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QUALITATIVE AND QUANTITATIVE COMPOSITION

Yellow, round, biconvex tablets debossed with 'SV 572' on one side and '50' on the other side. Each tablet contains 50 mg of dolutegravir (as dolutegravir sodium).

PHARMACEUTICAL FORM Film-coated tablets.

CLINICAL PARTICULARS

Indications Treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children over 12 years of age. **Dosage and Administration**

TIVICAY therapy should be initiated by a physician experienced in the management of HIV infection. TIVICAY can be taken with or without food. Method of Administration Adults

Patients infected with HIV-1 without resistance to the integrase class

The recommended dose of *TIVICAY* is 50 mg once daily. Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected) The recommended dose of *TIVICAY* is 50 mg twice daily. The decision to use *TIVICAY* for such patients should be informed by the integrase resistance pattern (see Clinical studies).

Adolescents

In patients who have not previously been treated with an integrase inhibitor, (12 to less than 18 years of age and weighing greater than or equal to 40 kg) the recommended dose of TIVICAY is 50 mg once daily. There are insufficient data to recommend a dose for TIVICAY in integrase inhibitor resistant children and adolescents under 18 years of age.

Children

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

There are limited data available on the use of TIVICAY in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (see Pharmacokinetics – Special Patient Populations).

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

Hepatic impairment

Populations).

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) (see Pharmacokinetics – Special Patient Populations).

Contraindications

TIVICAY must not be administered concurrently with medicinal products with narrow therapeutic windows, that are substrates of organic cation transporter 2 (OCT2), including but not limited to dofetilide, pilsicainide or fampridine (also known as dalfampridine). TIVICAY is contraindicated in patients with known hypersensitivity to dolutegravir or to any of the excipients.

Warnings and Precautions

 Hypersensitivity reactions Hypersensitivity reactions have been reported with ntegrase inhibitors, including TIVICAY, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise. fatique, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with TIVICAY or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

 Immune Reconstitution Syndrome In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and Pneumocystis iiroveci (P. carinii) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution. however, the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start

of TIVICAY therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in

initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients (see Adverse Reactions).

• Opportunistic infections

Patients receiving TIVICAY or any other antiretroviral therapy 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.

• Transmission of infection

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

Caution should be given to co-administering

medications (prescription and non-prescription) that may change the exposure of TIVICAY or medications that may have their exposure changed by TIVICAY (see Contraindications and Interactions). The recommended dose of TIVICAY is 50 mg twice

daily when co-administered with etravirine (without boosted protease inhibitors), efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's wort (see Interactions)

TIVICAY should not be co-administered with polyvalent cation-containing antacids. TIVICAY is recommended to be administered 2 hours before or

6 hours after these agents (see Interactions). TIVICAY is recommended to be administered 2 hours

before or 6 hours after taking calcium or iron supplements, or alternatively, administered with food (see Interactions).

TIVICAY increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control (see Interactions).

Interactions 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, MRP2 or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, TIVICAY is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters (e.g., reverse transcriptase and protease inhibitors. abacavir, zidovudine, maraviroc, opioid analgesics, antidepressants, statins, azole antifungals, proton pump inhibitors, erectile dysfunction agents, aciclovir,

valaciclovir, sitagliptin, adefovir). In drug interaction studies, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, ritonavir, methadone, efavirenz. lopinavir. atazanavir. darunavir, etravirine, fosamprenavir, rilpivirine, boceprevir, telaprevir, daclatasvir, and oral contraceptives containing norelgestimate and ethinyl estradiol.

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) (IC50 = 1.93μ M), multidrug and toxin extrusion transporter (MATE) 1 (IC50 = $6.34 \,\mu\text{M}$) and MATE2-K (IC50 = $24.8 \,\mu\text{M}$). Given dolutegravir's in vivo exposure, it has a low potential to affect the transport of MATE2-K substrates in vivo. In vivo, dolutegravir may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 or MATE1 (for example dofetilide, pilsicainide, fampridine [also known as dalfampridinel or metformin) (see Table 1).

In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC50 = 2.12 μ M) and OAT3 (IC50 = 1.97 μ M). in vivo pharmacokinetics of the OAT substrates tenofovir and para aminohippurate, and therefore has low propensity to cause drug interactions via inhibition of OAT transporters

Effect of Other Agents on the Pharmacokinetics of Dolutegravir Dolutegravir is eliminated mainly through metabolism

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

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

In vitro, dolutegravir is not a substrate of human organic anion transporting polypeptide (OATP)1B1, OATP1B3, or OCT1, therefore drugs that solely modulate these transporter are not expected to affect dolutegravir plasma concentration.

Efavirenz, etravirine, nevirapine, rifampicin, carbamazepine, and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly, and require TIVICAY dose adjustment to 50 mg twice daily. The effect of etravirine was mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir. Therefore no dolutegravir dose adjustment is

necessary when co-administered with etravirine and either lopinavir/ritonavir, darunavir/ritonavir, or atazanavir/ritonavir. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment of TIVICAY (see Table 1). A drug interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, lopinavir/ritonavir,

darunavir/ritonavir, rilpivirine, bocepre prednisone, rifabutin, daclatasvir, and ome a minimal effect on dolutegravir pharmaco therefore no TIVICAY dose adjustment is re co-administered with these drugs.

Selected drug interactions are presented Recommendations are based on either interaction studies or predicted interaction the expected magnitude of interaction for serious adverse events or loss of effi

| Concomitant Drug Class: Drug Name | Effect on Concentration of Dolutegravir | Clinical |
|---|---|-----------------------------|
| Drug Hume | or Concomitant | |
| HIV-1 Antiviral A | Drug Agents | |
| Non-nucleoside | Dolutegravir↓ | Etravirin |
| Reverse Transcriptase | AUC ↓ 71% C _{max} ↓ 52% | boosted inhibito |
| Inhibitor: | $C\tau \downarrow 88\%$ | plasma o |
| Etravirine (ETR) without | $ETR \leftrightarrow$ | concent recomm |
| boosted | | TIVICAY |
| protease inhibitors | | twice da co-admi |
| | | etravirin |
| | | boosted inhibito |
| | | should r |
| | | with etr co-admi |
| | | darunav |
| | | lopinavi INI-resist |
| Protease | Dolutegravir ↔ | Lopinavi |
| Inhibitor: Lopinavir/ | AUC ↑ 11% C _{max} ↑ 7% Cτ ↑ 28% | etravirin change (|
| ritonavir + | Cτ [↑] 28% | plasma o |
| Etravirine | | to a clini extent. I |
| | RTV ↔ | adjustm |
| Protease Inhibitor: | Dolutegravir↓ AUC↓25% | Darunav etravirin |
| Darunavir/ | $C_{max} \downarrow 12\%$ | change of |
| ritonavir + Etravirine | Cτ ↓ 36% | plasma o to a clini |
| | $\begin{array}{l} DRV\leftrightarrow\\ RTV\leftrightarrow \end{array}$ | extent. I |
| Non-nucleoside | Dolutegravir↓ | adjustm Efaviren |
| Reverse | AUC↓57% | doluteg |
| Transcriptase Inhibitor: | C _{max} ↓ 39% Cτ ↓ 75% | concent recomm |
| Efavirenz (EFV) | $EFV \leftrightarrow$ | TIVICAY |
| | | twice da co-admi |
| | | efaviren |
| | | combina not inclu |
| | | should b |
| | | possible patients |
| Non-nucleoside | Dolutegravir↓ | Co-admi |
| Reverse Transcriptase | | nevirapi potentia |
| Inhibitor: | | dolutegi |
| Nevirapine | | concent |
| | | has not |
| | | Effect of doluteg |
| | | likely sin |
| | | than tha The reco |
| | | of <i>TIVIC</i> twice da |
| | | co-admi |
| | | nevirapi combina |
| | | not inclu |
| | | should b possible |
| | | patients |
| Protease Inhibitor (PI): | Dolutegravir↑ | Atazana doluteg |
| Atazanavir | AUC ↑ 91% C _{max} ↑ 50% | concent |
| (ATV) | Cτ | adjustm necessar |
| Protease | Dolutegravir↑ | Atazana |
| Inhibitor: Atazanavir/ | AUC ↑ 62% C _{max} ↑ 34% | increase plasma o |
| ritonavir | $C_{max} \uparrow 34\%$ $C\tau \uparrow 121\%$ | No dose |
| (ATV/RTV) | ATV ↔ | necessar |
| | RTV ↔ | |
| Protease Inhibitor: | Dolutegravir↓ AUC↓59% | Tipranav decrease |
| Tipranavir/ | C _{max} ↓47% | concent |
| ritonavir (TPV/RTV) | Cτ ↓ 76% | recomm TIVICAY |
| (| $\begin{array}{c} TPV \leftrightarrow \\ RTV \leftrightarrow \end{array}$ | twice da |
| | | co-admi tipranav |
| | | Alternat |
| | | that do tipranav |
| | | should b |
| | | possible patients |
| Protease | Dolutegravir↓ | Fosampr |
| Inhibitor: Fosamprenavir/ | AUC ↓ 35% C _{max} ↓ 24% | decrease |
| ritonavir | $C_{max} \downarrow 24\%$ $C\tau \downarrow 49\%$ | based or |
| (FPV/RTV) | $FPV \leftrightarrow$ | did not i decrease |
| | $RTV \leftrightarrow$ | Phase III |
| | | dose adj necessar |
| | | patients |
| | | combina not inclu |
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| , a pl tm ru | boceprevir, telaprevir, and omeprazole had no or harmacokinetics, nent is required when 1gs. | Concomitant Drug Class: Drug Name | Effect on Concentration of Dolutegravir or Concomitant Drug | Clinical Comment |
|-----------------------|---|---|---|---|
| oi ec | presented in Table 1. n either drug d interactions due to eraction and potential ss of efficacy. Clinical Comment | Protease Inhibitor: Nelfinavir | Dolutegravir↔ | This interaction has n been studied. Althou an inhibitor of CYP3/ based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary. |
| t | F | Protease Inhibitor: Lopinavir/ ritonavir | $\begin{array}{l} DTG\leftrightarrow\\ AUC\downarrow 4\%\\ C_{\max}\leftrightarrow\\ C\tau\downarrow 6\% \end{array}$ | Lopinavir/ritonavir did not change dolutegra plasma concentration a clinically relevant |
| | Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of <i>TIVICAY</i> is 50 mg twice daily when | (LPV+RTV) Protease Inhibitor: Darunavir/ ritonavir | $\begin{array}{l} LPV \leftrightarrow \\ RTV \leftrightarrow \\ Dolutegravir \downarrow \\ AUC \downarrow 22\% \\ C_{max} \downarrow 11\% \\ C\tau \downarrow 38\% \end{array}$ | extent. No dose adjustment is necessar Darunavir/ritonavir d not change dolutegravir plasma concentration to a clinically relevant |
| | co-administered with etravirine without boosted protease inhibitors. <i>TIVICAY</i> | Nucleoside | Dolutegravir ↔ | extent. No dose adjustment is necessary. Tenofovir did not |
| | should not be used with etravirine without co-administration of darunavir/ritonavir or lopinavir/ritonavir in INI-resistant patients. | Reverse Transcriptase Inhibitor: Tenofovir | | change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessa |
| <i>→</i> | Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary. | Other Agents Dofetilide Pilsicainide | Dofetilide↑ Pilsicainide ↑ | Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration v inhibition of OCT2 transporter; |
| | Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary. Efavirenz decreased dolutegravir plasma concentrations. The | | | co-administration has not been studied. Dofetilide or pilsicainid co-administration with dolutegravir is contraindicated due to potential life-threateni toxicity caused by high dofetilide or pilsicainid concentration. |
| | recommended dose of <i>TIVICAY</i> is 50 mg twice daily when co-administered with efavirenz. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients. | Fampridine (also known as dalfampridine) | Fampridine ↑ | Co-administration of dolutegravir has the potential to cause seizures due to increase fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has r been studied. Fampridi |
| | Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of <i>TIVICAY</i> is 50 mg twice daily when co-administered with nevirapine. Alternative combinations that do not include nevirapine should be used where | Carbamazepine Phenytoin Phenobarbital | Dolutegravir \downarrow AUC \downarrow 49% C _{max} \downarrow 33% Ct \downarrow 73% | co-administration with dolutegravir is contraindicated. Carbamazepine decreased dolutegrav plasma concentration The recommended dose of <i>TIVICAY</i> is 50 mg twice daily wh co-administered with carbamazepine. Alternatives to carbamazepine shoul be used where possib for INI resistant patients. Co-administration wi these metabolic |
| | possible in INI-resistant patients. Atazanavir increased dolutegravir plasma concentration. No dose adjustment is | St. John's wort | | inducers has the potential to decrease dolutegravir plasma concentration due to enzyme induction an has not been studied Effect of these |
| | necessary. Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary. | | | metabolic inducers of dolutegravir exposur is likely similar to carbamazepine. The recommended dose of <i>TIVICAY</i> is 50 mg twice daily when co-administered with |
| | Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of <i>TIVICAY</i> is 50 mg twice daily when co-administered with tipranavir/ritonavir. | | | these metabolic inducers. Alternative combinations that do not include these metabolic inducers should be used when possible in INI-resista patients. |
| | Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients. Fosamprenavir/ritonavir decreases dolutegravir concentrations, but | Oxcarbazepine | Dolutegravir ↓ | This interaction has no been studied. Althoug an inducer of CYP3A4, based on data from other inducers, a clinically significant decrease in dolutegrav is not expected. No do adjustment is necessar |
| | based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients. Alternative combinations that do not include fosamprenavir/ ritonavir should be used where possible in INI resistant | Antacids containing polyvalent cations (e.g., Mg, Al) | Dolutegravir↓ AUC↓74% C _{max} ↓72% C24↓74% | Co-administration of antacids containing polyvalent cations decreased dolutegra plasma concentration <i>TIVICAY</i> is recommend to be administered 2 hours before or 6 hou after taking antacid products containing polyvalent cations. |

| Concomitant Drug Class: Drug Name | Effect on Concentration of Dolutegravir or Concomitant Drug | Clinical Comment |
|--|--|---|
| Calcium supplements | Dolutegravir↓ AUC↓39% C _{max} ↓37% C24↓39% | TIVICAY is recommended to be administered 2 hours before or 6 hours afte taking products containing calcium. If administered with foo TIVICAY can be taken the same time as calcium supplements. |
| Iron supplements | Dolutegravir↓ AUC↓54% C _{max} ↓57% C24↓56% | TIVICAY is recommend to be administered 2 hours before or 6 hou after taking products containing iron. If administered with foo TIVICAY can be taken the same time as iron supplements. |
| Metformin | Metformin↑ When co-administered with dolutegravir 50mg QD: Metformin AUC↑79% C _{max} ↑66% When co-administered with dolutegravir 50mg BID: Metformin AUC↑145 % C _{max} ↑111% | concentration. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to mainte |
| Rifampicin | $\begin{array}{l} \underset{\text{Cmax}}{\text{Cmax}} + 111\%\\ \text{Dolutegravir} \downarrow\\ \text{AUC} \downarrow 54\%\\ \text{Cmax} \downarrow 43\%\\ \text{Ct} \downarrow 72\% \end{array}$ | Rifampicin decreased dolutegravir plasma concentration. The recommended dose of <i>TIVICAY</i> is 50 mg twice daily when co-administered with rifampicin. Alternativ to rifampicin should b used where possible f in INI resistant patien |
| Oral | Effect of | Dolutegravir did not |
| contraceptives (Ethinyl estradiol (EE) and Norelgestromin (NGMN)) | dolutegravir: NGMN \leftrightarrow AUC \downarrow 2% C _{max} \downarrow 11% C $\tau \downarrow$ 7% | change ethinyl estradi and norelgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with <i>TIVICAY</i> . |
| Methadone | Effect of dolutegravir: Methadone \leftrightarrow AUC \downarrow 2% C _{max} \leftrightarrow 0% C $\tau \downarrow$ 1% | Dolutegravir did not change methadone plasma concentration to a clinically relevant extent. No dose adjustment of methadone is necessa when co-administered with <i>TIVICAY</i> . |
| Daclatasvir | Dolutegravir \leftrightarrow AUC \uparrow 33% C _{max} \uparrow 29% C τ \uparrow 45% Daclatasvir \leftrightarrow | Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir of not change daclatasvi plasma concentration No dose adjustment in necessary. |

versus time curve; C_{max}=maximum observed concentration, Ct=concentration at the end of dosing interval

Pregnancy and Lactation

Fertilit There are no data on the effects of TIVICAY on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility (see Pre-clinical Safety Data).

Pregnancy TIVICAY should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus. Women of childbearing potential (WOCBP) should undergo pregnancy testing before initiation of TIVICAY and should be advised to use effective contraception throughout treatment. If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on TIVICAY. the risks and benefits of continuing TIVICAY versus switching to another antiretroviral regimen should be assessed and switching to an alternative regimen

should be considered. In a birth outcome surveillance study in Botswana there have been 5 cases of neural tube defects reported in 1.683 deliveries (0.3%) to mothers taking dolutegravir-containing regimens from the time of conception, compared with 15 cases in 14,792 deliveries (0.1%) to mothers taking non-dolutegravir-containing

regimens from the time of conception (Prevalence Difference 0.20%: 95% CI 0.01-0.59). In the same study, one infant out of 3,840 deliveries (0.03%) to mothers who started dolutegravir during pregnancy had a neural tube defect, compared with

three infants out of 5,952 deliveries (0.05%) to mothers who started non-dolutegravir-containing regimens during pregnancy. A causal relationship of these events to the use of

dolutegravir has not been established. The incidence

of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As neural tube defects occur within the first 4 weeks of foetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.

Data analysed to date from other sources including the Antiretroviral Pregnancy Registry, clinical trials, and post-marketing data are insufficient to address the risk of neural tube defects with dolutegravir

More than 1,000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes In animal reproductive toxicity studies, no adverse development outcomes, including neural tube defects, were identified. Dolutegravir was shown to cross the

placenta in animals (see Pre-clinical Safety Data). Lactation Health experts recommend that where possible HIV infected women do not breast feed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.

It is expected that dolutegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans. Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Clinical trial data Adverse drug reactions (ADRs) identified in an analysis of pooled data from Phase IIb and Phase III clinical studies are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10) uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated

Table 2 Adverse reactions

| Table Z Auverse | reactions | |
|---|-------------|---|
| Immune system disorders | Uncommon | Hypersensitivity (see Warnings and Precautions) |
| | Uncommon | Immune Reconstitution Syndrome (see Warnings and Precautions) |
| Psychiatric | Common | Insomnia |
| disorders | Common | Abnormal dreams |
| | Common | Depression |
| | Common | Anxiety |
| | Uncommon | Suicidal ideation*, suicide attempt* *particularly in patients with a pre-existing history of depression or psychiatric illness |
| Nervous system | Very common | Headache |
| disorders | Common | Dizziness |
| Gastrointestinal | Very common | Nausea |
| disorders | Very common | Diarrhoea |
| | Common | Vomiting |
| | Common | Flatulence |
| | Common | Upper abdominal pain |
| | Common | Abdominal pain |
| | Common | Abdominal discomfort |
| Hepatobiliary disorders | Uncommon | Hepatitis |
| Skin and | Common | Rash |
| subcutaneous tissue disorders | Common | Pruritus |
| General disorders and administration site conditions | Common | Fatigue |

site conditions The safety profile was similar across the treatment

naïve, treatment experienced (and integrase naïve) and integrase resistant patient populations. Changes in laboratory chemistries

Increases in serum creatinine occurred within the first week of treatment with TIVICAY and remained stable through 48 weeks. In treatment naïve patients a mean hange from baseline of 9.96 µmol/L (range: -53 µmol/L to 54.8 µmol/L) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs, and were similar in treatment experienced patients. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (see Pharmacodynamics – Effects on Renal Function).

Small increases in total bilirubin (without clinical jaundice) were observed on dolutegravir and raltegravir (but not efavirenz) arms in the programme. These changes are not considered nically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see Pharmacokinetics – Metabolism)

Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with dolutegravir therapy.

Paediatric population Based on limited available data in children and

adolescents (12 to less than 18 years of age), there were no additional types of adverse reactions beyond those observed in the adult population. 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 Warnings and Precautions).

Post-marketing data Table 3 Post marketing adverse reaction

| able 3 Post ma | rketing adver | se reactions |
|-----------------------------------|---------------|--------------|
| Hepatobiliary disorders | Rare | Acute hepat |
| | Uncommon | Arthralgia |
| and connective issue disorders | Uncommon | Myalgia |
| nvestigations | Uncommon | Weight incr |

* Acute hepatic failure has been reported in a dolutegravir-containing regimen. The contribution of dolutegravir in these cases is unclear. Overdose

Symptoms and signs There is currently limited experience with overdosage in TIVICAY.

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

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

There is no specific treatment for an overdose of TIVICAY. 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

PHARMACOLOGICAL PROPERTIES Pharmacodynamics

Mechanism of action

TIVICAY 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. Strand transfer biochemical assays using purified HIV 1 integrase and pre-processed substrate DNA resulted in IC50 values of 2.7 nM and 12.6 nM. In vitro, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex (t 1/2 71 hours). Pharmacodynamic effects

In a randomized, dose-ranging trial, HIV 1-infected subjects treated with *TIVICAY* monotherapy demonstrated rapid and dose-dependent antiviral activity, with mean declines from baseline to day 11 in HIV-1 RNA of 1.5, 2.0, and 2.5 log10 for dolutegravir 2 mg, 10 mg, and 50 mg once daily, respectively. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group

Antiviral Activity in cell culture Peripheral blood mononuclear cells (PBMC) infected with HIV-1 strain BaL or HIV-1 strain NL432 gave DTG EC50s of 0.51 nM and 0.53 nM, respectively. MT-4 cells infected with HIV-1 strain IIIB and incubated with

0.71 and 2.1 nM. In a viral integrase susceptibility assay using the integrase coding region from 13 clinically diverse clade B isolates, dolutegravir demonstrated antiviral potency similar to laboratory strains, with a mean EC50 of 0.52 nM. When tested in PBMC assays against a panel consisting of 24 HIV-1 clinical isolates [group M (clade A, B, C, D, E, F and G) and group O] and 3 HIV-2 clinical isolates, the geometric mean EC50 was 0.20 nM and EC50 values ranged from 0.02 to 2.14 nM for HIV-1, while the geometric mean EC50 was 0.18 nM and EC50 values ranged from 0.09 to 0.61 nM for HIV-2 isolates.

Antiviral Activity in combination with other antiviral

No drugs with inherent anti-HIV activity were antagonistic with dolutegravir (in vitro assessments were conducted in checkerboard format in combination with stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc, adefovir and raltegravir). In addition, antivirals without inherent anti-HIV activity (ribavirin) had no apparent effect on dolutegravir activity. Effect of Human Serum and Serum Proteins In vitro studies suggested a 75-fold shift in EC50 of dolutegravir in the presence of 100% human serum (by method of extrapolation), and the protein adjusted EC90 (PA-EC90) in PBMCs was estimated to be 64 ng/mL. Dolutegravir trough concentration for a single 50 mg dose in integrase inhibitor naïve subjects was 1.20 µg/mL and therefore 19 times higher than the estimated PA-FC90

Resistance in vitro

Isolation from wild type HIV-1: Viruses highly resistant to dolutegravir were not observed during the 112 day passage of strain IIIB, with a 4.1-fold maximum fold change (FC) observed for the passaged resistant virus populations with substitutions at the conserved IN positions S153Y and S153F. Passage of the wild type HIV-1 strain NL432 in the presence of dolutegravir selected for E92Q (passage population virus FC=3.1) and G193E (passage population virus FC=3.2) substitutions on Day 56. Additional passage of wildtype subtype B, C, and A/G viruses in the presence of DTG selected for R263K, G118R, and S153T. Anti-HIV Activity Against Resistant Strains: Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent potency against 2 non-nucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant, and 2 PI-resistant HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wildtype strain.

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dolutegravir for 4 or 5 days resulted in EC50s of

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Integrase Inhibitor-Resistant HIV-1 Strains: Sixty integrase inhibitor-resistant mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) were produced from wild-type virus NL-432 using site-directed mutagenesis. Dolutegrav showed anti-HIV activity (susceptibility) with FC <5 against 27 of 28 integrase inhibitor-resistant mutant viruses with single substitutions including T66A/I/K, E92Q/V, Y143C/H/R Q148H/K/R, and N155H, while for raltegravir and elvitegravir there were 17/28 and 11/21 tested mutant viruses with FC <5, respectively. In addition, of the 32 integrase inhibitor-resistant mutan viruses with 2 or more substitutions, 23 of 32 showed FC <5 to dolutegravir compared with FC <5 for 4 of 32 for raltegravir and FC <5 for 2 of 25 tested for elvitegravir Integrase Inhibitor-Resistant HIV-2 Strains: Site directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with raltegravir who showed virologic failure. Overall the HIV-2 FCs observed were similar to HIV-1 FCs observed for similar pathway mutations. Dolutegravir FC was <5 against 4 HIV-2 viruses (S163D, G140A/Q148R, A153G/N155H/S163G and E92Q/T97A/N155H/S163D); for E92Q/N155H, dolutegravir FC was 8.5, and for G140S/Q148R dolutegravir FC was 17. Dolutegravir, raltegravir and elvitegravir all had had the same activity against site directed mutant HIV-2 with S163D as wildtype, and for the remaining mutant HIV-2 virus raltegravir FC ranges were 6.4 to 420 and elvitegravir FC ranges were 22 to 640. Clinical Isolates From Raltegravir Treatment Virologic

Failure Subjects: Thirty clinical isolate samples with genotypic and phenotypic resistance to raltegravir (median FC >81) were examined for susceptibility to dolutegravir (median FC 1.5) using Monogram Biosciences PhenoSense assay. The median FC to dolutegravir for isolates containing changes at G1405 + O148H was 3.75: G140S + Q148R was 13.3; T97A + Y143R was 1.05 and N155H was 1.37.

Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analyzed for susceptibility to dolutegravir using the Monogram Biosciences PhenoSense assay. Dolutegravir has a less than or equal to 10 FC against 93.9% of the 705 clinical isolates, of note 16 (9%) of the 184 isolates with Q148 +1 INSTI-resistance substitution and 25 (27%) of the 92 clinical isolates with Q148 + \geq 2 INSTI-resistance substitutions had greater than 10 fold change.

Resistance in vivo: integrase inhibitor naïve patients No INI-resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with TIVICAY 50 mg once daily in treatment–naive studies (SPRING-1, SPRING-2, SINGLE and FLAMINGO studies). In the SAILING study for treatment

experienced (and integrase naïve) patients (n=354 in the dolutegravir arm), treatment emergent integrase substitutions were observed at Week 48 in 4 of 17 subjects receiving dolutegravir with virologic failure. Of these four, 2 subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, 1 subject had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and 1 subject had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission (see Clinical Studies). Resistance in vivo: integrase inhibitor resistant patients The VIKING-3 study examined TIVICAY (plus optimized background therapy) in subjects with pre-existing INI resistance. Thirty six subjects (36/183) experienced protocol defined virologic failure through to Week 24. Of these, 32 had paired baseline and PDVF resistance data for analysis and 17/32 (53%) had treatment emergent mutations. Treatmentemergent mutations or mixtures of mutations observed were 1741 / M (n=1) F92O (n=2) T97A (n=9) $F138K/\Delta/T (n=8) G140S (n=2) Y143H (n=1) S147G$ (n=1), O148H/K/R (n=4), N155H (n=1) and E157E/O (n=1). Fourteen of the 17 subjects with virus exhibiting treatment-emergent mutations harboured O148 pathway virus present at baseline or historically. Five further subjects experienced PDVF between weeks 24 and 48. and 2 of these 5 had treatment emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74I (n=1), N155H (n=2).

The VIKING-4 study examined TIVICAY (plus optimized background therapy) in subjects with primary penotypic resistance to INIs at Screening in 30 sub Treatment-emergent mutations observed were consistent with those observed in the VIKING-3 study. Effects on Electrocardiogram

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single dose oral administrations of placebo, DTG 250 mg suspension (exposures approximately 3-fold of the 50 mg once-daily dose at steady state), and moxifloxacin (400 mg, active control) in random sequence. Dolutegravir did not prolong the QTc interval for 24 hours post dose. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) was 1.99 msec (1-sided 95% upper CI: 4.53 msec)

Effects on Renal Function The effect of TIVICAY on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as Population pharmacokinetic analysis of dolutegravir the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated in an open-label, randomized, 3 arm, parallel, placebo-controlled study in 37 healthy subjects, who were administered TIVICAY 50 mg once daily (n=12), 50 mg twice daily (n=13) or placebo once daily (n=12) for 14 days. A modest decrease in CrCl was observed with dolutegravir within the first week of treatment, consistent with that seen in clinical studies. Dolutegravir at both doses had no significant effect on GFR or ERPF. These data support in vitro studies which suggest that the small increases in creatinine observed in clinical studies are due to the nonpathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine. Pharmacokinetics

Dolutegravir pharmacokinetics is similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is between low to moderate. In Phase 1 studies in healthy subjects, between-subject CVb% for AUC and C_{max} ranged from ~20 to 40% and $C\tau$ from 30 to 65% across studies. The between-subject PK variability of DTG was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw%) is lower than between-subject variability.

The effect of severe hepatic impairment on the Dolutegravir is rapidly absorbed following oral pharmacokinetics of dolutegravir has not been studied administration, with median T_{max} at 2 to 3 hours post dose for tablet formulation. The linearity of **Polymorphisms in Drug Metabolising Enzymes** There is no evidence that common polymorphisms in dolutegravir pharmacokinetics is dependent of dose and formulation. Following oral administration of drug metabolising enzymes alter dolutegravin tablet formulations, in general, TIVICAY exhibited pharmacokinetics to a clinically meaningful extent. In a nonlinear pharmacokinetics with less than dosemeta-analysis using pharmacogenomics samples portional increases in plasma exposure from 2 to collected in clinical studies in healthy subjects, subjects 100 mg; however increase in dolutegravir exposure with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of appears dose proportional from 25 mg to 50 mg. dolutegravir and 46% higher AUC compared with TIVICAY may be administered with or without food. subjects with genotypes associated with normal Food increased the extent and slowed the rate of netabolism via UGT1A1 (n=41). Polymorphisms in absorption of dolutegravir. Bioavailability of CYP3A4, CYP3A5, and NR1I2 were not associated with dolutegravir depends on meal content: low, moderate, differences in the pharmacokinetics of dolutegravir. and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ 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 are not clinically significant.

The absolute bioavailability of dolutegravir has not been established.

Distribution

Dolutegravir is highly bound (approximately 99.3%) to human plasma proteins based on in vitro data. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is estimated at 12.5 L. Binding of dolutegravir to plasma teins was independent of concentration. Total blood and plasma drug-related radioactivity centration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. Free fraction of DTG in plasma is estimated at approximately 0.2 to 1.1% in healthy subjects, approximately 0.4 to 0.5% in subjects with moderate hepatic impairment, and 0.8 1.0% in subjects with severe renal impairment, and 0.5% in HIV-1 infected patients.

Dolutegravir is present in cerebrospinal fluid (CSF). In 12 treatment-naïve subjects receiving a regimen of dolutegravir plus abacavir/lamivudine (3TC) for 16 weeks, dolutegravir concentration in CSF averaged 15.4 ng/mL at Week 2 and 12.6 ng/mL at Week 16, ranging from 3.7 to 23.2 ng/mL (comparable to unbound plasma concentration). CSF:plasma concentration ratio of DTG ranged from 0.11 to 2.04%. Dolutegravir concentrations in CSF exceeded the IC50, supporting the median reduction from baseline in CSF HIV-1 RNA of 2.2 log after 2 weeks of therapy and 3.4 log after 16 weeks (see Pharmacodynamics).

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

Dolutegravir is primarily metabolized via UGT1A1 with a minor CYP3A component (9.7% of total dose administered in a human mass balance study) Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged drug is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the feces. It is unknown if all or part of this is due to unabsorbed drug or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is creted in the urine, represented by ether glucuronide of DTG (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).

Eliminatio Dolutegravir has a terminal half-life of ~14 hours and an apparent clearance (CL/F) of 0.56 L/hr. Special patient populations

Children

In a paediatric study including 23 antiretroviral treatment-experienced HIV-1 infected adolescents aged 12 to 18 years of age, the pharmacokinetics of Itegravir was evaluated in 10 adolescents and showed that TIVICAY 50 mg once daily dosage resulted in dolutegravir exposure in paediatric subjects comparable to that observed in adults who received TIVICAY 50 mg once daily (Table 4).

Table 4 Paediatric pharmacokinetic parameters (n=10)

Age/weight | TIVICAY | Dolutegravir Pharmacokinetic Parameter Estimates Dose Geometric Mean (CV%) AUC₍₀₋₂₄₎ C_{max} ւց.hr/mL |µg/mL 0.90 (38) 0.90 (59)

| 12 to <18 | 50 mg | 46 (43) | 3.49 (38) | 0.90 (59) |
|--------------------------|--------------------|--------------|------------|-------------|
| years | once | | | |
| ≥ 40 kg ª | daily ^a | | | |
| ^a One subject | t weighing 3 | 87 kg receiv | ed 35 mg o | once daily. |
| Flderly | | | | |

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 of >65 years old are limited. Renal impairment

Renal clearance of unchanged drug is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CrCl < 30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CrCl < 30mL/min) and matching healthy subjects were observed. No dosage adjustment is necessary for patients with renal impairment. There is limited information on dolutegravir in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment

Dolutegravir is primarily metabolized and eliminated by the liver. In a study comparing 8 subjects with

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The dolutegravir exposure in healthy subjects appear to be slightly higher (~20%) in women than men based on data obtained in a healthy subject study (males n=17, females n=24). Population PK analyses using pooled pharmacokinetic data from Phase 2b and Phase 3 adult trials revealed no clinically relevant effect of gender on the exposure of dolutegravir.

moderate hepatic impairment (Child-Pugh category B)

dose exposure of dolutegravir was similar between the

two groups. No dosage adjustment is necessary for

patients with mild to moderate hepatic impairment.

to 8 matched healthy adult controls, the single 50 mg

Population PK analyses using pooled pharmacokinetic data from Phase 2b and Phase 3 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.

Clinical Studies Antiretroviral naïve subjects

The efficacy of dolutegravir in HIV-infected, therapy naive subjects is based on data from two randomized, international, double-blind, active-controlled trials, 96 week data from SPRING-2 (ING113086) and SINGLE (ING114467). This is supported by 96 week data from an open-label and active-controlled study FLAMINGO (ING114915) and additional data from the open-label phase of SINGLE to 144 weeks.

In SPRING, 822 HIV-1 infected, antiretroviral therapy (ART)-naïve adults were randomized and received at least one dose of either TIVICAY 50 mg once daily or raltegravir 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, and 12% 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 (TIVICAY + 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. The primary endpoint and other week 48 outcomes (including outcomes by key baseline covariates) for SPRING-2 and SINGLE are shown in Table 5.

Table 5Virologic Outcomes of Randomized Treatment of SPRING-2 and SINGLE at 48 Weeks (Snapshot algorithm)

| | SPRING-2 | | SIN | SINGLE | |
|--|--|--|---|---|--|
| | TIVICAY 50 mg Once Daily + 2 NRTI N=411 | RAL 400 mg Twice Daily + 2 NRTI N=411 | TIVICAY 50 mg + ABC/3TC Once Daily N=414 | EFV/ TDF/FTC Once Daily N=419 | |
| HIV-1 RNA < 50 copies/mL* | 88% | 85% | 88% | 81% | |
| Treatment Difference* | 2.5% (9 -2.2%, | | 7.4% (9 2.5%, | | |
| Virologic non response† | 5% | 8% | 5% | 6% | |
| No virologic data at Week 48 window | 7% | 7% | 7% | 13% | |
| <u>Reasons</u> | | | | | |
| Discontinued study/study drug due to adverse event or death‡ | 2% | 1% | 2% | 10% | |
| Discontinued study/study drug for other reasons§ | 5% | 6% | 5% | 3% | |
| Missing data during window but on study | 0 | 0 | 0 | <1% | |
| HIV-1 RNA <5 | 0 copies/r | nL by bas | eline cova | riates | |
| Baseline Plasma Viral Load (copies/mL) | n / N (%) | n / N (%) | n / N (%) | n / N (%) | |
| ≤100,000 | 267 / 297 (90%) | 264 / 295 (89%) | 253 / 280 (90%) | 238 / 288 (83%) | |
| >100,000 | 94 / 114 (82%) | 87 / 116 (75%) | 111 / 134 (83%) | 100 / 131 (76%) | |
| Baseline CD4+ (cells/ mm ³) | | | | | |
| <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

C₂₄

μg/mL

| | SPRI | NG-2 | SINGLE | | |
|---|--|--|---|--------------------|--|
| | TIVICAY 50 mg Once Daily + 2 NRTI N=411 | RAL 400 mg Twice Daily + 2 NRTI N=411 | TIVICAY 50 mg + ABC/3TC Once Daily N=414 | TDF/FTC | |
| 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%) | |
| African- America/African Heritage/Other | 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 | 39 / 46 | 45 / 53 | 36 / 44 | |

Adjusted for baseline stratification factors. † Includes subjects who changed BR to new class or hanged 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.

(90%) (85%) (85%) (82%)

Includes subjects who discontinued due to an adverse event or death at any time point from Day 1 through the Week 48 window if this resulted in no virologic data on treatment during the Week 48 window. § Includes reasons such as withdrew consent, loss to ollow-up, moved, protocol deviation.

Notes: ABC/3TC = abacavir 600 mg, lamivudine 300 mg in the form of Kivexa/Epzicom fixed dose combination (FDC) EFV/TDF/FTC = efavirenz 600 mg, tenofovir 300 mg, mtricitabine 200 mg in the form of Atripla FDC. N = Number of subjects in each treatment group

In the SPRING-2 study through 96 weeks, virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir group (81%) was non-inferior to the raltegravir group (76%). The median change in CD4+ T cell count from baseline were 230 cells/mm³ in the group receiving *TIVICAY* and the raltegravir group at 48 weeks and 276 cells/mm³ in the group receiving dolutegravir compared to 264 cells/mm³ the raltegravir group at 96 weeks.

In the SINGLE study at Week 48, 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). At 96 weeks virologic suppression was maintained, the TIVICAY + ABC/3TC arm (80%) was superior to the EFV/TDF/FTC arm (72%), treatment difference was 8.0 (2.3, 13.8), p=0.006. The adjusted mean change in CD4+ T cell count from baseline were 267 cells/mm³ in the group receiving *TIVICAY* + ABC/3TC and 208 cells/mm³ for the EFV/TDF/FTC arm in SINGLE at 48 weeks. The adjusted difference and 95% CI was 58.9 (33.4, 84.4), p<0.001 (repeated measure model adjusting for the baseline stratification factors: baseline HIV-1 RNA and baseline CD4+ T cell count among other factors). 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. At 144 weeks in the open-label phase, virologic suppression was maintained, the TIVICAY + ABC/3TC arm (71%) was superior to the EFV/TDF/FTC arm (63%), treatment difference was 8.3 (2.0, 14.6).

In both SPRING-2 and SINGLE studies virologic suppression (HIV-1 RNA < 50 copies/mL) treatment fferences were comparable across baseline characteristics (gender, race and age)

Through 96 weeks in SINGLE and SPRING-2, no INI-resistant mutations or treatment emergent resistance in background therapy were isolated on the dolutegravir-containing arms. In SPRING-2, four subjects on the raltegravir arm failed with major NRTI mutations and one subject developed raltegravir resistance; in SINGLE, six subjects on the EFV/TDF/FTC arm failed with mutations associated with NNRTI resistance and one developed a major NRTI mutation. In FLAMINGO (ING114915), an open-label and active-controlled study, 484 HIV-1 infected antiretroviral naïve adults were randomized and received one dose of either TIVICAY 50 mg once daily or darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily, both administered with fixed-dose dual NRTI therapy (either ABC/3TC or TDF/FTC). At baseline, median patient age was 34 years, 15% were female, 28% non-white, 10% had hepatitis B and/or C co-infection, and 3% were CDC Class C; these

characteristics were similar between treatment groups. Virologic suppression (HIV-1 RNA <50 copies/mL) in the TIVICAY group (90%) was superior to the DRV/r group (83%) at 48 weeks. The adjusted difference in proportion and 95% CI were 7.1% (0.9, 13.2), p=0.025. At 96 weeks virologic suppression in the TIVICAY group (80%) was superior to the DRV/r group (68%). No treatment-emergent primary INI, PI or NRTI resistance mutations were observed for subjects in the *TIVICAY* or DRV+RTV treatment groups.

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 No INI-resistant mutations or treatment emergent resistance in background therapy were isolated with TIVICAY 50 mg once daily through 96 weeks.

Antiretroviral experienced (and integrase inhibitor

naïve) subjects In the international, multicentre, double-blind SAILING study (ING111762), 719 HIV-1 infected, ART-experienced adults were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator selected background regimen (BR) 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 subjects 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 6. Table 6 Virologic Outcomes of Randomized

Treatment of SAILING at 48 Weeks (Snapshot algorithm)

| | TIVICAY 50 mg Once Daily + BR N=354§ | RAL 400 mg Twice Daily + BR N=361§ |
|--|---|---|
| HIV-1 RNA <50 copies/mL | 71% | 64% |
| Adjusted Treatment Difference‡ | 7.4% (95% Cl | 0.7%, 14.2% |
| Virologic non response | 20% | 28% |
| No virologic data at Week 48 Reasons | 9% | 9% |
| Discontinued study/study drug due to adverse event or death‡ | 3% | 4% |
| Discontinued study/study drug for other reasons§ | 5% | 4% |
| Missing data during window but on study | 2% | 1% |
| HIV-1 RNA <50 copies/ | mL by baseline | covariates |
| Baseline Plasma Viral Load (copies/mL) | n / N (%) | n / N (%) |
| ≤50,000 copies/mL | 186 / 249 (75%) | 180 / 254 (71%) |
| >50,000 copies/mL | 65 / 105 | 50 / 107 |
| | (62%) | (47%) |
| Baseline CD4+ (cells/ mm ³) | 22/62/520/ | 20 / 50 /54 0/ |
| <50 50 to <200 | 33 / 62 (53%) 77 / 111 | 30 / 59 (51%) 76 / 125 |
| 50 10 1200 | (69%) | (61%) |
| 200 to <350 | 64 / 82 (78%) | 53 / 79 (67%) |
| ≥350 | 77 / 99 (78%) | 71 / 98 (73%) |
| Background Regimen | | |
| Phenotypic Susceptibility Score* <2 | 70 / 104 (67%) | 61 / 94 (65%) |
| Phenotypic Susceptibility Score* =2 | 181 / 250 (72%) | 169 / 267 (63%) |
| Genotypic Susceptibility Score* <2 | 155 / 216 (72%) | 129 / 192 (67%) |
| Genotypic Susceptibility Score* =2 DRV/r in BR | 96 / 138 (70%) | 101 / 169 (60%) |
| No DRV/r use | 143/214 | 126/209 |
| DRV/r use with Primary PI | (67%) | (60%) |
| mutations DRV/r use without Primary Pl mutations | 58/68 (85%) 50/72 (69%) | 50/75 (67%) 54/77 (70%) |
| Primary PI mutations Gender | | |
| Male | 172 / 247 | 156 / 238 |
| Iviale | (70%) | (66%) |
| Female | 79 / 107 (74%) | 74 / 123 (60%) |
| Race | 488 4 4 | 48-4 |
| White | 133 / 178 (75%) | 125 / 175 (71%) |
| African-America/African Heritage/Other | 118 / 175 (67%) | 105 / 185 (57%) |
| HAge (years) | (07/0) | (37/0) |
| <50 | 196 / 269 | 172 / 277 |
| | (73%) | (62%) |
| ≥50 | 55 / 85 (65%) | 58 / 84 (69%) |
| HIV sub type | 173 / 241 | 150 / 240 |
| Clade B | (72%) | 159 / 246 (65%) |
| Clade C | 34 / 55 (62%) | 29 / 48 (60%) |
| Clade C | 0., 00 (02,0) | |

§ 4 subjects were excluded from the efficacy analysis due to data integrity at one study site

The Phenotypic Susceptibility Score (PSS) and the Genotypic Susceptibility Score (GSS) were defined as the total number of ARTs in BR to which a subject's viral isolate showed susceptibility at baseline based upon phenotypic or genotypic resistance tests. Background regimen was restricted to ≤ 2 ART with at least one fully active agent, however, n=11 PSS 0, n=2 PSS 3. †Other clades included: Complex (43), F1 (32), A1 (18), BF (14), all others <10.

Notes: BR = background regimen, RAL = raltegravir; N = Number of subjects in each treatment group 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=0.030). Virologic suppression (HIV-1 RNA <50 copies/mL) treatment differences were comparable across the baseline characteristics of

nder, race, and HIV sub type. The mean changes in CD4+ T cell count from baseline were 113 cells/mm³ at week 24 and 162 cells/mm³ at week 48 in the group receiving TIVICAY and 106 cells/mm³ at week 24 and 153 cells/mm³ at week 48 for the raltegravir group. Statistically fewer subjects failed therapy with treatment-emergent resistance in the IN gene on TIVICAY

(4/354, 1%) than on raltegravir (17/361, 5%) (p=0.003). Integrase inhibitor resistant subjects In the Phase IIb, international, multicentre, open-label, single arm sequential cohort VIKING pilot study (ING112961), two sequential cohorts of subjects with multiclass resistance including resistance to HIV integrase inhibitors were enrolled to examine the

antiviral activity of TIVICAY 50 mg once daily (n=27) vs. 50 mg twice daily (n=24) after 10 days of functional

monotherapy. Responses were greater with twice daily (1.8 log10 change from baseline in HIV RNA) than with once daily dosing (1.5 log10 change from baseline, adjusted difference 0.3log10, p=0.017). Higher response rates with twice daily dosing were maintained with continued TIVICAY dosing and optimization of the background regimen through 48 weeks of therapy (33% vs. 71% <50 c/mL, ITT-E TLOVR analysis). A comparable safety profile was observed across doses. Subsequently, VIKING-3 examined the effect of TIVICAY 50 mg twice daily over 7 days of functional monotherapy, followed by optimized background therapy and continued TIVICAY twice daily treatment. 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. One hundred and eighty-three subjects enrolled, 133 with INI-resistance at Screening and 50 with only historical evidence of resistance (and not at Screening) resistance. 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 14 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. The Virological Outcome (VO) population excluded patients who stopped therapy for non-efficacy reasons, and those with major protocol deviations (incorrect dolutegravir dosing, intake of prohibited co-medication). The VO population is a subset of the ITT-E population

Mean change from baseline in HIV RNA at day 8 (primary endpoint) was 1.4log10 (95% CI -1.3, -1.5log10, p<0.001). Response was associated with baseline INI mutation pathway, as shown in Table 7.

Table 7 Virologic Response (Plasma HIV-1 RNA) at Day 8 by Derived baseline IN Resistance Mutation Group [Day 8 Virologic Outcome

| (VO) | Population] | | |
|--|--|---|----------------------------------|
| Derived IN Mutation Group | Number of subjects (VO population) | Mean change from baseline (SD) at Day 8 | %>1log10 decline at Day 8* |
| No Q148H/K/R mutations [#] | 124 | -1.60 (0.52) | 92% |
| Q148 + 1 secondary mutation^ | 35 | -1.18 (0.52) | 71% |
| Q148 + ≥2 secondary mutations^ | 20 | -0.92 (0.81) | 45% |
| | 5A, E92Q, or h | nce mutations N istorical evidenc | |

* Includes subjects with HIV RNA <50 copies/mL at Day 8 ^ G140A/C/S, E138A/K/T, L74I After the monotherapy phase, subjects had the

opportunity to optimize their background regimen when possible.

Of the 183 subjects who completed 24 weeks on study or discontinued before data cut-off. 126 (69%) had <50 copies/mL RNA at Week 24 (ITT-E, Snapshot algorithm). Subjects harbouring virus with Q148 with additional O148-associated secondary mutations had a lower response at Week 24. Background overall susceptibility score (OSS) was not associated with Week 24 response.
 Table 8
 Week 24 Virologic Response by Derived

baseline IN Resistance Mutation Group and OSS of OBR (HIV-1 RNA <50 c/mL, Snapshot

| algorithm), Week 24 VO Population | | | | | | | |
|---|---------------|----------------|----------------|----------------|-----------------|--|--|
| Derived IN Mutation Group | OSS=0 | OSS=1 | OSS=2 | OSS>2 | Total | | |
| No Q148H/K/R mutations ¹ | 4/4 (100%) | 35/40 (88%) | 40/48 (83%) | 17/22 (77%) | 96/114 (84%) | | |
| Q148 + 1 secondary mutation ² | 2/2 (100%) | 8/12 (67%) | 10/17 (59%) | - | 20/31 (65%) | | |
| Q148 +≥2 secondary mutations ² | 1/2 (50%) | 2/11 (18%) | 1/3 (33%) | - | 4/16 (25%) | | |
| ¹ N155H, Y143C/H/R, T66A, E92Q, or historical evidence | | | | | | | |

of INI resistance only

² G140A/C/S, E138A/K/T, L74I OSS: Overall susceptibility score [combined genotypic and phenotypic resistance (Monogram Biosciences Net Assessment)

The response rate at week 48 was sustained with 116/183 (63%) subjects having HIV-1 RNA <50 copies/mL (ITT-E, Snapshot algorithm). Response was also sustained through week 48 in subjects harbouring virus with Q148 with additional Q148-associated secondary mutations. The proportion of subjects with HIV RNA <50 copies/mL at Week 48 was 88/113 (78%) for No Q148 mutations, 19/31 (61%) for Q148+1 and 4/16(25%) for Q148+ \geq 2 secondary mutations (VO population, Snapshot algorithm). Background overall susceptibility score (OSS) was not associated with Week 48 response. Virologic suppression (HIV-1 RNA <50 copies/mL) was comparable across baseline characteristics (gender, race and age). The median change in CD4+ T cell count from baseline for VIKING-3 based on observed data was 61 cells/mm³ at Week 24 and 110 cells/mm³ at Week 48. In the multicentre, double blind, placebo controlled VIKING-4 study (ING116529), 30 HIV-1 infected, ART-experienced adults with current virological failure on an integrase inhibitor containing regimen and primary genotypic resistance to INIs at Screening, were randomized to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for days with all subjects receiving open label dolutegravir plus optimised background regimen from Day 8. At baseline, median patient age was 49 years, 20% were female, 58% non-white, and 23% had hepatitis B and/or C co-infection. Median baseline CD4+ was 160 cells/mm³ median duration of prior ART was 13 years, and 63% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 80% had ≥2 NRTI, 73% ≥1 NNRTI, and 67% ≥2 PI major mutations; 83% had non-R5 virus.

190 / 212 199 / 222 176 / 194 164 / 198

(90%) (90%) (91%) (83%)

Sixteen of 30 subjects (53%) harboured Q148 virus at baseline. The primary endpoint treatment comparison 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 at Day 8 of -1.2 log10 copies/mL (95% CI -1.5, -0.8 log10 copies/mL, p<0.001). The day 8 responses in this placebo controlled study were consistent with those seen in VIKING-3, including by baseline integrase resistance categories. At week 48, 12/30 (40%) subjects had HIV-1 RNA <50 copies/mL (ITT-E, Snapshot algorithm).

In a combined analysis of VIKING-3 and VIKING-4 (n=186, VO population), the proportion of subjects with HIV RNA <50 copies/mL at Week 48 was 123/186 (66%). The proportion of subjects with HIV RNA <50 copies/mL was 96/126 (76%) for No Q148 mutations, 22/41 (54%) for Q148+1 and 5/19 (26%) for Q148+≥2 secondary mutations

In a Phase I/II 48 week multicentre, open-label study (P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of TIVICAY was evaluated in combination regimens in HIV-1 infected infants, children and 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 less than 50 copies/mL. Twenty out of 23 adolescents (87%) had >1 log10 c/mL decrease from Baseline in HIV-1 RNA or HIV-1 RNA <400 c/mL at Week 24.

Four subjects had virologic failure none of which had INI resistance at the time of virologic failure. Pre-clinical Safety Data

Carcinogenesis/mutagenesis 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. Reproductive Toxicology

Fertility Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (33 times the 50 mg human clinical exposure based on AUC).

Pregnancy 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 (37.9 times the 50 mg 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 (0.56 times the 50 mg 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 (0.56 times the 50 mg human clinical exposure based on AUC). Animal toxicology and/or pharmacology The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose oxicity 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 32 and 1.2 times the 50 mg human clinical exposure based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local drug administration, mg/kg or mg/m² metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 30 times the human mg/kg equivalent dose (based on 50 kg human), and 11 times the human mg/m² equivalent dose for a total daily clinical dose of 50 mg.

PHARMACEUTICAL PARTICULARS List of Excipients Tablet Core: Mannitol Microcrystalline Cellulose Povidone K29/32 Sodium Starch Glycolate Sodium Stearyl Fumarate Tablet coating: Polyvinyl alcohol-partially hydrolyzed Macrogol/PEG Talc Iron oxide vellow Incompatibilities No incompatibilities have been identified. Shelf Life The expiry date is indicated on the packaging. **Special Precautions for Storage** Do not store above 30°C. Nature and Contents of Container TIVICAY tablets are supplied in HDPE (high density polvethylene) bottles Instructions for Use/Handling There are no special requirements for use or handling of this product. Not all presentations are available in every country. Manufactured by: Glaxo Operations UK Limited* SG12 0DJ United Kingdom Packed by: Glaxo Wellcome, S.A. Avda Extremadura 3 09400 Aranda De Duero Burgos, Spain *Member of GSK group of companies Trade marks are owned by or licensed to the ViiV Healthcare group of companies. © 2020 ViiV Healthcare group of companies or its licensors. Version number: GDS16/IPI11 Date of issue: 06 Aug 2019



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