ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. **NAME OF THE MEDICINAL PRODUCT**

Tivicay 50 mg film-coated tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Film-coated tablet (tablet).

Yellow, round, biconvex tablets approximately 9 mm in diameter debossed with ‘SV 572’ on one side and ‘50’ on the other side.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age.

4.2 **Posology and method of administration**

Tivicay should be prescribed by physicians experienced in the management of HIV infection.

**Posology**

**Adults**

*Patients infected with HIV-1 without documented or clinically suspected resistance to the integrase class*

The recommended dose of dolutegravir is 50 mg (one tablet) orally once daily.

Tivicay should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). Please refer to section 4.5.

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

The recommended dose of dolutegravir is 50 mg (one tablet) twice daily. The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern (see section 5.1).

Co-administration of Tivicay with some medicines should be avoided in this population (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). Please refer to section 4.4 and 4.5.

**Missed doses**
If the patient misses a dose of Tivicay, the patient should take Tivicay as soon as possible, providing the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

**Adolescents aged 12 and above**

In adolescents (aged from 12 to 17 years and weighing at least 40 kg) infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir is 50 mg once daily.

**Elderly**

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

**Renal impairment**

No dosage adjustment is required in patients with mild, moderate or severe (CrCl < 30 mL/min, not on dialysis) renal impairment. No data are available in subjects receiving dialysis although differences in pharmacokinetics are not expected in this population (see section 5.2).

**Hepatic impairment**

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available in patients with severe hepatic impairment (Child-Pugh grade C); therefore dolutegravir should be used with caution in these patients (see section 5.2).

**Paediatric population**

The safety and efficacy of Tivicay in children aged less than 12 years or weighing less than 40 kg has not yet been established. In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for Tivicay in children and adolescents. Currently available data are described in section 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

**Method of administration**

Oral use.

Tivicay can be taken with or without food (see section 5.2). In the presence of integrase class resistance, Tivicay should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations) (see section 5.2).

### 4.3 Contraindications

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

Co-administration with dofetilide (see section 4.5).

### 4.4 Special warnings and precautions for use

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

**Integrase class resistance of particular concern**

The decision to use dolutegravir in the presence of integrase class resistance should take into account that the activity of dolutegravir is considerably compromised for viral strains harbouring Q148+>2 secondary mutations from G140A/C/S, E138A/K/T, L74I (see section 5.1). To what extent dolutegravir provides added efficacy in the presence of such integrase class resistance is uncertain.

**Hypersensitivity reactions**

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

**Immune Reactivation Syndrome**

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves’ disease) have also been reported to occur in the setting of immune reconstitution, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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

**Opportunistic infections**

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

**Drug interactions**

Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. This includes co-administration with medicinal products that reduce dolutegravir exposure (e.g. magnesium/aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents, tipranavir/ritonavir, rifampicin and certain anti-epileptic drugs) (see section 4.5).

Metformin concentrations may be increased by dolutegravir. Patients should be monitored during therapy and a dose adjustment of metformin may be required (see section 4.5).

**Osteonecrosis**

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

### 4.5 Interaction with other medicinal products and other forms of interaction

**Effect of other agents on the pharmacokinetics of dolutegravir**

All factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance.

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore medicinal products that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir (see Table 1).
Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration (see Table 1).

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

Effect of dolutegravir on the pharmacokinetics of other agents

*In vitro*, dolutegravir demonstrated no direct, or weak inhibition (IC50>50 μM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir does not seem to have an effect on midazolam, a CYP3A4 probe, however, a weak inhibition can presently not be excluded. Based on these data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of these enzymes or transporters.

*In vitro*, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) 1. *In vivo*, a 10-14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 or MATE-1 (e.g. dofetilide, metformin) (see Table 1 and section 4.3).

In vitro, dolutegravir inhibited the renal uptake transporters (OAT1) and OAT3. Based on the lack of effect on the *in vivo* pharmacokinetics of the OAT substrate tenofovir, *in vivo* inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been studied *in vivo*. Dolutegravir may increase plasma concentrations of medical products in which excretion is dependent upon OAT3.

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

Interaction table

Interactions between dolutegravir and co-administered medicinal products are listed in Table 1 (increase is indicated as “↑”, decrease as “↓”, no change as “↔”, area under the concentration versus time curve as “AUC”, maximum observed concentration as “Cmax”).

**Table 1: Drug Interactions**

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Geometric mean change (%)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 Antiviral Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-nucleoside Reverse Transcriptase Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td>Dolutegravir ↓ AUC ↓ 71% Cmax ↓ 52% Cτ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)</td>
<td>Etravirine decreased plasma dolutegravir concentration, which may result in loss of virologic response and possible resistance to dolutegravir. Tivicay should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir (see further below in table).</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Dolutegravir ↓ AUC ↓ 57% Cmax ↓ 39% Cτ ↓ 75% Efavirenz ↔ (historical controls)</td>
<td>The recommended dose of Tivicay is 50 mg twice daily when co-administered with efavirenz. In the presence of integrase class resistance alternative combinations that do not include efavirenz should be considered (see section 4.4).</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Dolutegravir Effects</td>
<td>Note</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Dolutegravir ↓</td>
<td>The recommended dose of Tivicay is 50 mg twice daily when co-administered with nevirapine. In the presence of integrase class resistance alternative combinations that do not include nevirapine should be considered (see section 4.4).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Dolutegravir ↔</td>
<td>No dose adjustment is necessary.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC ↑ 12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ ↑ 13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\tau}$ ↑ 22%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Rilpivirine ↔</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nucleoside Reverse Transcriptase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Dolutegravir ↔</td>
<td>No dose adjustment is necessary.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC ↓ 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ ↓ 3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\tau}$ ↓ 8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Tenofovir ↔</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protease Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Dolutegravir ↑</td>
<td>No dose adjustment is necessary.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC ↑ 91%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ ↑ 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\tau}$ ↑ 180%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/ritonavir</td>
<td>Dolutegravir ↑</td>
<td>No dose adjustment is necessary.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC ↑ 62%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ ↑ 34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\tau}$ ↑ 121%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tipranavir/ritonavir (TPV+RTV)</td>
<td>Dolutegravir ↓</td>
<td>The recommended dose of Tivicay is 50 mg twice daily when co-administered with tipranavir/ritonavir the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided (see section 4.4).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC ↓ 59%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ ↓ 47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\tau}$ ↓ 76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(induction of UGT1A1 and CYP3A enzymes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir/ ritonavir (FPV+RTV)</td>
<td>Dolutegravir ↓</td>
<td>No dose adjustment is necessary in the absence of integrase class resistance. In the presence of integrase class resistance alternative combinations that do not include fosamprenavir/ritonavir should be considered.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC ↓ 35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ ↓ 24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\tau}$ ↓ 49%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(induction of UGT1A1 and CYP3A enzymes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease Inhibitor:</td>
<td>Dolutegravir ↔</td>
<td>No dose adjustment is necessary.</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>(Not studied)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease Inhibitor:</td>
<td>Dolutegravir ↓</td>
<td>No dose adjustment is necessary.</td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>AUC ↓ 32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ ↓ 11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{24}$ ↓ 38%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(induction of UGT1A1 and CYP3A enzymes)

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Dolutegravir Effects</th>
<th>No dose adjustment is necessary.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir + etravirine</td>
<td>Dolutegravir ↔ AUC ↑ 10% Cₘₐₓ ↑ 7% Ct ↑ 28% LPV ↔ RTV ↔</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir + etravirine</td>
<td>Dolutegravir ↓ AUC ↓ 25% Cₘₐₓ ↓ 12% Ct ↓ 37% DRV ↔ RTV ↔</td>
<td></td>
</tr>
<tr>
<td>Other Antiviral agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Dolutegravir ↑ AUC ↑ 25% Cₘₐₓ ↑ 19% Ct ↑ 37% Telaprevir ↔ (historical controls) (inhibition of CYP3A enzyme)</td>
<td></td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Dolutegravir ↔ AUC ↑ 7% Cₘₐₓ ↑ 5% Ct ↑ 8%</td>
<td></td>
</tr>
<tr>
<td>Other agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Dofetilide ↑ (Not studied, potential increase via inhibition of OCT2 transporter) Tivicay and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration (see section 4.3).</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbamazepine</td>
<td>Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes) Co-administration with these enzyme inducers should be avoided.</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aazole anti-fungal agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Dolutegravir ↔ (Not studied) No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herbal products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Dolutegravir ↓ (Not studied, decrease expected due to induction of Co-administration with St. John’s wort is strongly discouraged.</td>
<td></td>
</tr>
<tr>
<td><strong>Antacids and supplements</strong></td>
<td><strong>UGT1A1 and CYP3A enzymes</strong></td>
<td><strong>Magnesium/ aluminium-containing antacid</strong></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Magnesium/ aluminium-containing antacid</td>
<td>Dolutegravir ↓ AUC ↓ 74% C&lt;sub&gt;max&lt;/sub&gt; ↓ 72% (Complex binding to polyvalent ions)</td>
<td>Magnesium/ aluminium-containing antacid should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>Dolutegravir ↓ AUC ↓ 39% C&lt;sub&gt;max&lt;/sub&gt; ↓ 37% C&lt;sub&gt;24&lt;/sub&gt; ↓ 39% (Complex binding to polyvalent ions)</td>
<td>Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).</td>
</tr>
<tr>
<td>Iron supplements</td>
<td>Dolutegravir ↓ AUC ↓ 54% C&lt;sub&gt;max&lt;/sub&gt; ↓ 57% C&lt;sub&gt;24&lt;/sub&gt; ↓ 56% (Complex binding to polyvalent ions)</td>
<td></td>
</tr>
<tr>
<td>Multivitamin</td>
<td>Dolutegravir ↓ AUC ↓ 33% C&lt;sub&gt;max&lt;/sub&gt; ↓ 35% C&lt;sub&gt;24&lt;/sub&gt; ↓ 32% (Complex binding to polyvalent ions)</td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>Dolutegravir ↔ AUC ↑ 11% C&lt;sub&gt;max&lt;/sub&gt; ↑ 6% Ct ↑ 17%</td>
<td>No dose adjustment is necessary.</td>
</tr>
<tr>
<td><strong>Antidiabetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Metformin ↑ Dolutegravir ↔ (Not studied. Increase of metformin expected, due to inhibition of OCT-2 transporter)</td>
<td>Close monitoring of metformin efficacy and safety is recommended when starting or stopping dolutegravir in patients receiving metformin. A dose adjustment of metformin may be necessary.</td>
</tr>
<tr>
<td><strong>Antimycobacterials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Dolutegravir ↓ AUC ↓ 54% C&lt;sub&gt;max&lt;/sub&gt; ↓ 43% Ct ↓ 72% (induction of UGT1A1 and CYP3A enzymes)</td>
<td>The recommended dose of Tivicay is 50 mg twice daily when co-administered with rifampicin in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided (see section 4.4).</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Dolutegravir ↔ AUC ↓ 5% C&lt;sub&gt;max&lt;/sub&gt; ↑ 16% Ct ↓ 30% (induction of UGT1A1 and CYP3A enzymes)</td>
<td>No dose adjustment is necessary.</td>
</tr>
<tr>
<td><strong>Oral contraceptives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol (EE) and Norgestromin (NGMN)</td>
<td>Dolutegravir ↔ EE ↔ AUC ↑ 3%</td>
<td>Dolutegravir had no pharmacodynamic effect on Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and progesterone. No dose</td>
</tr>
</tbody>
</table>
C<sub>max</sub> ↓ 1%
NGMN ↔
AUC ↓ 2%
C<sub>max</sub> ↓ 11%

**adjustment of oral contraceptives is necessary when co-administered with Tivicay.**

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Methadone</th>
<th>Dolutegravir ↔ Methadone</th>
<th>AUC ↓ 2%</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; ↔ 0%</th>
<th>Cτ ↓ 1%</th>
<th>No dose adjustment is necessary of either agent.</th>
</tr>
</thead>
</table>

Paediatric population
Interaction studies have only been performed in adults.

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**
There are no or limited amount of data from the use of dolutegravir in pregnant women. The effect of dolutegravir on human pregnancy is unknown. In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Tivicay should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus. There are no or limited amount of data from the use of dolutegravir in pregnant women.

**Breast-feeding**
It is unknown whether dolutegravir is excreted in human milk. Available toxicological data in animals has shown excretion of dolutegravir in milk. In lactating rats that received a single oral dose of 50 mg/kg at 10 days postpartum, dolutegravir was detected in milk at concentrations typically higher than blood. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

**Fertility**
There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility (see section 5.3).

### 4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of dolutegravir on driving performance or the ability to operate machines. However, patients should be informed that dizziness has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of dolutegravir should be borne in mind when considering the patient's ability to drive or operate machinery.

### 4.8 Undesirable effects

**Summary of the safety profile**
The safety profile is based on pooled data from Phase IIb and Phase III clinical studies in 980 previously untreated patients, 357 previously treated patients unexposed to integrase inhibitors and 234 patients with prior treatment failure that included an integrase inhibitor (including integrase class resistance). The most severe adverse reaction, seen in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see section 4.4). The most commonly seen treatment emergent adverse reactions were nausea (15%), diarrhoea (16%) and headache (14%).

The safety profile was similar across the different treatment populations mentioned above.
Tabulated list of adverse reactions
The adverse reactions considered at least possibly related to dolutegravir are listed by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 2 Adverse Reactions

<table>
<thead>
<tr>
<th>Body system/disorders</th>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>Uncommon</td>
<td>Hypersensitivity (see section 4.4) **</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>Common</td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Abnormal dreams</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Very common</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Dizziness</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Very common</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Very common</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Flatulence</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Upper abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Abdominal discomfort</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>Uncommon</td>
<td>Hepatitis</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Common</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Pruritus</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Common</td>
<td>Fatigue</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Common</td>
<td>Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Creatine phosphokinase (CPK) elevations</td>
</tr>
</tbody>
</table>

**see below under Description of selected adverse reactions.

Description of selected adverse reactions

*Changes in laboratory biochemistries*
Increases in serum creatinine occurred within the first week of treatment with Tivicay and remained stable through 48 weeks. A mean change from baseline of 9.96 μmol/L was observed after 48 weeks of treatment. Creatinine increases were comparable by various background regimens. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.

*Co-infection with Hepatitis B or C*
In Phase III studies patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of Tivicay therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see section 4.4).

*Immune response syndrome*
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.
Autoimmune disorders (such as Graves’ disease) 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).

Paediatric population
Based on limited available data in adolescents (12 to less than 18 years of age and weighing at least 40 kg), there were no additional types of adverse reactions beyond those observed in the adult population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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

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

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific treatment for an overdose of dolutegravir. If overdose occurs, the patient should be treated supportively with appropriate monitoring, as necessary. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05AX12

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

Pharmacodynamic effects

Antiviral activity in cell culture
The IC50 for dolutegravir in various labstrains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7-2 nM. Similar IC50s were seen for clinical isolates without any major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC50 value was 0.2 nM (range 0.02-2.14). The mean IC50 for 3 HIV-2 isolates was 0.18 nM (range 0.09-0.61).

Antiviral activity in combination with other antiviral agents
No antagonistic effects in vitro were seen with dolutegravir and other antiretrovirals tested agents: stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc and raltegravir. In addition, no antagonistic effects were seen for dolutegravir and adefovir, and ribavirin had no apparent effect on dolutegravir activity.

Effect of human serum
In 100% human serum, the mean protein fold shift was 75 fold, resulting in protein adjusted IC90 of 0.064 ug/mL.

Resistance

Resistance in vitro
Serial passage is used to study resistance evolution in vitro. When using the lab-strain HIVIII during passage over 112 days, mutations selected appeared slowly, with substitutions at positions S153Y and F, resulting in a maximal fold change in susceptibility of 4 (range 2-4). These mutations were not selected in patients treated with dolutegravir in the clinical studies. Using strain NL432, mutations E92Q (FC 3) and G193E (also FC 3) were selected. The E92Q mutation has been selected in patients with pre-existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

In further selection experiments using clinical isolates of subtype B, mutation R263K was seen in all five isolates (after 20 weeks and onwards). In subtype C (n=2) and A/G (n=2) isolates the integrase substitution R263K was selected in one isolate, and G118R in two isolates. R263K was reported from two ART experienced, INI naive individual patients with subtypes B and C in the clinical program, but without effects on dolutegravir susceptibility in vitro. G118R lowers the susceptibility to dolutegravir in site directed mutants (FC 10), but was not detected in patients receiving dolutegravir in the Phase III program.

Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q and T66I) do not affect the in vitro susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase inhibitor associated mutations (for raltegravir/elvitegravir) are added to these primary mutations in experiments with site directed mutants, dolutegravir susceptibility is still unchanged (FC <2 vs wild type virus), except in the case of the Q148-mutation, where a FC of 5-10 or higher is seen with the combination of secondary mutations. The effect by the Q148-mutations (H/R/K) was also verified in passage experiments with site directed mutants. In serial passage with strain NL432, starting with site directed mutants harbouring N155H or E92Q, no further selection of resistance was seen (FC unchanged around 1). In contrast, starting with mutants harbouring mutation Q148H (FC 1), a variety of secondary mutations were seen with a consequent increase of FC to values >10.

A clinically relevant phenotypic cut-off value (FC vs wild type virus) has not been determined; genotypic resistance was a better predictor for outcome.

Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analyzed for susceptibility to dolutegravir. Dolutegravir has a <10 FC against 94% of the 705 clinical isolates.

Resistance in vivo
In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase IIb and Phase III, no development of resistance to the integrase class, or to the NRTI class was seen (n=876, follow-up of 48-96 weeks).

In patients with prior failed therapies, but naive to the integrase class (SAILING study), integrase inhibitor substitutions were observed in 4/354 patients (follow-up 48 weeks) treated with dolutegravir, which was given in combination with an investigator selected background regimen (BR). Of these four, two subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, one subject had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and one subject had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission. The R263K mutation was also selected in vitro (see above).

In the presence of integrase class-resistance (VIKING-3 study) the following mutations were selected in 31 patients with protocol defined virological failure through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimized background agents): L74L/M (n=1), E92Q (n=2), T97A (n=8), E138K/A (n=7), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), and N155H (n=1) and E157E/Q (n=1). Treatment emergent integrase resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic).

Effects on electrocardiogram
No relevant effects were seen on the QTc interval, with doses exceeding the clinical dose by approximately three fold.

Clinical efficacy and safety
Previously untreated patients

The efficacy of Tivicay in HIV-infected, therapy naïve subjects is based on the analyses of 48-week data from two randomized, international, double-blind, active-controlled trials, SPRING-2 (ING113086) and SINGLE (ING114467).

In SPRING-2, 822 adults were randomized and received at least one dose of either Tivicay 50 mg once daily or raltegravir (RAL) 400 mg twice daily, both administered with fixed-dose dual NRTI therapy (either ABC/3TC or TDF/FTC). At baseline, median patient age was 36 years, 14% were female, 15% non-white, 11% had hepatitis B and/or C co-infection and 2% were CDC Class C, these characteristics were similar between treatment groups.

In SINGLE, 833 subjects were randomized and received at least one dose of either Tivicay 50 mg once daily with fixed-dose abacavir-lamivudine (DTG + ABC/3TC) or fixed-dose efavirenz-tenofovir-emtricitabine (EFV/TDF/FTC). At baseline, median patient age was 35 years, 16% were female, 32% non-white, 7% had hepatitis C co-infection and 4% were CDC Class C, these characteristics were similar between treatment groups.

Week 48 outcomes (including outcomes by key baseline covariates) for SPRING-2 and SINGLE are shown in Table 3.

| Table 3 Response in SPRING-2 and SINGLE at 48 Weeks (Snapshot algorithm, <50 copies/mL) |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| SPRING-2 | SINGLE |
| HIV-1 RNA <50 copies/mL | | | |
| Treatment Difference* | 2.5% (95% CI: -2.2%, 7.1%) | 7.4% (95% CI: 2.5%, 12.3%) |
| Virologic non-response† | 5% | 8% | 5% | 6% |
| Baseline Viral Load (cps/mL) | | | | |
| ≤100,000 | 88% | 85% | 88% | 81% |
| >100,000 | 94% / 114 (82%) | 87% / 116 (75%) | 111% / 134 (83%) | 100% / 131 (76%) |
| Baseline CD4+ (cells/mm³) | | | | |
| <200 | 43 / 55 (78%) | 34 / 50 (68%) | 45 / 57 (79%) | 48 / 62 (77%) |
| 200 to <350 | 128 / 144 (89%) | 118 / 139 (85%) | 143 / 163 (88%) | 126 / 159 (79%) |
| ≥350 | 190 / 212 (90%) | 199 / 222 (90%) | 176 / 194 (91%) | 164 / 198 (83%) |
| NRTI backbone | | | | |
| ABC/3TC | 145 / 169 (86%) | 142 / 164 (87%) | N/A | N/A |
| TDF/FTC | 216 / 242 (89%) | 209 / 247 (85%) | N/A | N/A |
| Gender | | | | |
| Male | 308 / 348 (89%) | 305 / 355 (86%) | 307 / 347 (88%) | 291 / 356 (82%) |
| Female | 53 / 63 (84%) | 46 / 56 (82%) | 57 / 67 (85%) | 47 / 63 (75%) |
| Race | | | | |
| White | 306 / 346 (88%) | 301 / 352 (86%) | 255 / 284 (90%) | 238 / 285 (84%) |
| Non white | 55 / 65 (85%) | 50 / 59 (85%) | 109 / 130 (84%) | 99 / 133 (74%) |
| Age (years) | | | | |
| <50 | 324 / 370 (88%) | 312 / 365 (85%) | 319 / 361 (88%) | 302 / 375 (81%) |
| ≥50 | 37 / 41 (90%) | 39 / 46 (85%) | 45 / 53 (85%) | 36 / 44 (82%) |
| Median CD4 change from baseline | 230 | 230 | 246‡ | 187‡ |

* Adjusted for baseline stratification factors.
† Includes subjects who changed BR to new class or changed BR not permitted per protocol or due to lack of efficacy prior to Week 48 (for SPRING-2 only), subjects who discontinued prior to Week 48 for lack or
loss of efficacy and subjects who are ≥50 copies in the 48 week window.

‡ Adjusted mean treatment difference was statistically significant (p<0.001)

In the SINGLE study, virologic suppression (HIV-1 RNA <50 copies/mL) in the Tivicay + ABC/3TC arm was 88%, which was superior to the EFV/TDF/FTC arm (81%), based on the primary analysis (p=0.003). This analysis was pre-specified and adjusted for multiplicity. The median time to viral suppression was 28 days in the group receiving Tivicay + ABC/3TC and 84 days in the EFV/TDF/FTC arm in SINGLE at 48 weeks (p<0.0001). This analysis was pre-specified and adjusted for multiplicity.

Through 48 weeks in SPRING-2 and SINGLE, no INI-resistant mutations or treatment emergent resistance in background therapy were isolated on the Tivicay-containing arms. In SPRING-2, four subjects on the RAL arm failed with major NRTI mutations and one subject developed raltegravir resistance; in SINGLE, four subjects on the EFV/TDF/FTC arm failed with mutations associated with NNRTI resistance and one developed a major NRTI mutation.

Sustained virological response was demonstrated in the SPRING-1 study (ING112276), in which 88% of patients receiving Tivicay 50 mg (n=51) once daily had HIV-1 RNA <50 copies/mL, compared to 72% of patients in the efavirenz group (n=50) at 96 weeks. In patients treated with Tivicay 50 mg once daily, de novo resistance to the integrase class, or the NRTI background agents were not detected during 96 weeks of follow-up.

Patients with prior treatment failure, but not exposed to the integrase class

In the international multicentre, double-blind SAILING study (ING111762), 719 HIV-1 infected, antiretroviral therapy (ART)-experienced adults were randomized and received either Tivicay 50 mg once daily or raltegravir 400 mg twice daily with investigator selected background regimen consisting of up to 2 agents (including at least one fully active agent). At baseline, median patient age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C co-infection, and 46% were CDC Class C. All patients had at least two class ART resistance, and 49% of subjects had at least 3-class ART resistance at baseline.

Week 48 outcomes (including outcomes by key baseline covariates) for SAILING are shown in Table 4.

Table 4 Response in SAILING at 48 Weeks (Snapshot algorithm, <50 copies/mL)

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt;50 copies/mL</th>
<th>Tivicay 50 mg Once Daily + BR N=354§</th>
<th>RAL 400 mg Twice Daily + BR N=361§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>71%</td>
<td>64%</td>
</tr>
<tr>
<td>Adjusted treatment difference‡</td>
<td>7.4% (95% CI: 0.7%, 14.2%)</td>
<td></td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>20%</td>
<td>28%</td>
</tr>
<tr>
<td>Baseline Viral Load (copies/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50,000 copies/mL</td>
<td>186 / 249 (75%)</td>
<td>180 / 254 (71%)</td>
</tr>
<tr>
<td>&gt;50,000 copies/mL</td>
<td>65 / 105 (62%)</td>
<td>50 / 107 (47%)</td>
</tr>
<tr>
<td>Baseline CD4+ (cells/ mm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>33 / 62 (53%)</td>
<td>30 / 59 (51%)</td>
</tr>
<tr>
<td>50 to &lt;200</td>
<td>77 / 111 (69%)</td>
<td>76 / 125 (61%)</td>
</tr>
<tr>
<td>200 to &lt;350</td>
<td>64 / 82 (78%)</td>
<td>53 / 79 (67%)</td>
</tr>
<tr>
<td>≥350</td>
<td>77 / 99 (78%)</td>
<td>71 / 98 (73%)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt;50 copies/mL by Background Regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotypic Susceptibility Score* &lt;2</td>
<td>155 / 216 (72%)</td>
<td>129 / 192 (67%)</td>
</tr>
<tr>
<td>Genotypic Susceptibility Score* ≥2</td>
<td>96 / 138 (70%)</td>
<td>101 / 169 (60%)</td>
</tr>
<tr>
<td>Use of DRV without PI mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50 / 72 (69%)</td>
<td>54 / 77 (70%)</td>
</tr>
<tr>
<td>No</td>
<td>201 / 282 (71%)</td>
<td>176 / 284 (62%)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt;50 copies/mL by Gender</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In the SAILING study, virologic suppression (HIV-1 RNA <50 copies/mL) in the Tivicay arm (71%) was statistically superior to the raltegravir arm (64%), at Week 48 (p=0.03).

Statistically fewer subjects failed therapy with treatment-emergent integrase resistance on Tivicay (4/354, 1%) than on raltegravir (17/361, 5%) (p=0.003) (refer to section ‘Resistance in vivo’ above for details).

**Patients with prior treatment failure that included an integrase inhibitor (and integrase class resistance)**

In the multicentre, open-label, single arm VIKING-3 study (ING112574), HIV-1 infected, ART-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received Tivicay 50 mg twice daily with the current failing background regimen for 7 days but with optimised background ART from Day 8. The study enrolled 183 patients, 133 with INI-resistance at Screening and 50 with only historical evidence of resistance (and not at Screening) resistance. Raltegravir/elvitegravir was part of the current failing regimen in 90/183 patients (part of prior failing therapies in the others). At baseline, median patient age was 48 years, 23% were female, 29% non-white, and 20% had hepatitis B and/or C co-infection. Median baseline CD4+ was 140 cells/mm³, median duration of prior ART was 13 years, and 56% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 79% had ≥2 NRTI, 75% ≥1 NNRTI, and 71% ≥2 PI major mutations; 62% had non-R5 virus.

Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4log₁₀ copies/mL (95% CI -1.3 to -1.5log₁₀, p<0.001). Response was associated with baseline INI mutation pathway, as shown in Table 5. Patients who stopped dolutegravir therapy for non-eficacy reasons, or who were protocol deviations for incorrect dolutegravir dosing or prohibited medication use are excluded in the analysis of the Virological Outcome (VO) population.

**Table 5 Virologic response (day 8) after 7 days of functional monotherapy, in patients with RAL/EVG as part of current failing regimen, VIKING 3**
In patients without a primary mutations detected at baseline (N=60) (i.e. RAL/EVG not part of current failing therapy) there was a 1.63 log_{10} reduction in viral load at day 8.

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. Based on 24-week data for all 183 patients, 126 (69%) had <50 copies/mL RNA at Week 24 (Snapshot algorithm). Corresponding response for the VO population was 75% (120/161).

The response was lower when the Q148-mutation was present at baseline, and in particular in the presence of ≥2 secondary mutations, Table 6. The overall susceptibility score (OSS) of the optimised background regimen (OBR) was not associated with Week 24 response.

**Table 6 Response by baseline Resistance, Week 24 VO Population (HIV-1 RNA <50 c/mL, Snapshot algorithm)**

<table>
<thead>
<tr>
<th>Derived IN Mutation Group</th>
<th>OSS=0</th>
<th>OSS=1</th>
<th>OSS=2</th>
<th>OSS&gt;2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No primary IN mutation¹</td>
<td>2/2 (100%)</td>
<td>15/20 (75%)</td>
<td>19/21 (90%)</td>
<td>9/12 (75%)</td>
<td>45/55 (82%)</td>
</tr>
<tr>
<td>No Q148H/K/R mutations²</td>
<td>2/2 (100%)</td>
<td>20/20 (100%)</td>
<td>21/27 (78%)</td>
<td>8/10 (80%)</td>
<td>51/59 (86%)</td>
</tr>
<tr>
<td>Q148 + 1 secondary mutation³</td>
<td>2/2 (100%)</td>
<td>8/12 (67%)</td>
<td>10/17 (59%)</td>
<td>-</td>
<td>20/31 (65%)</td>
</tr>
<tr>
<td>Q148 +≥2 secondary mutations³</td>
<td>1/2 (50%)</td>
<td>2/11 (18%)</td>
<td>1/3 (33%)</td>
<td>-</td>
<td>4/16 (25%)</td>
</tr>
</tbody>
</table>

¹ Historical or phenotypic evidence of INI resistance only.
² N155H, Y143C/H/R, T66A, E92Q
³ G140A/C/S, E138A/K/T, L74I

OSS: combined genotypic and phenotypic resistance (Monogram Biosciences Net Assessment)

At Week 24 the median change in CD4+ T cell count from baseline was 61 cells/mm³ for VIKING-3 based on observed data.

In the double blind, placebo controlled VIKING-4 study (ING116529), 30 HIV-1 infected, ART-experienced adults with primary genotypic resistance to INIs at Screening, were randomised to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days followed by an open label phase with all subjects receiving dolutegravir. The primary endpoint at Day 8 showed that dolutegravir 50 mg twice daily was superior to placebo, with an adjusted mean treatment difference for the change from Baseline in Plasma HIV-1 RNA of -1.2 log_{10} copies/mL (95% CI -1.5 - -0.8log_{10} copies/mL, p<0.001). The day 8 responses in this placebo controlled study were fully in line with those seen in VIKING-3 (not placebo controlled), including by baseline integrase resistance categories.

**Paediatric population**

In a Phase I/II 48 week multicentre, open-label study (P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of Tivicay will be evaluated in combination regimens in HIV-1 infected adolescents.

At 24 weeks, 16 of 23 (70%) adolescents (12 to less than 18 years of age) treated with Tivicay once daily (35 mg n=4, 50 mg n=19) plus OBR achieved viral load <50 copies/mL.
Four subjects had virologic failure none of which had INI resistance at the time of virologic failure. The European Medicines Agency has deferred the obligation to submit the results of studies with Tivicay in paediatric patients aged 4 weeks to below 12 years with HIV infection (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is low to moderate. In Phase I studies in healthy subjects, between-subject CVb% for AUC and C_max ranged from ~20 to 40% and C_t from 30 to 65% across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw%) is lower than between-subject variability.

Absorption
Dolutegravir is rapidly absorbed following oral administration, with median T_max at 2 to 3 hours post dose for tablet formulation.

Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir AUC_{(0-∞)} by 33%, 41%, and 66%, increased C_max by 46%, 52%, and 67%, prolonged T_max to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, Tivicay is recommended to be taken with food by patients infected with HIV with integrase class resistance (see section 4.2).

The absolute bioavailability of dolutegravir has not been established.

Distribution
Dolutegravir is highly bound (>99%) to human plasma proteins based on in vitro data. The apparent volume of distribution is 17 L to 20 L in HIV-infected patients, based on a population pharmacokinetic analysis.

Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC50).

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

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

Elimination
Dolutegravir has a terminal half-life of ~14 hours. The apparent oral clearance (CL/F) is approximately 1L/hr in HIV-infected patients based on a population pharmacokinetic analysis.
Linearity/non-linearity
The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, in general, dolutegravir exhibited nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg for the tablet formulation. With 50 mg twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg once daily.

Pharmacokinetic/pharmacodynamic relationship(s)
In a randomized, dose-ranging trial, HIV-1–infected subjects treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity, with mean decline in HIV-1 RNA of 2.5 log_{10} at day 11 for 50 mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

Special patient populations

Children
The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to <18 years of age) showed that Tivicay 50 mg once daily oral dosage resulted in dolutegravir exposure comparable to that observed in adults who received Tivicay 50 mg orally once daily.

Elderly
Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.

Pharmacokinetic data for dolutegravir in subjects >65 years of age are limited.

Renal impairment
Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr <30 mL/min) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 40% in subjects with severe renal impairment. The mechanism for the decrease is unknown. No dosage adjustment is considered necessary for patients with renal impairment. Tivicay has not been studied in patients on dialysis.

Hepatic impairment
Dolutegravir is primarily metabolized and eliminated by the liver. A single dose of 50 mg of dolutegravir was administered to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 matched healthy adult controls. While the total dolutegravir concentration in plasma was similar, a 1.5- to 2-fold increase in unbound exposure to dolutegravir was observed in subjects with moderate hepatic impairment compared to healthy controls. No dosage adjustment is considered necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of Tivicay has not been studied.

Polymorphisms in drug metabolising enzymes
There is no evidence that common polymorphisms in drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41).

Gender
Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials revealed no clinically relevant effect of gender on the exposure of dolutegravir.

Race
Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials revealed no clinically relevant effect of race on the exposure of dolutegravir. The pharmacokinetics of dolutegravir following single dose oral administration to Japanese subjects appear similar to observed parameters in Western (US) subjects.

Co-infection with Hepatitis B or C
Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited data on subjects with hepatitis B co-infection.

5.3 Preclinical safety data

Dolutegravir was not mutagenic or clastogenic using in vitro tests in bacteria and cultured mammalian cells, and an in vivo rodent micronucleus assay. Dolutegravir was not carcinogenic in long term studies in the mouse and rat.

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (24 times the 50 mg twice daily human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (27 times the 50 mg twice daily human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity (0.40 times the 50 mg twice daily human clinical exposure based on AUC). In rabbits, maternal toxicity (decreased food consumption, scant/no faeces/urine, suppressed body weight gain) was observed at 1000 mg/kg (0.40 times the 50 mg twice daily human clinical exposure based on AUC).

The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 21 and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local active substance administration, mg/kg or mg/m² metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50 kg human), and 5 times the human mg/m² equivalent dose for a clinical dose of 50 mg twice daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Mannitol (E421)
Microcrystalline cellulose
Povidone K29/32
Sodium starch glycolate
Sodium stearyl fumarate

Tablet coating
Polyvinyl alcohol-partially hydrolyzed
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide yellow (E172)
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
HDPE (high density polyethylene) bottles closed with polypropylene screw closures, with a polyethylene faced induction heat seal liner. The bottles contain 30 or 90 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER
ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)
EU/1/13/892/001
EU/1/13/892/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

GLAXO WELLCOME, S.A.
Avda. Extremadura 3,
09400 Aranda de Duero,
Burgos
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

• At the request of the European Medicines Agency;
• Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 50 mg film coated tablets
dolutegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/001
EU/1/13/892/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tivicay 50 mg
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 50 mg tablets
dolutegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/001
EU/1/13/892/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
B. PACKAGE LEAFLET
Package leaflet: Information for the patient

Tivicay 50 mg film coated tablets
dolutegravir

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Tivicay is and what it is used for
2. What you need to know before you take Tivicay
3. How to take Tivicay
4. Possible side effects
5. How to store Tivicay
6. Contents of the pack and other information

1. What Tivicay is and what it is used for

Tivicay contains the active ingredient dolutegravir. Dolutegravir belongs to a group of anti-retroviral medicines called integrase inhibitors (INIs).

Tivicay is used to treat HIV (human immunodeficiency virus) infection in adults and adolescents over 12 years old.

Tivicay does not cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. As a result of that, it also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body to fight infection.

Not everyone responds to treatment with Tivicay in the same way. Your doctor will monitor the effectiveness of your treatment.

Tivicay is always used in combination with other anti-retroviral medicines (combination therapy). To control your HIV infection, and to stop your illness from getting worse, you must keep taking all your medicines, unless your doctor tells you to stop taking any.

2. What you need to know before you take Tivicay

Don’t take Tivicay:
- if you are allergic to dolutegravir or any of the other ingredients of this medicine (listed in section 6).
- if you are taking another medicine called doxetilide (to treat heart conditions).
  → If you think any of these apply to you, tell your doctor.

Warnings and precautions
Look out for important symptoms
Some people taking medicines for HIV infection develop other conditions, which can be serious. These include:

- symptoms of infections and inflammation
- joint pain, stiffness and bone problems

You need to know about important signs and symptoms to look out for while you’re taking Tivicay.

→ Read the information ‘Other possible side effects’ in Section 4 of this leaflet.

Protect other people
HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. It is important to take precautions to avoid infecting other people through sexual contact or blood transfer. To protect other people from becoming infected with HIV:

→ Use a condom when you have oral or penetrative sex.

→ Don’t risk blood transfer – for example, don’t share needles.

Discuss with your doctor the precautions needed to avoid infecting other people.

Children
Do not give this medicine to children under 12 years of age, weighing less than 40 kg or with HIV infection that is resistant to other medicines similar to Tivicay. The use of Tivicay in children under 12 has not yet been studied.

Other medicines and Tivicay
Tell your doctor if you are taking, have recently taken or are planning to take any other medicines. This includes herbal medicines and other medicines bought without a prescription.

Don’t take Tivicay with the following medicine:

- dofetilide, used to treat heart conditions

Some medicines can affect how Tivicay works, or make it more likely that you will have side effects. Tivicay can also affect how some other medicines work.

Tell your doctor if you are taking any of the medicines in the following list:

- metformin, to treat diabetes
- medicines called antacids, to treat indigestion and heartburn. Do not take an antacid during the 6 hours before you take Tivicay, or for at least 2 hours after you take it. (See also Section 3).
- calcium supplements, iron supplements and multivitamins. Do not take a calcium supplement, iron supplement or multivitamin during the 6 hours before you take Tivicay, or for at least 2 hours after you take it (see also Section 3).
- etravirine, efavirenz, fosamprenavir/ritonavir, nevirapine or tipranavir/ritonavir, to treat HIV infection
- rifampicin, to treat tuberculosis (TB) and other bacterial infections
- phenytoin and phenobarbital, to treat epilepsy
- oxcarbamazepine and carbamazepine, to treat epilepsy or bipolar disorder
- St. John’s wort (Hypericum perforatum), a herbal remedy to treat depression

→ Tell your doctor or pharmacist if you are taking any of these. Your doctor may decide to adjust your dose or that you need extra check ups.

Pregnancy and breast feeding
If you are pregnant, if you become pregnant, or if you are planning to have a baby:

→ Talk to your doctor about the risks and benefits of taking Tivicay.

Women who are HIV-positive must not breast feed because HIV infection can be passed on to the baby in breast milk. If you’re breast feeding, or thinking about breast feeding:
Talk to your doctor.

Driving and using machines
Tivicay can make you dizzy and have other side effects that make you less alert.
→ Don’t drive or operate machinery unless you are sure you’re not affected.

3. How to take Tivicay
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- The usual dose is one 50 mg tablet once a day; if you are taking certain other medicines (see section 2, earlier in this leaflet), the dose is one 50 mg tablet twice a day; or
- For the treatment of HIV that is resistant to other medicines similar to Tivicay, the usual dose of Tivicay is one 50 mg tablet, twice a day.

Your doctor will decide on the correct dose of Tivicay for you.

Swallow the tablet with some liquid. Tivicay can be taken with or without food. When Tivicay is taken twice a day, your doctor may advise you to take with food.

Use in children and adolescents
Children and adolescents aged between 12 and 17 years and weighing at least 40 kg can take the adult dose of one tablet (50 mg), once a day. Tivicay should not be used in children and adolescents with HIV infection that is resistant to other medicines similar to Tivicay.

Antacid medicines
Antacids, to treat indigestion and heartburn, can stop Tivicay being absorbed into your body and make it less effective.
Do not take an antacid during the 6 hours before you take Tivicay, or for at least 2 hours after you take it. Other acid-lowering medicines like ranitidine and omeprazole can be taken at the same time as Tivicay.
→ Talk to your doctor for further advice on taking acid-lowering medicines with Tivicay.

Calcium supplements, iron supplements or multivitamins
Calcium supplements, iron supplements or multivitamins can stop Tivicay being absorbed into your body and make it less effective.
Do not take a calcium or iron supplement during the 6 hours before you take Tivicay, or for at least 2 hours after you take it.
→ Talk to your doctor for further advice on taking calcium supplements, iron supplements or multivitamins with Tivicay.

If you take more Tivicay than you should
If you take too many tablets of Tivicay, contact your doctor or pharmacist for advice. If possible, show them the Tivicay pack.

If you forget to take Tivicay
If you miss a dose, take it as soon as you remember. But if your next dose is due within 4 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before.
→ Don’t take a double dose to make up for a missed dose.

Don’t stop taking Tivicay without advice from your doctor
Take Tivicay for as long as your doctor recommends. Don’t stop unless your doctor advises you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.
4. Possible side effects

Like all medicines, this medicine can cause side effects, but not everybody gets them.

When you’re being treated for HIV, it can be hard to tell whether a symptom is a side effect of Tivicay or other medicines you are taking, or an effect of the HIV disease itself. So it is very important to talk to your doctor about any changes in your health.

Allergic reactions
These are uncommon in people taking Tivicay. Signs include:
- skin rash
- a high temperature (fever)
- lack of energy (fatigue)
- swelling, sometimes of the face or mouth (angioedema), causing difficulty in breathing
- muscle or joint aches.
→ See a doctor straight away. Your doctor may decide to carry out tests on your liver, kidneys or blood, and may tell you to stop taking Tivicay.

Very common side effects
These may affect more than 1 in 10 people:
- headache
- diarrhoea
- feeling sick (nausea).

Common side effects
These may affect up to 1 in 10 people:
- rash
- itching (pruritus)
- being sick (vomiting)
- stomach pain (abdominal pain)
- stomach (abdominal) discomfort
- insomnia
- dizziness
- abnormal dreams
- lack of energy (fatigue)
- wind (flatulence)
- increase in the level of liver enzymes
- increase in the level of enzymes produced in the muscles (creatine phosphokinase).

Uncommon side effects
These may affect up to 1 in 100 people:
- inflammation of the liver (hepatitis)

If you get any side effects
→ Talk to your doctor. This includes any possible side effects not listed in this leaflet.

Other possible side effects
People taking combination therapy for HIV may get other side effects.

Symptoms of infection and inflammation
People with advanced HIV infection (AIDS) have weak immune systems, and are more likely to develop serious infections (opportunistic infections). Such infections may have been “silent” and not detected by the weak immune system before treatment was started. After starting treatment, the immune system becomes
stronger, and may attack the infections, which can cause symptoms of infection or inflammation. Symptoms usually include fever, plus some of the following:

- headache
- stomach ache
- difficulty breathing

In rare cases, as the immune system becomes stronger, it can also attack healthy body tissue (autoimmune disorders). The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection. Symptoms may include:

- palpitations (rapid or irregular heartbeat) or tremor
- hyperactivity (excessive restlessness and movement)
- weakness beginning in the hands and feet and moving up towards the trunk of the body.

If you get any symptoms of infection and inflammation or if you notice any of the symptoms above:

→ Tell your doctor immediately. Don’t take other medicines for the infection without your doctor’s advice.

Joint pain, stiffness and bone problems

Some people taking combination therapy for HIV develop a condition called osteonecrosis. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:

- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Signs of osteonecrosis include:

- stiffness in the joints
- aches and pains in the joints (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms:

→ Tell your doctor.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tivicay

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated after EXP on the carton and bottle.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tivicay contains
- The active substance is dolutegravir. Each tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir.
- The other ingredients are mannitol (E421), microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, polyvinyl alcohol-partially hydrolyzed, titanium dioxide (E171), macrogol, talc and iron oxide yellow (E172).

**What Tivicay looks like and contents of the pack**
Tivicay film-coated tablets are yellow, round, biconvex tablets marked with the code ‘SV 572’ on one side and ‘50’ on the other side. The film-coated tablets are provided in bottles containing 30 or 90 tablets. Not all pack sizes may be available in your country.

**Marketing Authorisation Holder**
ViiV Healthcare UK Limited
980 Great West Road
Brentford, Middlesex
TW8 9GS
United Kingdom.

**Manufacturer**
Glaxo Wellcome, S.A.
Avda. Extremadura 3
09400 Aranda De Duero
Burgos, Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
ViiV Healthcare sprl/bvba
Tél/Tel: + 32 (0) 10 85 65 00

**Lietuva**
GlaxoSmithKline Lietuva UAB
Tel: + 370 5 264 90 00
info.lt@gsk.com

**България**
ГлаксоСмитКлайн ЕООД
Тел.: + 359 2 953 10 34

**Luxembourg/Luxemburg**
ViiV Healthcare sprl/bvba
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 65 00

**Česká republika**
GlaxoSmithKline, s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

**Magyarország**
GlaxoSmithKline Kft.
Tel.: + 36 1 225 5300

**Danmark**
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
dk-info@gsk.com

**Malta**
GlaxoSmithKline (Malta) Limited
Tel: + 356 21 238131

**Deutschland**
ViiV Healthcare GmbH
Tel.: + 49 (0)89 203 0038-10
viiv.med.info@viiivhealthcare.com

**Nederland**
ViiV Healthcare BV
Tel: + 31 (0)30 6986060
contact-nl@viiivhealthcare.com

**Eesti**
GlaxoSmithKline Eesti OÜ
Tel: + 372 6676 900
estonia@gsk.com

**Norge**
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no
This leaflet was last revised in [month YYYY].

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.