine mean changes of 0.1 mg/dL (range: -0.3 mg/dL to 0.6 mg/dL) for creatinine and -13.3 mL/min/1.73 m^2 (range: -63.7 mL/min/1.73 m^2 to 40.1 mL/min/1.73 m^2) for eGFR were observed. In patients who entered the studies with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in patients with normal renal function. These increases do not reflect a change in actual glomerular filtration rate (GFR).

Changes in lipid laboratory tests
In studies in treatment-naïve patients receiving emtricitabine + tenofovir alafenamide (FTC + TAF) or emtricitabine + tenofovir disoproxil fumarate (FTC + TDF), both given with elvitegravir + cobicistat as a fixed-dose combination tablet, increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, direct low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, and triglycerides at Week 144. The median increase from baseline for these parameters was greater in patients receiving FTC + TAF compared with patients receiving FTC + TDF ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL- and HDL-cholesterol, and triglycerides). Median (Q1, Q3) change from baseline at Week 144 in total cholesterol to HDL-cholesterol ratio was 0.2 (-0.3, 0.7) in patients receiving FTC + TAF and 0.1 (-0.4, 0.6) in patients receiving FTC + TDF ($p = 0.006$ for the difference between treatment groups).

Switching from a TDF-based regimen to Odefsey may lead to slight increases in lipid parameters. In a study of virologically suppressed patients switching from FTC/RPV/TDF to Odefsey (Study GS-US-366-1216), increases from baseline were observed in fasting values of total cholesterol, direct LDL cholesterol, HDL cholesterol, and triglycerides in the Odefsey arm; and no clinically relevant

changes from baseline in median fasting values for total cholesterol to HDL-cholesterol ratio were observed in either treatment arm at Week 96. In a study of virologically suppressed patients switching from EFV/FTC/TDF to Odefsey (Study GS-US-366-1160), decreases from baseline were observed in the fasting values of total cholesterol and HDL cholesterol in the Odefsey arm; no clinically relevant changes from baseline in median fasting values for total cholesterol to HDL-cholesterol ratio, direct LDL cholesterol or triglycerides were observed in either treatment arm at Week 96.

Cortisol
In the pooled Phase 3 TMC278-C209 and TMC278-C215 studies of treatment-naïve patients, at Week 96, there was an overall mean change from baseline in basal cortisol of -19.1 (-30.85; -7.37) nmol/L in the rilpivirine arm and of -0.6 (-13.29; 12.17) nmol/L in the efavirenz arm. At Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the rilpivirine arm (+18.4 ± 8.36 nmol/L) than in the efavirenz arm (+54.1 ± 7.24 nmol/L). Mean values for the rilpivirine arm for both basal and ACTH-stimulated cortisol at Week 96 were within the normal range. These changes in adrenal safety parameters were not clinically relevant. There were no clinical signs or symptoms suggestive of adrenal or gonadal dysfunction in adults.

Description of selected adverse reactions

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Immune Reactivation Syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of 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 4.4).

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 4.4).

Severe skin reactions
Severe skin reactions with systemic symptoms have been reported during post-marketing experience of emtricitabine/rilpivirine/tenofovir disoproxil fumarate including rashes accompanied by fever, blisters, conjunctivitis, angioedema, elevated liver function tests, and/or eosinophilia.

Paediatric population

The safety of emtricitabine + tenofovir alafenamide was evaluated through 48 weeks in an open-label clinical study (GS-US-292-0106) in which 50 HIV-1 infected, treatment-naïve paediatric patients aged 12 to < 18 years received emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat as a fixed-dose combination tablet. In this study, the safety profile in adolescent patients was similar to that in adults (see section 5.1).

The safety assessment of rilpivirine is based on Week 48 data from one single-arm open-label study (TMC278-C213) in 36 paediatric patients 12 to < 18 years and weighing at least 32 kg. No patients discontinued rilpivirine due to adverse reactions. No new adverse reactions were identified compared to those seen in adults. Most adverse reactions were Grade 1 or 2. Adverse reactions (all grades) of very common frequency were headache, depression, somnolence and nausea. No Grade 3-4 laboratory

abnormalities for AST/ALT or Grade 3-4 adverse reactions of transaminase increased were reported (see section 5.1).

Other special populations

Patients with renal impairment
The safety of emtricitabine + tenofovir alafenamide was evaluated through 144 weeks in an open-label clinical study (GS-US-292-0112), in which 248 HIV-1 infected patients who were either treatment-naïve (n = 6) or virologically suppressed (n = 242) with mild to moderate renal impairment (estimated glomerular filtration rate by Cockcroft-Gault method [$eGFR_{CG}$]: 30-69 mL/min) received emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat as a fixed-dose combination tablet. The safety profile in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (see section 5.1).

The safety of emtricitabine + tenofovir alafenamide was evaluated through 48 weeks in a single arm, open-label clinical study (GS-US-292-1825) in which 55 virologically suppressed HIV-1 infected patients with end stage renal disease ($eGFR_{CG}$ < 15 mL/min) on chronic haemodialysis received emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat as a fixed-dose combination tablet. There were no new safety issues identified in patients with end stage renal disease on chronic haemodialysis receiving emtricitabine + tenofovir alafenamide, given with elvitegravir + cobicistat as a fixed-dose combination tablet (see section 5.2).

Patients co-infected with HIV and HBV
The safety of emtricitabine + tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]) was evaluated in 72 HIV/HBV co-infected patients receiving treatment for HIV in an open-label clinical study (GS-US-292-1249), through Week 48, in which patients were switched from another antiretroviral regimen (which included TDF in 69 of 72 patients) to E/C/F/TAF. Based on these limited data, the safety profile of emtricitabine + tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet, in patients with HIV/HBV co-infection, was similar to that in patients with HIV-1 monoinfection.

In patients co-infected with hepatitis B or C virus receiving rilpivirine, the incidence of hepatic enzyme elevation was higher than in patients receiving rilpivirine who were not co-infected. The pharmacokinetic exposure of rilpivirine in co-infected patients was comparable to that in patients without co-infection.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary including observation of the clinical status of the patient and monitoring of vital signs and ECG (QT interval).

There is no specific antidote for overdose with Odefsey. Up to 30% of the emtricitabine dose can be removed by haemodialysis. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. It is not known whether emtricitabine or tenofovir can be removed by

peritoneal dialysis. Since rilpivirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations, ATC code: J05AR19

Mechanism of action and pharmacodynamic effects

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and analogue of 2'-deoxycytidine. Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine triphosphate. Emtricitabine triphosphate competitively inhibits HIV-1 reverse transcriptase (RT), resulting in deoxyribonucleic acid (DNA) chain termination. Emtricitabine has activity against HIV-1, HIV-2, and HBV.

Rilpivirine is a diarylpyrimidine NNRTI of HIV-1. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 RT. Rilpivirine does not inhibit the human cellular DNA polymerases α, β and mitochondrial DNA polymerase γ.

Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil fumarate in loading tenofovir into peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV RT, resulting in DNA chain termination. Tenofovir has activity against HIV-1, HIV-2 and HBV.

Antiviral activity *in vitro*

The combinations of emtricitabine, rilpivirine, and tenofovir alafenamide were not antagonistic and showed synergistic effects with each other in cell culture combination antiviral activity assays.

The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI CCR5 cell line, and PBMCs. The 50% effective concentration (EC_{50}) values for emtricitabine were in the range of 0.0013 to 0.64 μM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 subtype A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 μM) and showed activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 μM).

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM (0.27 ng/mL). Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/mL), group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/mL), and showed limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2,510 to 10,830 nM (920 to 3,970 ng/mL).

The antiviral activity of tenofovir alafenamide against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4+-T lymphocytes. The EC_{50} values for tenofovir alafenamide were in the range of 2.0 to 14.7 nM. Tenofovir alafenamide displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O),

including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and showed activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

Resistance

Considering all of the available *in vitro* data and data generated in treatment-naïve patients, the following resistance-associated mutations in HIV-1 RT, when present at baseline, may affect the activity of Odefsey: K65R, K70E, K101E, K101P, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, M184I, M184V, Y188L, H221Y, F227C, M230I, M230L and the combination of L100I and K103N.

A negative impact by NNRTI mutations other than those listed above (e.g., mutations K103N or L100I as single mutations) cannot be excluded, since this was not studied *in vivo* in a sufficient number of patients.

As with other antiretroviral medicinal products, resistance testing and/or historical resistance data should guide the use of Odefsey (see section 4.4).

In vitro
Reduced susceptibility to emtricitabine is associated with M184V/I mutations in HIV-1 RT.

Rilpivirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI-resistant HIV-1. The most commonly observed amino acid substitutions that emerged included: L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C, and M230I.

HIV-1 isolates with reduced susceptibility to tenofovir alafenamide expressed a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed.

In treatment-naïve adult patients
In the Week 144 pooled analysis of antiretroviral-naïve patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in the Phase 3 studies GS-US-292-0104 and GS-US-292-0111, the development of one or more primary resistance-associated mutations was observed in HIV-1 isolates from 12 of 866 (1.4%) patients treated with E/C/F/TAF. Among these 12 HIV-1 isolates, the mutations that emerged were M184V/I (n = 11) and K65R/N (n = 2) in RT and T66T/A/I/V (n = 2), E92Q (n = 4), Q148Q/R (n = 1), and N155H (n = 2) in integrase.

In the Week 96 pooled analysis for patients receiving emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) + rilpivirine hydrochloride in the Phase 3 clinical studies TMC278-C209 and TMC278-C215, HIV-1 isolates from 43 patients had an amino acid substitution associated with NNRTI (n = 39) or NRTI (n = 41) resistance. The NNRTI resistance-associated mutations that developed most commonly were: V90I, K101E, E138K/Q, V179I, Y181C, V189I, H221Y and F227C. The presence of V90I and V189I at baseline did not affect the response. Fifty-two percent of HIV-1 isolates with emergent resistance in the rilpivirine arm developed concomitant NNRTI and NRTI mutations, most frequently E138K and M184V. The mutations associated with NRTI resistance that developed in 3 or more patient isolates were: K65R, K70E, M184V/I and K219E.

Through Week 96, fewer patients in the rilpivirine arm with baseline viral load ≤ 100,000 copies/mL had emerging resistance-associated substitutions and/or phenotypic resistance to rilpivirine (7/288) than patients with baseline viral load > 100,000 copies/mL (30/262).

In virologically suppressed patients
One patient with emergent resistance (M184M/I) was identified in a clinical study of virologically suppressed patients who switched from a regimen containing emtricitabine + tenofovir disoproxil fumarate to E/C/F/TAF in a fixed-dose combination (FDC) tablet (GS-US-292-0109, n = 959).

Through Week 96, in patients who switched to Odefsey from emtricitabine/rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF) or efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) (Studies GS-US-366-1216 and GS-US-366-1160; n = 754), no treatment-emergent resistance-associated mutations were detected.

In patients co-infected with HIV and HBV
In a clinical study of HIV virologically suppressed patients co-infected with chronic hepatitis B, who received E/C/F/TAF for 48 weeks (GS-US-292-1249, n = 72), 2 patients qualified for resistance analysis. In these 2 patients, no amino acid substitutions associated with resistance to any of the components of E/C/F/TAF were identified in HIV-1 or HBV.

Cross-resistance

Emtricitabine-resistant viruses with the M184V/I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

In a panel of 67 HIV-1 recombinant laboratory strains with one resistance-associated mutation at RT positions associated with NNRTI resistance, the only single resistance-associated mutations associated with a loss of susceptibility to rilpivirine were K101P and Y181V/I. The K103N substitution alone did not result in reduced susceptibility to rilpivirine, but the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine. In another study, the Y188L substitution resulted in a reduced susceptibility to rilpivirine of 9-fold for clinical isolates and 6-fold for site-directed mutants.

In patients receiving rilpivirine hydrochloride in combination with FTC/TDF in Phase 3 studies (TMC278-C209 and TMC278-C215 pooled data), most HIV-1 isolates with emergent phenotypic resistance to rilpivirine had cross-resistance to at least one other NNRTI (28/31).

The K65R and also the K70E substitution result in reduced susceptibility to abacavir, didanosine, lamivudine, emtricitabine, and tenofovir, but retain sensitivity to zidovudine.

Clinical data

Clinical efficacy of Odefsey was established from studies conducted with emtricitabine + tenofovir alafenamide when given with elvitegravir + cobicistat as an E/C/F/TAF FDC tablet, from studies conducted with rilpivirine when given with FTC/TDF as individual components or as a FTC/RPV/TDF FDC tablet, and from studies conducted with Odefsey.

Emtricitabine + tenofovir alafenamide containing regimens
Treatment-naïve and virologically suppressed HIV-1 infected adult patients
In Study GS-US-292-0104 and Study GS-US-292-0111, patients received either E/C/F/TAF (n = 866) or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) (n = 867) once daily, both given as FDC tablets.

The mean age was 36 years (range 18-76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies/mL (range 1.3-7.0) and 23% of patients had baseline viral loads > 100,000 copies/mL. The mean baseline CD4+ cell count was 427 cells/mm^3 (range 0-1,360) and 13% had CD4+ cell counts < 200 cells/mm^3.

In Studies GS-US-292-0104 and GS-US-292-0111, E/C/F/TAF demonstrated statistical superiority in achieving HIV-1 RNA < 50 copies/mL when compared to E/C/F/TDF at Week 144. The difference in percentage was 4.2% (95% CI: 0.6% to 7.8%). Pooled treatment outcomes at 48 and 144 weeks are shown in Table 3.

In Study GS-US-292-0109, the efficacy and safety of switching from either EFV/FTC/TDF, FTC/TDF plus atazanavir (boosted by either cobicistat or ritonavir), or E/C/F/TDF to E/C/F/TAF FDC tablet were evaluated in a randomised, open-label study of virologically suppressed (HIV-1 RNA < 50 copies/mL) HIV-1 infected adults (n = 959 switching to E/C/F/TAF, n = 477 Stayed on Baseline Regimen [SBR]). Patients had a mean age of 41 years (range 21-77), 89% were male, 67% were White, and 19% were Black. The mean baseline CD4+ cell count was 697 cells/mm^3 (range 79-1,951).

In Study GS-US-292-0109, switching from a tenofovir disoproxil fumarate-based regimen to E/C/F/TAF was superior in maintaining HIV-1 RNA < 50 copies/mL compared to staying on the baseline regimen. Pooled treatment outcomes at 48 weeks are shown in Table 3.

Table 3: Virologic outcomes of Studies GS-US-292-0104, GS-US-292-0111 at Week 48 and Week 144[a], and GS-US-292-0109 at Week 48[a]

	Treatment-naïve adults in Studies GS-US-292-0104 and GS-US-292-0111[b]				**Virologically suppressed adults in Study GS-US-292-0109**	
	Week 48		**Week 144**		**Week 48**	
	E/C/F/TAF (n = 866)	**E/C/F/TDF (n = 867)**	**E/C/F/TAF (n = 866)**	**E/C/F/TDF (n = 867)**	**E/C/F/TAF (n = 959)**	**Baseline regimen (n = 477)**
HIV-1 RNA < 50 copies/mL	92%	90%	84%	80%	97%	93%
Treatment difference	2.0% (95% CI: -0.7% to 4.7%)		4.2% (95% CI: 0.6% to 7.8%)		4.1% (95% CI: 1.6% to 6.7%, p < 0.001[c])	
HIV-1 RNA ≥ 50 copies/mL[d]	4%	4%	5%	4%	1%	1%
No virologic data in Week 48 or 144 window	4%	6%	11%	16%	2%	6%
Discontinued study drug due to AE or death[e]	1%	2%	1%	3%	1%	1%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[f]	2%	4%	9%	11%	1%	4%
Missing data during window but on study drug	1%	< 1%	1%	1%	0%	<1%
HIV-1 RNA < 20 copies/mL	84%	84%	81%	76%		
Treatment difference	0.4% (95% CI: -3.0% to 3.8%)		5.4% (95% CI: 1.5% to 9.2%)			

	Treatment-naïve adults in Studies GS-US-292-0104 and GS-US-292-0111[b]				Virologically suppressed adults in Study GS-US-292-0109	
	Week 48		Week 144		Week 48	
	E/C/F/TAF (n = 866)	E/C/F/TDF (n = 867)	E/C/F/TAF (n = 866)	E/C/F/TDF (n = 867)	E/C/F/TAF (n = 959)	Baseline regimen (n = 477)
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by prior treatment regimen[d]						
EFV/FTC/TDF					96%	90%
FTC/TDF plus boosted atazanavir					97%	92%
E/C/F/TDF					98%	97%

a Week 48 window was between Day 294 and 377 (inclusive); Week 144 window was between Day 966 and 1,049 (inclusive).

b In both studies, patients were stratified by baseline HIV-1 RNA (≤ 100,000 copies/mL, > 100,000 copies/mL to ≤ 400,000 copies/mL, or > 400,000 copies/mL), by CD4+ cell count (< 50 cells/µL, 50-199 cells/µL, or ≥ 200 cells/µL), and by region (US or ex US).

c P-value for the superiority test comparing the percentages of virologic success was from the CMH (Cochran-Mantel-Haenszel) test stratified by the prior treatment regimen (EFV/FTC/TDF, FTC/TDF plus boosted atazanavir, or E/C/F/TDF).

d Includes patients who had ≥ 50 copies/mL in the Week 48 or Week 144 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

e Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

f Includes patients who discontinued for reasons other than an AE, death, or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

In Studies GS-US-292-0104 and GS-US-292-0111, the rate of virologic success was similar across patient subgroups (age, gender, race, baseline HIV-1 RNA, or baseline CD4+ cell count).

The mean increase from baseline in CD4+ cell count was 230 cells/mm^3 in E/C/F/TAF-treated patients and 211 cells/mm^3 in E/C/F/TDF-treated patients (p = 0.024) at Week 48 and 326 cells/mm^3 in E/C/F/TAF-treated patients and 305 cells/mm^3 in E/C/F/TDF-treated patients (p = 0.06) at Week 144.

Rilpivirine-containing regimens
Treatment-naïve HIV-1 infected adult patients
The efficacy of rilpivirine is based on the analyses of 96 weeks data from two randomised, double-blind, controlled studies in treatment-naïve patients (TMC278-C209 and emtricitabine + tenofovir disoproxil fumarate subset of TMC278-C215).

In the pooled analysis for TMC278-C209 and TMC278-C215 of 1,096 patients who received a background regimen (BR) of FTC/TDF, demographic and baseline characteristics were balanced between the rilpivirine and efavirenz (EFV) arms. The median age was 36 years, 78% were male and 62% White and 24% Black/African American. Median plasma HIV-1 RNA was 5.0 $\log_{10}$ copies/mL and median CD4+ cell count was 255 cells/mm^3.

Overall response and a subgroup analysis of the virologic response (< 50 HIV-1 RNA copies/mL) at both 48 weeks and 96 weeks, and virologic failure by baseline viral load (pooled data from the two Phase 3 clinical studies, TMC278-C209 and TMC278-C215, for patients receiving the FTC/TDF BR) are presented in Table 4.

Table 4: Virologic outcomes of randomised treatment of Studies TMC278-C209 and TMC278-C215 (pooled data for patients receiving rilpivirine hydrochloride or efavirenz in combination with FTC/TDF) at Week 48 (primary) and Week 96

	RPV + FTC/TDF (n = 550)	EFV + FTC/TDF (n = 546)	RPV + FTC/TDF (n = 550)	EFV + FTC/TDF (n = 546)
	Week 48		Week 96	
Overall response (HIV-1 RNA < 50 copies/mL (TLOVR[a]))[b]	83.5% (459/550)	82.4% (450/546)	76.9% (423/550)	77.3% (422/546)
By baseline viral load (copies/mL)				
≤ 100,000	**89.6% (258/288)**	**84.8% (217/256)**	**83.7% (241/288)**	**80.8% (206/255)**
> 100,000	76.7% (201/262)	80.3% (233/290)	69.5% (182/262)	74.2% (216/291)
Non-response				
Virologic failure (all patients)	9.5% (52/550)	4.2% (23/546)	11.5% (63/550)[c]	5.1% (28/546)[d]
By baseline viral load (copies/mL)				
≤ 100,000	**4.2% (12/288)**	**2.3% (6/256)**	**5.9% (17/288)**	**2.4% (6/255)**
> 100,000	15.3% (40/262)	5.9% (17/290)	17.6% (46/262)	7.6% (22/291)
Death	0	0.2% (1/546)	0	0.7% (4/546)
Discontinued due to adverse event (AE)	2.2% (12/550)	7.1% (39/546)	3.6% (20/550)	8.1% (44/546)
Discontinued for non-AE reason[e]	4.9% (27/550)	6.0% (33/546)	8% (44/550)	8.8% (48/546)

EFV = efavirenz; RPV = rilpivirine

a ITT TLOVR = Intention to treat time to loss of virologic response.

b The difference of response rate at Week 48 is 1% (95% confidence interval -3% to 6%) using normal approximation.

c There were 17 new virologic failures between the Week 48 primary analysis and Week 96 (6 patients with baseline viral load ≤ 100,000 copies/mL and 11 patients with baseline viral load > 100,000 copies/mL). There were also reclassifications in the Week 48 primary analysis with the most common being reclassification from virologic failure to discontinued for non-AE reasons.

d There were 10 new virologic failures between the Week 48 primary analysis and Week 96 (3 patients with baseline viral load ≤ 100,000 copies/mL and 7 patients with baseline viral load > 100,000 copies/mL). There were also reclassifications in the Week 48 primary analysis with the most common being reclassification from virologic failure to discontinued for non-AE reasons.

e e.g., lost to follow up, non-compliance, withdrew consent.

FTC/TDF + rilpivirine hydrochloride was non-inferior in achieving HIV-1 RNA < 50 copies/mL compared to FTC/TDF + efavirenz.

Odefsey regimen

Virologically suppressed HIV-1 infected adult patients

In Study GS-US-366-1216, the efficacy and safety of switching from FTC/RPV/TDF to Odefsey were evaluated in a randomised, double-blind study of virologically suppressed HIV-1 infected adults. Patients had a mean age of 45 years (range 23−72), 90% were male, 75% were White, and 19% were Black. The mean baseline CD4+ cell count was 709 cells/mm^3 (range: 104-2,527).

In Study GS-US-366-1160, the efficacy and safety of switching from EFV/FTC/TDF to Odefsey were evaluated in a randomised, double-blind study of virologically suppressed HIV-1 infected adults. Patients had a mean age of 48 years (range 19−76), 87% were male, 67% were White, and 27% were Black. The mean baseline CD4+ cell count was 700 cells/mm^3 (range 140−1,862).

Treatment outcomes of Studies GS-US-366-1216 and GS-US-366-1160 are presented in Table 5.

Table 5: Virologic outcomes of Studies GS-US-366-1216 and GS-US-366-1160 at Weeks 48[a] and 96[b]

	GS-US-366-1216				GS-US-366-1160			
	Week 48		Week 96		Week 48		Week 96	
	ODE (n = 316)	FTC/RPV /TDF (n = 313)[c]	ODE (n = 316)	FTC/RPV /TDF (n = 313)[c]	ODE (n = 438)	EFV/FTC /TDF (n = 437)	ODE (n = 438)	EFV/FTC /TDF (n = 437)
HIV-1 RNA < 50 copies/mL	94%	94%	89%	88%	90%	92%	85%	85%
Treatment difference	-0.3% (95% CI: -4.2% to 3.7%)		0.7% (95% CI: -4.3% to 5.8%)		-2.0% (95% CI: -5.9% to 1.8%)		0% (95% CI: -4.8% to 4.8%)	
HIV-1 RNA ≥ 50 copies/mL[d]	1%	0%	1%	1%	1%	1%	1%	1%
No virologic data in Week 48 or 96 window	6%	6%	10%	11%	9%	7%	14%	14%
Discontinued study drug due to AE or death and last available HIV-1 RNA < 50 copies/mL	2%	1%	2%	3%	3%	1%	4%	3%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[e]	4%	4%	8%	8%	5%	5%	10%	11%
Missing data during window but on study drug	< 1%	1%	1%	0	1%	1%	<1%	0

ODE = Odefsey

a Week 48 window was between Day 295 and 378 (inclusive).

b Week 96 window was between Day 631 and 714 (inclusive).

c One patient who was not on FTC/RPV/TDF prior to screening was excluded from the analysis.

d Includes patients who had ≥ 50 copies/mL in the Week 48 or Week 96 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

e Includes patients who discontinued for reasons other than an adverse event (AE), death, or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

At Week 96, switching to Odefsey was non-inferior in maintaining HIV-1 RNA < 50 copies/mL when compared to patients who stayed on FTC/RPV/TDF or on EFV/FTC/TDF in respective studies.

In Study GS-US-366-1216, the mean change from baseline in CD4+ cell count at Week 96 was 12 cells/mm^3 in patients who switched to Odefsey and 16 cells/mm^3 in those who remained on FTC/RPV/TDF. In Study GS-US-366-1160, the mean change from baseline in CD4+ cell count at Week 96 was 12 cells/mm^3 in patients who switched to Odefsey and 6 cells/mm^3 in those who stayed on EFV/FTC/TDF.

HIV-1 infected adult patients with mild to moderate renal impairment
In Study GS-US-292-0112, the efficacy and safety of E/C/F/TAF FDC tablet were evaluated in an open-label clinical study of 242 HIV-1 infected, virologically suppressed patients with mild to moderate renal impairment ($eGFR_{CG}$: 30-69 mL/min).

The mean age was 58 years (range 24-82), with 63 patients (26%) who were ≥ 65 years of age. Seventy-nine percent were male, 63% were White, 18% were Black, and 14% were Asian. Thirty-five percent of patients were on a treatment regimen that did not contain tenofovir disoproxil fumarate. At baseline, median $eGFR_{CG}$ was 56 mL/min, and 33% of patients had an $eGFR_{CG}$ from 30 to 49 mL/min. The mean baseline CD4+ cell count was 664 cells/mm^3 (range 126-1,813).

At Week 144, 83.1% (197/237 patients) maintained HIV-1 RNA < 50 copies/mL after switching to E/C/F/TAF FDC tablet.

In Study GS-US-292-1825, the efficacy and safety of E/C/F/TAF were evaluated in a single arm, open-label clinical study in which 55 HIV-1 infected adults with end stage renal disease ($eGFR_{CG}$ < 15 mL/min) on chronic haemodialysis for at least 6 months before switching to E/C/F/TAF FDC tablet. Patients were virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months before switching.

The mean age was 48 years (range 23-64). Seventy-six percent were male, 82% were Black and 18% were White. Fifteen percent of patients identified as Hispanic/Latino. The mean baseline CD4+ cell count was 545 cells/mm^3 (range 205-1473). At Week 48, 81.8% (45/55 patients) maintained HIV-1 RNA < 50 copies/mL after switching to E/C/F/TAF. There were no clinically significant changes in fasting lipid laboratory tests in patients who switched.

Patients co-infected with HIV and HBV
In open-label Study GS-US-292-1249, the efficacy and safety of E/C/F/TAF were evaluated in adult patients co-infected with HIV-1 and chronic hepatitis B. Sixty-nine of the 72 patients were on prior TDF-containing antiretroviral therapy. At the start of treatment with E/C/F/TAF, the 72 patients had been HIV-suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months with or without suppression of HBV DNA and had compensated liver function. The mean age was 50 years (range 28-67), 92% of patients were male, 69% were White, 18% were Black, and 10% were Asian. The mean baseline CD4+ cell count was 636 cells/mm^3 (range 263-1,498). Eighty-six percent of patients (62/72) were HBV suppressed (HBV DNA < 29 IU/mL) and 42% (30/72) were HBeAg positive at baseline.

Of the patients who were HBeAg positive at baseline, 1/30 (3.3%) achieved seroconversion to anti-HBe at Week 48. Of the patients who were HBsAg positive at baseline, 3/70 (4.3%) achieved seroconversion to anti-HBs at Week 48.

At Week 48, 92% of patients (66/72) maintained HIV-1 RNA < 50 copies/mL after switching to E/C/F/TAF. The mean change from baseline in CD4+ cell count at Week 48 was -2 cells/mm^3. Ninety-two percent (66/72 patients) had HBV DNA < 29 IU/mL using missing = failure analysis at Week 48. Of the 62 patients who were HBV suppressed at baseline, 59 remained suppressed and 3 had missing data. Of the 10 patients who were not HBV suppressed at baseline (HBV DNA ≥ 29 IU/mL), 7 became suppressed, 2 remained detectable, and 1 had missing data. Alanine aminotransferase (ALT) normalisation was achieved in 40% (4/10) of subjects with ALT greater than upper limit of normal (ULN) at baseline.

There are limited clinical data on the use of E/C/F/TAF in HIV/HBV co-infected patients who are treatment-naïve.

Changes in measures of bone mineral density
In studies in treatment-naïve adult patients, E/C/F/TAF was associated with smaller reductions in bone mineral density (BMD) compared to E/C/F/TDF through 144 weeks of treatment as measured by dual energy X ray absorptiometry (DXA) analysis of hip (mean change: -0.8% versus -3.4%, p < 0.001) and lumbar spine (mean change: -0.9% versus -3.0%, p < 0.001).

Small improvements in BMD were noted at 48 weeks after switching to E/C/F/TAF compared to maintaining the tenofovir disoproxil fumarate-containing regimen.

In Odefsey studies in virologically suppressed adult patients, increases in BMD were noted at 96 weeks after switching to Odefsey compared to minimal changes with maintaining FTC/RPV/TDF or EFV/FTC/TDF at the hip (mean change 1.6% for Odefsey versus -0.6% for FTC/RPV/TDF, $p<0.001$; 1.8% for Odefsey versus -0.6% for EFV/FTC/TDF, $p<0.001$) and the spine (mean change 2.0% for Odefsey versus -0.3% for FTC/RPV/TDF, $p<0.001$; 1.7% for Odefsey versus 0.1% for EFV/FTC/TDF, $p<0.001$).

Changes in measures of renal function
In studies in treatment-naïve adult patients, E/C/F/TAF was associated with lower impact on renal safety parameters (as measured after 144 weeks treatment by $eGFR_{CG}$ and urine protein to creatinine ratio [UPCR] and after 96 weeks treatment by urine albumin to creatinine ratio [UACR]) compared to E/C/F/TDF. Through 144 weeks of treatment, no subject discontinued E/C/F/TAF due to a treatment-emergent renal adverse event compared with 12 subjects who discontinued E/C/F/TDF ($p < 0.001$). In studies in virologically suppressed adult patients, through 96 weeks of treatment there were minimal changes or decreases in albuminuria (UACR) in patients receiving Odefsey compared with increases from baseline in patients who stayed on FTC/RPV/TDF or EFV/FTC/TDF. See also section 4.4.

Paediatric population

Emtricitabine + tenofovir alafenamide regimen
In Study GS-US-292-0106, the efficacy, safety, and pharmacokinetics of E/C/F/TAF FDC tablet were evaluated in an open-label study of 50 HIV-1 infected, treatment-naïve adolescents. Patients had a mean age of 15 years (range 12-17), were 56% female, 12% Asian, and 88% Black. At baseline, median plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL, median CD4+ cell count was 456 cells/mm^3 (range 95 to 1,110), and median CD4+% was 23% (range 7-45). Overall, 22% had baseline plasma HIV-1 RNA > 100,000 copies/mL.

At 48 weeks, 92% (46/50) achieved HIV-1 RNA < 50 copies/mL, similar to response rates in studies of treatment-naïve HIV-1 infected adults. No emergent resistance to E/C/F/TAF was detected through Week 48.

Rilpivirine-containing regimen
The pharmacokinetics, safety, tolerability, and efficacy of rilpivirine 25 mg once daily, in combination with an investigator-selected BR containing two NRTIs, were evaluated in Study TMC278-C213, a single-arm, open-label Phase 2 study in antiretroviral-naïve HIV-1 infected paediatric patients 12 to < 18 years of age and weighing at least 32 kg. The median duration of exposure for patients was 63.5 weeks.

Thirty-six patients had a median age of 14.5 years and were 55.6% female, 88.9% Black, and 11.1% Asian. The median baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL, and the median baseline CD4+ cell count was 414 cells/mm^3. The proportion of patients with HIV-1 RNA < 50 copies/mL at Week 48 (TLOVR) was 72.2% (26/36). The combination of NRTIs most frequently used together with rilpivirine was FTC/TDF (24 subjects [66.7%]).

The proportion of responders was higher in subjects with a baseline viral load ≤ 100,000 copies/mL (78.6%, 22/28) as compared to those with a baseline viral load > 100,000 copies/mL (50.0%, 4/8). The proportion of virologic failures was 22.2% (8/36).

The European Medicines Agency has deferred the obligation to submit the results of studies with Odefsey in one or more subsets of the paediatric population in the treatment of human HIV-1 infection (see section 4.2 for information on paediatric use).

Pregnancy

Rilpivirine (one of the components of Odefsey) in combination with a background regimen was evaluated in Study TMC114HIV3015 in 19 pregnant women during the 2nd and 3rd trimesters, and postpartum. The pharmacokinetic data demonstrate that total exposure (AUC) to rilpivirine as a part of an antiretroviral regimen was approximately 30% lower during pregnancy compared with postpartum (6-12 weeks). The virologic response was generally preserved throughout the study: of the 12 patients that completed the study, 10 patients were suppressed at the end of the study; in the other 2 patients an increase in viral load was observed only postpartum, for at least 1 patient due to suspected suboptimal adherence. No mother to child transmission occurred in all 10 infants born to the mothers who completed the study and for whom the HIV status was available. Rilpivirine was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of rilpivirine in HIV-1 infected adults (see sections 4.4 and 5.2).

5.2 Pharmacokinetic properties

Absorption

Odefsey: Emtricitabine and tenofovir alafenamide exposures were bioequivalent when comparing one Odefsey 200/25/25 mg film-coated tablet to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (150/150/200/10 mg) fixed-dose combination tablet following single dose administration to healthy subjects (n = 82) under fed conditions. Rilpivirine exposures were bioequivalent when comparing Odefsey 200/25/25 mg to one rilpivirine (as hydrochloride) 25 mg film-coated tablet following single dose administration to healthy subjects (n = 95) under fed conditions.

Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-1 infected subjects, the (mean ± SD) area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10.0 ± 3.1 h•µg/mL. The mean steady-state plasma trough concentration at 24 hours post-dose was equal to or greater than the mean *in vitro* IC_{90} value for anti-HIV-1 activity. The absolute bioavailability of emtricitabine from 200 mg hard capsules was estimated to be 93%. Emtricitabine systemic exposure was unaffected when emtricitabine was administered with food.

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4 to 5 hours. The absolute bioavailability of rilpivirine is unknown. Relative to fasting conditions, the administration of Odefsey to healthy adult subjects with food resulted in increased rilpivirine exposure (AUC) by 13-72%.

Tenofovir alafenamide is rapidly absorbed following oral administration, with peak plasma concentrations occurring at 15-45 minutes post-dose. Relative to fasting conditions, the administration of Odefsey to healthy adult subjects with food resulted in increased tenofovir alafenamide exposure (AUC) by 45-53%.

It is recommended that Odefsey be taken with food.

Distribution

In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02-200 µg/mL.

In vitro binding of rilpivirine to human plasma proteins is approximately 99.7%, primarily to albumin.

In vitro binding of tenofovir to human plasma proteins is < 0.7% and is independent of concentration over the range of 0.01-25 µg/mL. *Ex vivo* binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%.

Biotransformation

The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). Emtricitabine did not inhibit *in vitro* drug metabolism mediated by any of the major human CYP isoforms involved in drug biotransformation. Also, emtricitabine did not inhibit uridine-5'-diphosphoglucuronyl transferase (UGT), the enzyme responsible for glucuronidation.

In vitro experiments indicate that rilpivirine hydrochloride primarily undergoes oxidative metabolism mediated by the CYP3A system.

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. *In vivo,* tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of tenofovir alafenamide given with emtricitabine, cobicistat and elvitegravir resulted in tenofovir diphosphate concentrations > 4-fold higher in PBMCs and > 90% lower concentrations of tenofovir in plasma as compared to a 245 mg oral dose of tenofovir disoproxil (as fumarate) given with emtricitabine, cobicistat and elvitegravir.

In vitro, tenofovir alafenamide is not metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4. Upon co-administration with the moderate CYP3A inducer probe efavirenz, tenofovir alafenamide exposure was not significantly affected. Following administration of tenofovir alafenamide, plasma [^{14}C] -radioactivity showed a time-dependent profile, with tenofovir alafenamide as the most abundant species in the initial few hours and uric acid in the remaining period.

Elimination

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 mL/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

The terminal elimination half-life of rilpivirine is approximately 45 hours. After single dose oral administration of [^{14}C]-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.

Renal excretion of intact tenofovir alafenamide is a minor pathway with < 1% of the dose eliminated in urine. Tenofovir alafenamide is mainly eliminated following metabolism to tenofovir. Tenofovir is renally eliminated by both glomerular filtration and active tubular secretion.

Pharmacokinetics in special populations

Age, gender and ethnicity
No clinically relevant pharmacokinetic differences due to age, gender or ethnicity have been identified for emtricitabine, rilpivirine or tenofovir alafenamide.

Paediatric population
The pharmacokinetics of rilpivirine in antiretroviral-naïve HIV-1 infected paediatric patients 12 to < 18 years of age receiving rilpivirine 25 mg once daily was comparable to that in treatment-naïve HIV-1 infected adults receiving rilpivirine 25 mg once daily. There was no impact of body weight on rilpivirine pharmacokinetics in paediatric patients in Study C213 (33 to 93 kg), similar to what was observed in adults. The pharmacokinetics of rilpivirine in paediatric patients < 12 years of age is under investigation.

Exposures of emtricitabine and tenofovir alafenamide given with elvitegravir + cobicistat achieved in 24 paediatric patients aged 12 to < 18 years were similar to exposures achieved in treatment-naïve adults (Table 6).

Table 6: Pharmacokinetics of emtricitabine and tenofovir alafenamide in antiretroviral-naïve adolescents and adults

	Adolescents			**Adults**		
	Emtricitabine + tenofovir alafenamide			**Emtricitabine + tenofovir alafenamide**		
	FTC[a]	TAF[b]	TFV[b]	FTC[a]	TAF[c]	TFV[c]
AUC_{tau} (ng•h/mL)	14,424.4 (23.9)	242.8 (57.8)	275.8 (18.4)	11,714.1 (16.6)	206.4 (71.8)	292.6 (27.4)
C_{max} (ng/mL)	2,265.0 (22.5)	121.7 (46.2)	14.6 (20.0)	2,056.3 (20.2)	162.2 (51.1)	15.2 (26.1)
C_{tau} (ng/mL)	102.4 (38.9)[b]	N/A	10.0 (19.6)	95.2 (46.7)	N/A	10.6 (28.5)

FTC = emtricitabine; TAF = tenofovir alafenamide; TFV = tenofovir, N/A = not applicable
Data are presented as mean (%CV).
a n = 24 adolescents (GS-US-292-0106); n = 19 adults (GS-US-292-0102).
b n = 23 adolescents (GS-US-292-0106, population PK analysis).
c n = 539 (TAF) or 841 (TFV) adults (GS-US-292-0111 and GS-US-292-0104, population PK analysis).

Renal impairment
No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl ≥ 15 mL/min and < 30 mL/min) in a Phase 1 study of tenofovir alafenamide. In a separate Phase 1 study of emtricitabine alone, mean systemic emtricitabine exposure was higher in patients with severe renal impairment (estimated CrCl < 30 mL/min) (33.7 µg•h/mL) than in subjects with normal renal function (11.8 µg•h/mL). The safety of emtricitabine + tenofovir alafenamide has not been established in patients with severe renal impairment (estimated CrCl ≥ 15 mL/min and < 30 mL/min).

Exposures of emtricitabine and tenofovir in 12 patients with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis who received emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat as a fixed-dose combination tablet (E/C/F/TAF) in Study GS-US-292-1825 were significantly higher than in patients with normal renal function. No clinically relevant differences in tenofovir alafenamide pharmacokinetics were observed in patients with end stage renal disease on chronic haemodialysis as compared to those with normal renal function. There were no new safety issues identified in patients with end stage renal disease on chronic haemodialysis receiving

emtricitabine + tenofovir alafenamide, given with elvitegravir + cobicistat as a fixed-dose combination tablet (see section 4.8).

There are no pharmacokinetic data on emtricitabine or tenofovir alafenamide in patients with end stage renal disease (estimated CrCl < 15 mL/min) not on chronic haemodialysis. The safety of emtricitabine and tenofovir alafenamide has not been established in these patients.

The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. In patients with severe renal impairment or end-stage renal disease, plasma concentrations may be increased due to alteration of drug absorption, distribution and/or metabolism secondary to renal dysfunction. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (see section 4.9).

Hepatic impairment
The pharmacokinetics of emtricitabine have not been studied in patients with varying degrees of hepatic insufficiency; however emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited.

Rilpivirine hydrochloride is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment (Child-Pugh Class A) to 8 matched controls and 8 patients with moderate hepatic impairment (Child-Pugh Class B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment. However, it may not be excluded that the pharmacologically active, unbound, rilpivirine exposure is significantly increased in moderate impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child Pugh Class C) (see section 4.2).

Clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, total plasma concentrations of tenofovir alafenamide and tenofovir are lower than those seen in subjects with normal hepatic function. When corrected for protein binding, unbound (free) plasma concentrations of tenofovir alafenamide in severe hepatic impairment and normal hepatic function are similar.

Hepatitis B and/or hepatitis C virus co-infection
The pharmacokinetics of emtricitabine, rilpivirine and tenofovir alafenamide have not been fully evaluated in patients co-infected with hepatitis B and/or C virus.

Pregnancy and postpartum
After taking rilpivirine 25 mg once daily as part of an antiretroviral regimen, the total exposure of rilpivirine was lower during pregnancy (similar for the 2nd and 3rd trimester) compared with postpartum. The decrease in the unbound free fraction of rilpivirine exposure (i.e., active) during pregnancy compared to postpartum was less pronounced than for total exposure of rilpivirine.

In women receiving rilpivirine 25 mg once daily during the 2nd trimester of pregnancy, mean intra-individual values for total rilpivirine C_{max}, AUC_{24h} and C_{min} values were 21%, 29% and 35% lower, respectively, as compared to postpartum; during the 3rd trimester of pregnancy, C_{max}, AUC_{24h} and C_{min} values were 20%, 31% and 42% lower, respectively, as compared to postpartum.

5.3 Preclinical safety data

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Non-clinical data on rilpivirine hydrochloride reveal no special hazard for humans based on studies of safety pharmacology, drug disposition, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Liver toxicity associated with liver enzyme induction was observed in rodents. In dogs cholestasis-like effects were noted.

Carcinogenicity studies with rilpivirine in mice and rats revealed tumorigenic potential specific for these species, but are regarded as of no relevance for humans.

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced bone mineral density in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of Odefsey. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 4 and 17 times greater, respectively, than those expected after administration of Odefsey.

Tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays.

Because there is a lower tenofovir exposure in rats and mice after the administration of tenofovir alafenamide compared to tenofovir disoproxil fumarate, carcinogenicity studies and a rat peri-postnatal study were conducted only with tenofovir disoproxil fumarate. No special hazard for humans was revealed in conventional studies of carcinogenic potential and toxicity to reproduction and development. Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Povidone
Polysorbate 20

Film-coating

Polyvinyl alcohol
Titanium dioxide
Macrogol
Talc
Iron oxide black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf life after opening until the end of the product's shelf life.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner containing 30 film-coated tablets. Each bottle contains silica gel desiccant and polyester coil.

The following pack size is available: outer cartons containing 1 bottle of 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Janssen Cilag S.P.A., Via C. Janssen 04100, Borgo S. Michele, Latina, Italy

8. MARKETING AUTHORISATION HOLDER

J-C Health Care Ltd, Kibbutz Shefayim 6099000, Israel

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