SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

EDURANT 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains rilpivirine hydrochloride equivalent to 25 mg rilpivirine.

Excipient with known effect

Each film-coated tablet contains 56 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, round, biconvex, film-coated tablet with a diameter of 6.4 mm, debossed with “TMC” on one side and “25” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EDURANT, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and paediatric patients weighing at least 25 kg without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, and with a viral load ≤ 100,000 HIV-1 RNA copies/ml (see sections 4.4 and 5.1).

Genotypic resistance testing should guide the use of EDURANT (see sections 4.4 and 5.1).

4.2 Posology and method of administration

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

Posology

The recommended dose of EDURANT in adult and paediatric patients weighing at least 25 kg is **one** 25 mg tablet taken once daily. EDURANT **must be taken with a meal** (see section 5.2).

Dispersible tablets
EDURANT is also available as EDURANT 2.5 mg dispersible tablets for paediatric patients aged 2 to less than 18 years weighing at least 14 kg and less than 25 kg. The recommended dosage of EDURANT in these paediatric patients is based on body weight. A difference in bioavailability of 1 x 25 mg film-coated tablets and 10 x 2.5 mg dispersible tablets was observed, therefore they are not interchangeable.
Dose adjustment

For patients concomitantly receiving rifabutin, the EDURANT dose should be increased to 50 mg (two tablets of 25 mg each) taken once daily. When rifabutin co-administration is stopped, the EDURANT dose should be decreased to 25 mg once daily (see section 4.5).

Missed dose

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

If a patient vomits within 4 hours of taking the medicine, another EDURANT tablet should be taken with a meal. If a patient vomits more than 4 hours after taking the medicine, the patient does not need to take another dose of EDURANT until the next regularly scheduled dose.

Special populations

Elderly

There is limited information regarding the use of EDURANT in patients > 65 years of age. No dose adjustment of EDURANT is required in older patients (see section 5.2). EDURANT should be used with caution in this population.

Renal impairment

EDURANT has mainly been studied in patients with normal renal function. No dose adjustment of rilpivirine is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, rilpivirine should be used with caution. In patients with severe renal impairment or end-stage renal disease, the combination of rilpivirine with a strong CYP3A inhibitor (e.g., ritonavir-boosted HIV protease inhibitor) should only be used if the benefit outweighs the risk (see section 5.2).

Treatment with rilpivirine resulted in an early small increase of mean serum creatinine levels which remained stable over time and is not considered clinically relevant (see section 4.8).

Hepatic impairment

There is limited information regarding the use of EDURANT in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). No dose adjustment of EDURANT is required in patients with mild or moderate hepatic impairment. EDURANT should be used with caution in patients with moderate hepatic impairment. EDURANT has not been studied in patients with severe hepatic impairment (Child-Pugh score C). Therefore, EDURANT is not recommended in patients with severe hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of EDURANT in children less than 2 years or weighing less than 14 kg have not been established. No data are available.

Pregnancy

Lower exposures of rilpivirine were observed during pregnancy, therefore viral load should be monitored closely. Alternatively, switching to another ART regimen could be considered (see sections 4.4, 4.6, 5.1 and 5.2).

Method of administration

EDURANT must be taken orally, once daily **with a meal** (see section 5.2). It is recommended that the film-coated tablet be swallowed whole with water and not be chewed or crushed.

4.3 Contraindications

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

EDURANT should not be co-administered with the following medicinal products, as significant decreases in rilpivirine plasma concentrations may occur (due to CYP3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of EDURANT (see section 4.5):

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifampicin, rifapentine
- proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole
- the systemic glucocorticoid dexamethasone, except as a single dose treatment
- St John's wort (*Hypericum perforatum*).

4.4 Special warnings and precautions for use

Virologic failure and development of resistance

EDURANT has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. The list of rilpivirine resistance-associated mutations

presented in section 5.1 should only guide the use of EDURANT in the treatment-naïve population.

In the pooled efficacy analysis from the phase 3 trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) in adults through 96 weeks, patients treated with rilpivirine with a baseline viral load > 100,000 HIV-1 RNA copies/ml had a greater risk of virologic failure (18.2% with rilpivirine versus 7.9% with efavirenz) compared to patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/ml (5.7% with rilpivirine versus 3.6% with efavirenz). The greater risk of virologic failure for patients in the rilpivirine arm was observed in the first 48 weeks of these trials (see section 5.1). Patients with a baseline viral load > 100,000 HIV-1 RNA copies/ml who experienced virologic failure exhibited a higher rate of treatment-emergent resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class. More patients who failed virologically on rilpivirine than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance (see section 5.1).

Findings in adolescents and paediatric patients in trial TMC278-C213 were generally in line with these data. No virological failures were observed in trial TMC278HTX2002 (for details see section 5.1).

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

As with other antiretroviral medicinal products, resistance testing should guide the use of rilpivirine (see section 5.1).

Cardiovascular

At supra-therapeutic doses (75 and 300 mg once daily), rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG) (see sections 4.5, 4.8 and 5.2). EDURANT at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. EDURANT should be used with caution when co-administered with medicinal products with a known risk of Torsade de Pointes.

Immune reactivation syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.8).

Pregnancy

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

Important information about some of the ingredients of EDURANT

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

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that affect rilpivirine exposure

Rilpivirine is primarily metabolised by cytochrome P450 (CYP)3A. Medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine (see section 5.2). Co-administration of rilpivirine and medicinal products that induce CYP3A has been observed to decrease the plasma concentrations of rilpivirine, which could reduce the therapeutic effect of rilpivirine.

Co-administration of rilpivirine and medicinal products that inhibit CYP3A has been observed to increase the plasma concentrations of rilpivirine.

Co-administration of rilpivirine with medicinal products that increase gastric pH may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of EDURANT.

Medicinal products that are affected by the use of rilpivirine

Rilpivirine at the recommended dose is not likely to have a clinically relevant effect on the exposure of medicinal products metabolised by CYP enzymes.

Rilpivirine inhibits P-glycoprotein *in vitro* (IC_{50} is 9.2 μM). In a clinical study, rilpivirine did not significantly affect the pharmacokinetics of digoxin. However, it may not be completely excluded that rilpivirine can increase the exposure to other medicines transported by P-glycoprotein that are more sensitive to intestinal P-gp inhibition, e.g., dabigatran etexilate.

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

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

Interaction table

Interaction studies have only been performed in adults.

Interactions between rilpivirine and co-administered medicinal products are listed in Table 1 (increase is indicated as "↑", decrease as "↓", no change as "↔", not applicable as "NA", confidence interval as "CI").

Table 1: INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
Antiretrovirals		
HIV NRTIs/N[t]RTIs		
Didanosine*[#] 400 mg once daily	didanosine AUC ↑ 12% didanosine C_{min} NA didanosine C_{max} ↔ rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↔	No dose adjustment is required. Didanosine should be administered at least two hours before or at least four hours after rilpivirine.
Tenofovir disoproxil *[#] 245 mg once daily	tenofovir AUC ↑ 23% tenofovir C_{min} ↑ 24% tenofovir C_{max} ↑ 19% rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↔	No dose adjustment is required.
Other NRTIs (abacavir, emtricitabine, lamivudine, stavudine and zidovudine)	Not studied. No clinically relevant drug-drug interactions are expected.	No dose adjustment is required.
HIV NNRTIs		
NNRTIs (delavirdine, efavirenz, etravirine, nevirapine)	Not studied.	It is not recommended to co-administer rilpivirine with other NNRTIs.
HIV PIs – with co-administration of low dose ritonavir		
Darunavir/ritonavir*[#] 800/100 mg once daily	darunavir AUC ↔ darunavir C_{min} ↓ 11% darunavir C_{max} ↔ rilpivirine AUC ↑ 130% rilpivirine C_{min} ↑ 178% rilpivirine C_{max} ↑ 79% (inhibition of CYP3A enzymes)	Concomitant use of rilpivirine with ritonavir-boosted PIs causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required.
Lopinavir/ritonavir (soft gel capsule)*[#] 400/100 mg twice daily	lopinavir AUC ↔ lopinavir C_{min} ↓ 11% lopinavir C_{max} ↔ rilpivirine AUC ↑ 52% rilpivirine C_{min} ↑ 74% rilpivirine C_{max} ↑ 29% (inhibition of CYP3A enzymes)	
Other boosted PIs (atazanavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir, tipranavir/ritonavir)	Not studied.	

HIV PIs – without co-administration of low dose ritonavir		
Unboosted PIs (atazanavir, fosamprenavir, indinavir, nelfinavir)	Not studied. Increased exposure of rilpivirine is expected. (inhibition of CYP3A enzymes)	No dose adjustment is required.
CCR5 Antagonists		
Maraviroc	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
HIV Integrase Strand Transfer Inhibitors		
Raltegravir*	raltegravir AUC ↑ 9% raltegravir C_{min} ↑ 27% raltegravir C_{max} ↑ 10% rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↔	No dose adjustment is required.
Other Antiviral Agents		
Ribavirin	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
Simeprevir*	simeprevir AUC ↔ simeprevir C_{min} ↔ simeprevir C_{max} ↑ 10% rilpivirine AUC ↔ rilpivirine C_{min} ↑ 25% rilpivirine C_{max} ↔	No dose adjustment is required.
OTHER AGENTS		
ANTICONVULSANTS		
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with these anticonvulsants as co-administration may result in loss of therapeutic effect of rilpivirine (see section 4.3).
AZOLE ANTIFUNGAL AGENTS		
Ketoconazole*[#] 400 mg once daily	ketoconazole AUC ↓ 24% ketoconazole C_{min} ↓ 66% ketoconazole C_{max} ↔ (induction of CYP3A due to high rilpivirine dose in the study) rilpivirine AUC ↑ 49% rilpivirine C_{min} ↑ 76% rilpivirine C_{max} ↑ 30% (inhibition of CYP3A enzymes)	At the recommended dose of 25 mg once daily, no dose adjustment is required when rilpivirine is co-administered with ketoconazole.

Fluconazole Itraconazole Posaconazole Voriconazole	Not studied. Concomitant use of EDURANT with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine. (inhibition of CYP3A enzymes)	No dose adjustment is required.
ANTIMYCOBACTERIALS		
Rifabutin* 300 mg once daily[†]	rifabutin AUC ↔ rifabutin C_{min} ↔ rifabutin C_{max} ↔ 25-*O*-desacetyl-rifabutin AUC ↔ 25-*O*-desacetyl-rifabutin C_{min} ↔ 25-*O*-desacetyl-rifabutin C_{max} ↔	Throughout co-administration of rilpivirine with rifabutin, the rilpivirine dose should be increased from 25 mg once daily to 50 mg once daily. When rifabutin co-administration is stopped, the rilpivirine dose should be decreased to 25 mg once daily.
300 mg once daily (+ 25 mg once daily rilpivirine)	rilpivirine AUC ↓ 42% rilpivirine C_{min} ↓ 48% rilpivirine C_{max} ↓ 31%	
300 mg once daily (+ 50 mg once daily rilpivirine)	rilpivirine AUC ↑ 16%* rilpivirine C_{min} ↔* rilpivirine C_{max} ↑ 43%* * compared to 25 mg once daily rilpivirine alone (induction of CYP3A enzymes)	
Rifampicin*[#] 600 mg once daily	rifampicin AUC ↔ rifampicin C_{min} NA rifampicin C_{max} ↔ 25-desacetyl-rifampicin AUC ↓ 9% 25-desacetyl-rifampicin C_{min} NA 25-desacetyl-rifampicin C_{max} ↔ rilpivirine AUC ↓ 80% rilpivirine C_{min} ↓ 89% rilpivirine C_{max} ↓ 69% (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with rifampicin as co-administration is likely to result in loss of therapeutic effect of rilpivirine (see section 4.3).
Rifapentine	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with rifapentine as co-administration is likely to result in loss of therapeutic effect of rilpivirine (see section 4.3).
MACROLIDE ANTIBIOTICS		
Clarithromycin Erythromycin	Not studied. Increased exposure of rilpivirine is expected. (inhibition of CYP3A enzymes)	Where possible, alternatives such as azithromycin should be considered.

GLUCOCORTICOIDS		
Dexamethasone (systemic, except for single dose use)	Not studied. Dose dependent decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine should not be used in combination with systemic dexamethasone (except as a single dose) as co-administration may result in loss of therapeutic effect of rilpivirine (see section 4.3). Alternatives should be considered, particularly for long-term use.
PROTON PUMP INHIBITORS		
Omeprazole*[#] 20 mg once daily	omeprazole AUC ↓ 14% omeprazole C_{min} NA omeprazole C_{max} ↓ 14% rilpivirine AUC ↓ 40% rilpivirine C_{min} ↓ 33% rilpivirine C_{max} ↓ 40% (reduced absorption due to gastric pH increase)	Rilpivirine must not be used in combination with proton pump inhibitors as co-administration is likely to result in loss of therapeutic effect of rilpivirine (see section 4.3).
Lansoprazole Rabeprazole Pantoprazole Esomeprazole	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (reduced absorption due to gastric pH increase)	
H_2-RECEPTOR ANTAGONISTS		
Famotidine*[#] 40 mg single dose taken 12 hours before rilpivirine	rilpivirine AUC ↓ 9% rilpivirine C_{min} NA rilpivirine C_{max} ↔	The combination of rilpivirine and H_2-receptor antagonists should be used with particular caution. Only H_2-receptor antagonists that can be dosed once daily should be used. A strict dosing schedule, with intake of H_2-receptor antagonists at least 12 hours before or at least 4 hours after rilpivirine should be used.
Famotidine*[#] 40 mg single dose taken 2 hours before rilpivirine	rilpivirine AUC ↓ 76% rilpivirine C_{min} NA rilpivirine C_{max} ↓ 85% (reduced absorption due to gastric pH increase)	
Famotidine*[#] 40 mg single dose taken 4 hours after rilpivirine	rilpivirine AUC ↑ 13% rilpivirine C_{min} NA rilpivirine C_{max} ↑ 21%	
Cimetidine Nizatidine Ranitidine	Not studied. (reduced absorption due to gastric pH increase)	

ANTACIDS		
Antacids (e.g., aluminium or magnesium hydroxide, calcium carbonate)	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (reduced absorption due to gastric pH increase)	The combination of rilpivirine and antacids should be used with particular caution. Antacids should only be administered either at least 2 hours before or at least 4 hours after rilpivirine.
NARCOTIC ANALGESICS		
Methadone* 60-100 mg once daily, individualised dose	R(-) methadone AUC ↓ 16% R(-) methadone C_{min} ↓ 22% R(-) methadone C_{max} ↓ 14% rilpivirine AUC ↔* rilpivirine C_{min} ↔* rilpivirine C_{max} ↔* * based on historic controls	No dose adjustments are required when initiating co-administration of methadone with rilpivirine. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
ANTIARRHYTHMICS		
Digoxin*	digoxin AUC ↔ digoxin C_{min} NA digoxin C_{max} ↔	No dose adjustment is required.
ANTICOAGULANTS		
Dabigatran etexilate	Not studied. A risk for increases in dabigatran plasma concentrations cannot be excluded. (inhibition of intestinal P-gp)	The combination of rilpivirine and dabigatran etexilate should be used with caution.
ANTIDIABETICS		
Metformin* 850 mg single dose	metformin AUC ↔ metformin C_{min} NA metformin C_{max} ↔	No dose adjustment is required.
HERBAL PRODUCTS		
St John's wort *(Hypericum perforatum)*	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with products containing St John's wort as co-administration may result in loss of therapeutic effect of rilpivirine (see section 4.3).
ANALGESICS		
Paracetamol*[#] 500 mg single dose	paracetamol AUC ↔ paracetamol C_{min} NA paracetamol C_{max} ↔ rilpivirine AUC ↔ rilpivirine C_{min} ↑ 26% rilpivirine C_{max} ↔	No dose adjustment is required.

ORAL CONTRACEPTIVES		
Ethinylestradiol* 0.035 mg once daily Norethindrone* 1 mg once daily	ethinylestradiol AUC ↔ ethinylestradiol C_{min} ↔ ethinylestradiol C_{max} ↑ 17% norethindrone AUC ↔ norethindrone C_{min} ↔ norethindrone C_{max} ↔ rilpivirine AUC ↔* rilpivirine C_{min} ↔* rilpivirine C_{max} ↔* * based on historic controls	No dose adjustment is required.
HMG CO-A REDUCTASE INHIBITORS		
Atorvastatin*[#] 40 mg once daily	atorvastatin AUC ↔ atorvastatin C_{min} ↓ 15% atorvastatin C_{max} ↑ 35% rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↓ 9%	No dose adjustment is required.
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS		
Sildenafil*[#] 50 mg single dose	sildenafil AUC ↔ sildenafil C_{min} NA sildenafil C_{max} ↔ rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↔	No dose adjustment is required.
Vardenafil Tadalafil	Not studied.	No dose adjustment is required.

* The interaction between rilpivirine and the medicinal product was evaluated in a clinical study. All other drug-drug interactions shown are predicted.

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

[†] This interaction study has been performed with a dose higher than the recommended dose for rilpivirine.

QT prolonging medicinal products

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicinal products that prolong the QTc interval of the ECG. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the ECG (see section 5.1). EDURANT should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of rilpivirine (see

sections 4.4, 5.1 and 5.2). Lower exposures of rilpivirine were observed during pregnancy, therefore viral load should be monitored closely.

Animal studies do not indicate reproductive toxicity (see section 5.3).

The use of rilpivirine may be considered during pregnancy, if necessary.

Breast-feeding

It is not known whether rilpivirine is excreted in human milk. Rilpivirine is excreted in the milk of rats. Because of the potential for adverse reactions in breastfed infants, mothers should be instructed not to breast-feed if they are receiving rilpivirine.

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed.

Fertility

No human data on the effect of rilpivirine on fertility are available. No clinically relevant effects on fertility were seen in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

EDURANT has no or negligible influence on the ability to drive and use machines. However, fatigue, dizziness and somnolence have been reported in some patients taking EDURANT and should be considered when assessing a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

During the clinical development programme (1,368 patients in the phase 3 controlled trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE)), 55.7% of subjects experienced at least one adverse drug reaction (see section 5.1). The most frequently reported adverse drug reactions (ADRs) (≥ 2%) that were at least of moderate intensity were depression (4.1%), headache (3.5%), insomnia (3.5%), rash (2.3%), and abdominal pain (2.0%). The most frequent serious treatment-related ADRs were reported in 7 (1.0%) patients receiving rilpivirine. The median duration of exposure for patients in the rilpivirine arm and efavirenz arm was 104.3 and 104.1 weeks, respectively. Most ADRs occurred in the first 48 weeks of treatment.

Selected treatment-emergent clinical laboratory abnormalities (grade 3 or grade 4), considered as ADRs, reported in EDURANT treated patients were increased pancreatic amylase (3.8%), increased AST (2.3%), increased ALT (1.6%), increased LDL cholesterol (fasted, 1.5%), decreased white blood cell count (1.2%), increased lipase (0.9%), increased bilirubin (0.7%), increased triglycerides (fasted, 0.6%), decreased haemoglobin (0.1%), decreased platelet count (0.1%), and increased total cholesterol (fasted, 0.1%).

Tabulated summary of adverse reactions

ADRs reported in adult patients treated with rilpivirine are summarised in Table 2. The ADRs are listed by system organ class (SOC) and frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, ADRs are presented in order of decreasing frequency.

Table 2: ADRs reported in antiretroviral treatment-naïve HIV-1 infected adult patients treated with Rilpivirine (pooled data from the week 96 analysis of the phase 3 ECHO and THRIVE trials) N=686

System Organ Class (SOC)	**Frequency Category**	**ADRs (Rilpivirine + BR)**
Blood and lymphatic system disorders	common	decreased white blood cell count decreased haemoglobin decreased platelet count
Immune system disorders	uncommon	immune reactivation syndrome
Metabolism and nutrition disorders	very common	increased total cholesterol (fasted) increased LDL cholesterol (fasted)
	common	decreased appetite increased triglycerides (fasted)
Psychiatric disorders	very common	insomnia
	common	abnormal dreams depression sleep disorders depressed mood
Nervous system disorders	very common	headache dizziness
	common	somnolence
Gastrointestinal disorders	very common	nausea increased pancreatic amylase
	common	abdominal pain vomiting increased lipase abdominal discomfort dry mouth
Hepatobiliary disorders	very common	increased transaminases
	common	increased bilirubin
Skin and subcutaneous tissue disorders	common	rash
General disorders and administration site conditions	common	fatigue

BR=background regimen
N=number of subjects

Laboratory abnormalities

In the rilpivirine arm in the week 96 analysis of the phase 3 ECHO and THRIVE trials, mean change from baseline in total cholesterol (fasted) was 5 mg/dl, in HDL cholesterol (fasted) 4 mg/dl, in LDL cholesterol (fasted) 1 mg/dl, and in triglycerides (fasted) -7 mg/dl.

Description of selected adverse reactions

Immune reactivation syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Paediatric population (12 to less than 18 years of age)

TMC278-C213 Cohort 1
The safety assessment is based on the week 48 analysis of the single-arm, open-label, phase 2 trial, TMC278-C213 Cohort 1, in which 36 antiretroviral treatment-naïve HIV-1 infected adolescent patients weighing at least 32 kg received rilpivirine (25 mg once daily) in combination with other antiretroviral agents (see section 5.1). The median duration of exposure for patients was 63.5 weeks. There were no patients who discontinued treatment due to ADRs. No new ADRs were identified compared to those seen in adults.

Most ADRs were grade 1 or 2. The most common ADRs reported in Study TMC278-C213 Cohort 1 (all grades, greater than or equal to 10%) were headache (19.4%), depression (19.4%), somnolence (13.9%), and nausea (11.1%). No grade 3-4 laboratory abnormalities for AST/ALT or grade 3-4 ADRs of transaminase increased were reported.

There were no new safety concerns identified in the week 240 analysis of the TMC278-C213 Cohort 1 trial in adolescents.

Paediatric population (2 to less than 12 years of age)
TMC278-C213 Cohort 2
Cohort 2 of the single-arm, open-label phase 2 trial, TMC278-C213 was designed to evaluate the safety of the rilpivirine weight adjusted doses 12.5, 15 and 25 mg once daily in antiretroviral treatment-naïve HIV-1 infected patients (6 to less than 12 years of age and weighing at least 17 kg) (see section 5.1). The median duration of exposure for patients in the week 48 analysis (including post-week 48 extension) was 69.5 (range 35 to 218) weeks.

All ADRs were mild or moderate, ADRs reported in at least 2 participants, regardless of severity were: decreased appetite (3/18, 16.7%), vomiting (2/18, 11.1%), ALT increased (2/18, 11.1%), AST increased (2/18, 11.1%), and rash (2/18, 11.1%). There were no patients who discontinued treatment due to ADRs. No new ADRs were identified compared to those seen in adults.

TMC278HTX2002
The single arm, open-label phase 2 trial, TMC278HTX2002, was designated to evaluate the safety of rilpivirine weight-adjusted doses 12.5, 15 and 25 mg once daily in virologically suppressed HIV-1 infected patients (2 to less12 years of age and weighing at least 10 kg) (see section 5.1). The median duration of exposure for patients in the week 48 analysis was 48.4 (range 47 to 52) weeks.

All ADRs were mild or moderate. ADRs reported in at least 2 participants, regardless of severity were: vomiting (4/26, 15.4%), abdominal pain (3/26, 11.5%), nausea (2/26, 7.7%), ALT increased (3/26, 11.5%), AST increased (2/26, 7.7%), and decreased appetite (2/26, 7.7%). There were no patients who discontinued treatment due to ADRs. No new ADRs were identified compared to those seen in adults.

The safety and efficacy of rilpivirine in children less than 2 years or weighing less than 14 kg have not been established.

Other special populations

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no specific antidote for overdose with EDURANT. Human experience of overdose with rilpivirine is limited. Symptoms of overdose may include headache, nausea, dizziness and/or abnormal dreams. Treatment of overdose with rilpivirine consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, non-nucleoside reverse transcriptase inhibitors, ATC code: J05AG05.

Mechanism of action

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

Antiviral activity *in vitro*

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM

(0.27 ng/ml). Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2,510 to 10,830 nM (920 to 3,970 ng/ml), treatment of HIV-2 infection with rilpivirine is not recommended in the absence of clinical data.

Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/ml) and group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/ml).

Resistance

In cell culture

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

Resistance to rilpivirine was determined as a fold change in EC_{50} value (FC) above the biological cut-off (BCO) of the assay.

In treatment-naïve adult subjects

For the resistance analysis, a broader definition of virologic failure was used than in the primary efficacy analysis. In the week 48 pooled resistance analysis from the phase 3 trials, 62 (of a total of 72) virologic failures in the rilpivirine arm had resistance data at baseline and time of failure. In this analysis, the resistance-associated mutations (RAMs) associated with NNRTI resistance that developed in at least 2 rilpivirine virologic failures were: V90I, K101E, E138K, E138Q, V179I, Y181C, V189I, H221Y, and F227C. In the trials, the presence of the mutations V90I and V189I, at baseline, did not affect response. The E138K substitution emerged most frequently during rilpivirine treatment, commonly in combination with the M184I substitution. In the week 48 analysis, 31 out of 62 of rilpivirine virologic failures had concomitant NNRTI and NRTI RAMs; 17 of those 31 had the combination of E138K and M184I. The most common mutations were the same in the week 48 and week 96 analyses.

In the week 96 pooled resistance analysis, lower rates of virologic failure were observed in the second 48 weeks than in the first 48 weeks of treatment. From the week 48 to the week 96 analysis, 24 (3.5%) and 14 (2.1%) additional virologic failures occurred in the rilpivirine and efavirenz arm, respectively. Of these virologic failures, 9 out of 24 and 4 out of 14 were in subjects with a baseline viral load < 100,000 copies/ml, respectively.

In treatment-naïve paediatric subjects 12 to less than 18 years

In the week 240 resistance analysis of TMC278-C213 Cohort 1, rilpivirine resistance-associated mutations (RAMs) were observed in 46.7% (7/15) of subjects with virologic failure and post-baseline genotypic data. All subjects with rilpivirine RAMs also had at least 1 treatment-emergent NRTI RAM at the last post-baseline time point with genotypic data.

In treatment-naïve paediatric subjects 6 to less than 12 years of age
In the final resistance analysis of the TMC278-C213 Cohort 2, rilpivirine RAMs were observed in 83.3% (5/6) of subjects with post-baseline genotypic data; of these, 2/6 occurred within the first 48 weeks and 4 subjects with rilpivirine RAMs also had at least 1 treatment-emergent NRTI RAM at the last post-baseline time point with genotypic data.

In virologically suppressed paediatric subjects 2 to less than 12 years of age
In the TMC278HTX2002 trial, no subjects experienced virologic failure and no treatment-emergent resistance was observed.
Considering all of the available *in vitro* and *in vivo* data in treatment-naïve subjects, the following resistance-associated mutations, when present at baseline, may affect the activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, and M230L. These rilpivirine resistance-associated mutations should only guide the use of EDURANT in the treatment-naïve population. These resistance-associated mutations were derived from *in vivo* data involving treatment-naïve subjects only and therefore cannot be used to predict the activity of rilpivirine in subjects who have virologically failed an antiretroviral-containing regimen.

As with other antiretroviral medicinal products, resistance testing should guide the use of EDURANT.

Cross-resistance

Site-directed NNRTI mutant virus

In a panel of 67 HIV-1 recombinant laboratory strains with one resistance-associated mutation at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity against 64 (96%) of these strains. The single resistance-associated mutations associated with a loss of susceptibility to rilpivirine were: K101P, Y181I and Y181V. The K103N substitution did not result in reduced susceptibility to rilpivirine by itself, but the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine.

Recombinant clinical isolates

Rilpivirine retained sensitivity (FC ≤ BCO) against 62% of 4,786 HIV-1 recombinant clinical isolates resistant to efavirenz and/or nevirapine.

Treatment-naïve HIV-1 infected adult patients

In the week 96 pooled resistance analysis of the phase 3 trials (ECHO and THRIVE), 42 out of 86 subjects with virologic failure on rilpivirine showed treatment-emergent resistance to rilpivirine (genotypic analysis). In these patients, phenotypic cross-resistance to other NNRTIs was noted as follows: etravirine 32/42, efavirenz 30/42, and nevirapine 16/42. In patients with a baseline viral load ≤ 100,000 copies/ml, 9 out of 27 patients with virologic failure on rilpivirine showed treatment-emergent resistance to rilpivirine (genotypic analysis), with the following frequency of phenotypic cross-resistance: etravirine 4/9, efavirenz 3/9, and nevirapine 1/9.

Effects on electrocardiogram

The effect of rilpivirine at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady-state. EDURANT at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc.

When supratherapeutic doses of 75 mg once daily and 300 mg once daily of rilpivirine were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10.7 (15.3) and 23.3 (28.4) ms, respectively. Steady-state administration of rilpivirine 75 mg once daily and 300 mg once daily resulted in a mean C_{max} approximately 2.6-fold and 6.7-fold, respectively, higher than the mean

steady-state C_{max} observed with the recommended 25 mg once daily dose of rilpivirine.

Clinical efficacy and safety

Adult population

Treatment-naïve adult subjects

The evidence of efficacy of rilpivirine is based on the analysis of 96 week data from 2 randomised, double-blinded, active-controlled, phase 3 trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE). The trials were identical in design, with the exception of the background regimen (BR). In the week 96 efficacy analysis, the virologic response rate [confirmed undetectable viral load (< 50 HIV-1 RNA copies/ml)] was evaluated in patients receiving rilpivirine 25 mg once daily in addition to a BR versus patients receiving efavirenz 600 mg once daily in addition to a BR. Similar efficacy for rilpivirine was seen in each trial demonstrating non-inferiority to efavirenz.

Antiretroviral treatment-naïve HIV-1 infected patients were enroled who had a plasma HIV-1 RNA ≥ 5,000 copies/ml and were screened for susceptibility to N(t)RTIs and for absence of specific NNRTI resistance-associated mutations. In ECHO, the BR was fixed to the N(t)RTIs, tenofovir disoproxil fumarate plus emtricitabine. In THRIVE, the BR consisted of 2 investigator-selected N(t)RTIs: tenofovir disoproxil fumarate plus emtricitabine or zidovudine plus lamivudine or abacavir plus lamivudine. In ECHO, randomisation was stratified by screening viral load. In THRIVE, randomisation was stratified by screening viral load and by N(t)RTI BR.

This analysis included 690 patients in ECHO and 678 patients in THRIVE who had completed 96 weeks of treatment or discontinued earlier.

In the pooled analysis for ECHO and THRIVE, demographics and baseline characteristics were balanced between the rilpivirine arm and the efavirenz arm. Table 3 displays selected baseline disease characteristics of the patients in the rilpivirine and efavirenz arms.

Table 3: Baseline disease characteristics of antiretroviral treatment-naïve HIV-1 infected adult subjects in the ECHO and THRIVE trials (pooled analysis)

	Pooled data from the ECHO and THRIVE trials	
	Rilpivirine + BR N=686	**Efavirenz + BR N=682**
Baseline disease characteristics		
Median baseline plasma HIV-1 RNA (range), log_{10} copies/ml	5.0 (2-7)	5.0 (3-7)
Median baseline CD4+ cell count (range), x 10^6 cells/l	249 (1-888)	260 (1-1,137)
Percentage of subjects with: hepatitis B/C virus co-infection	7.3%	9.5%
Percentage of patients with the following background regimens:		
tenofovir disoproxil fumarate plus emtricitabine	80.2%	80.1%
zidovudine plus lamivudine	14.7%	15.1%
abacavir plus lamivudine	5.1%	4.8%

BR=background regimen

Table 4 below shows the results of the week 48 and the week 96 efficacy analysis for patients treated with rilpivirine and patients treated with efavirenz from the pooled data from the ECHO and THRIVE trials. The response rate (confirmed undetectable

viral load < 50 HIV-1 RNA copies/ml) at week 96 was comparable between the rilpivirine arm and the efavirenz arm. The incidence of virologic failure was higher in the rilpivirine arm than the efavirenz arm at week 96; however, most of the virologic failures occurred within the first 48 weeks of treatment. Discontinuations due to adverse events were higher in the efavirenz arm at week 96 than the rilpivirine arm. Most of these discontinuations occurred in the first 48 weeks of treatment.

Table 4: Virologic outcome in adult subjects in the ECHO and THRIVE trials (pooled data in the week 48 (primary) and week 96 analysis; ITT-TLOVR*)

	Outcome in the week 48 analysis			***Outcome in the week 96 analysis***		
	Rilpivirine + BR N=686	**Efavirenz + BR N=682**	**Observed difference (95% CI)** [±]	**Rilpivirine + BR N=686**	**Efavirenz + BR N=682**	**Observed difference (95% CI)** [±]
Response (confirmed < 50 HIV-1 RNA copies/ml)[§#]	84.3% (578/686)	82.3% (561/682)	2.0 (-2.0; 6.0)	77.6% (532/686)	77.6% (529/682)	0 (-4.4; 4.4)
Non-response						
Virologic failure[†]						
Overall	9.0% (62/686)	4.8% (33/682)	ND	11.5% (79/686)	5.9% (40/682)	ND
≤ 100,000	3.8% (14/368)	3.3% (11/330)	ND	5.7% (21/368)	3.6% (12/329)	ND
> 100,000	15.1% (48/318)	6.3% (22/352)	ND	18.2% (58/318)	7.9% (28/353)	ND
Death	0.1% (1/686)	0.4% (3/682)	ND	0.1% (1/686)	0.9% (6/682)	ND
Discontinued due to adverse event (AE)	2.0% (14/686)	6.7% (46/682)	ND	3.8% (26/682)	7.6% (52/682)	ND
Discontinued for non-AE reason[¶]	4.5% (31/686)	5.7% (39/682)	ND	7.0% (48/682)	8.1% (55/682)	ND
Response by subcategory						
By background NRTI						
Tenofovir/ emtricitabine	83.5% (459/550)	82.4% (450/546)	1.0 (-3.4; 5.5)	76.9% (423/550)	77.3% (422/546)	-0.4% (-5.4; 4.6)
Zidovudine/ lamivudine	87.1% (88/101)	80.6% (83/103)	6.5 (-3.6; 16.7)	81.2% (82/101)	76.7% (79/103)	4.5% (-6.8; 15.7)
Abacavir/ lamivudine	88.6% (31/35)	84.8% (28/33)	3.7 (-12.7; 20.1)	77.1% (27/35)	84.8% (28/33)	-7.7% (-26.7; 11.3)
By baseline viral load (copies/ml)						
≤ 100,000	90.2% (332/368)	83.6% (276/330)	6.6 (1.6; 11.5)	84.0% (309/368)	79.9% (263/329)	4.0 (-1.7; 9.7)
> 100,000	77.4% (246/318)	81.0% (285/352)	-3.6 (-9.8; 2.5)	70.1% (223/318)	75.4% (266/353)	-5.2 (-12.0;1.5)
By baseline CD4 count (× 10^6 cells/l)						
< 50	58.8% (20/34)	80.6% (29/36)	-21.7 (-43.0; -0.5)	55.9% (19/34)	69.4% (25/36)	-13.6 (-36.4; 9.3)
≥ 50-< 200	80.4% (156/194)	81.7% (143/175)	-1.3 (-9.3; 6.7)	71.1% (138/194)	74.9% (131/175)	-3.7 (-12.8; 5.4)
≥ 200-< 350	86.9% (272/313)	82.4% (253/307)	4.5 (-1.2; 10.2)	80.5% (252/313)	79.5% (244/307)	1.0 (-5.3; 7.3)
≥ 350	90.3% (130/144)	82.9% (136/164)	7.4 (-0.3; 15.0)	85.4% (123/144)	78.7% (129/164)	6.8 (-1.9; 15.4)

BR=background regimen; CI=confidence interval; N=number of subjects per treatment group; ND=not determined.

* Intent-to-treat time to loss of virologic response.

± Based on normal approximation.

§ Subjects achieved virologic response (two consecutive viral loads < 50 copies/ml) and maintained it through week 48/96.

Predicted difference of response rates (95% CI) for the week 48 analysis: 1.6% (-2.2%; 5.3%) and for the week 96 analysis: -0.4% (-4.6%; 3.8%); both p-value < 0.0001 (non-inferiority at 12% margin) from logistic regression model, including stratification factors and study.

† Virologic failure in pooled efficacy analysis: includes subjects who were rebounder (confirmed viral load ≥ 50 copies/ml after being responder) or who were never suppressed (no confirmed viral load < 50 copies/ml, either ongoing or discontinued due to lack or loss of efficacy).

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

At week 96, the mean change from baseline in CD4+ cell count was $+228 \times 10^6$ cells/l in the rilpivirine arm and $+219 \times 10^6$ cells/l in the efavirenz arm in the pooled analysis of the ECHO and THRIVE trials [estimated treatment difference (95% CI): 11.3 (-6.8; 29.4)].

From the week 96 pooled resistance analysis, the resistance outcome for patients with protocol defined virological failure, and paired genotypes (baseline and failure) is shown in Table 5.

Table 5: Resistance outcome by background NRTI regimen used (pooled data from the ECHO and THRIVE trials in the week 96 resistance analysis)

	tenofovir/ emtricitabine	zidovudine/ lamivudine	abacavir/ lamivudine	All*
Rilpivirine-treated				
Resistance# to emtricitabine/lamivudine % (n/N)	6.9 (38/550)	3.0 (3/101)	8.6 (3/35)	6.4 (44/686)
Resistance to rilpivirine % (n/N)	6.5 (36/550)	3.0 (3/101)	8.6 (3/35)	6.1 (42/686)
Efavirenz-treated				
Resistance to emtricitabine/lamivudine % (n/N)	1.1 (6/546)	1.9 (2/103)	3.0 (1/33)	1.3 (9/682)
Resistance to efavirenz % (n/N)	2.4 (13/546)	2.9 (3/103)	3.0 (1/33)	2.5 (17/682)

* The number of patients with virologic failure and paired genotypes (baseline and failure) were 71, 11, and 4 for rilpivirine and 30, 10, and 2 for efavirenz, for the tenofovir/emtricitabine, zidovudine/lamivudine, and abacavir/lamivudine regimens, respectively.

Resistance was defined as the emergence of any resistance-associated mutation at failure.

For those patients failing therapy with rilpivirine and who developed resistance to rilpivirine, cross-resistance to other approved NNRTIs (etravirine, efavirenz, nevirapine) was generally seen.

Study TMC278-C204 was a randomised, active-controlled, phase 2b trial in antiretroviral treatment-naïve HIV-1 infected adult patients consisting of 2 parts: an initial partially blinded dose-finding part [(rilpivirine) doses blinded] up to 96 weeks, followed by a long-term, open-label part. In the open-label part of the trial, patients originally randomised to one of the three doses of rilpivirine were all treated with rilpivirine 25 mg once daily in addition to a BR, once the dose for the phase 3 studies was selected. Patients in the control arm received efavirenz 600 mg once daily in addition to a BR in both parts of the study. The BR consisted of 2 investigator-selected N(t)RTIs: zidovudine plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine.

Study TMC278-C204 enroled 368 HIV-1 infected treatment-naïve adult patients who had a plasma HIV-1 RNA ≥ 5,000 copies/ml, previously received ≤ 2 weeks of treatment with an N(t)RTI or protease inhibitor, had no prior use of NNRTIs and

were screened for susceptibility to N(t)RTI and for absence of specific NNRTI resistance-associated mutations.

At 96 weeks, the proportion of patients with < 50 HIV-1 RNA copies/ml receiving rilpivirine 25 mg (N=93) compared to patients receiving efavirenz (N=89) was 76% and 71%, respectively. The mean increase from baseline in CD4+ counts was 146×10^6 cells/l in patients receiving rilpivirine 25 mg and 160×10^6 cells/l in patients receiving efavirenz.

Of those patients who were responders at week 96, 74% of patients receiving rilpivirine remained with undetectable viral load (< 50 HIV-1 RNA copies/ml) at week 240 compared to 81% of patients receiving efavirenz. There were no safety concerns identified in the week 240 analyses.

Paediatric population

In treatment-naïve paediatric subjects 12 to less than 18 years
The pharmacokinetics, safety, tolerability and efficacy of rilpivirine 25 mg once daily, in combination with an investigator-selected BR containing two NRTIs, was evaluated in trial TMC278-C213 Cohort 1, a single-arm, open-label phase 2 trial in antiretroviral treatment-naïve HIV-1 infected adolescent subjects weighing at least 32 kg. This analysis included 36 patients who had completed at least 48 weeks of treatment or discontinued earlier.

The 36 subjects had a median age of 14.5 years (range: 12 to 17 years), and were 55.6% female, 88.9% Black and 11.1% Asian. The median baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies per ml, and the median baseline CD4+ cell count was 414×10^6 cells/l (range: 25 to 983×10^6 cells/l).

Table 6 summarises the week 48 and week 240 virologic outcome results for trial TMC278-C213 Cohort 1. Six subjects discontinued due to virological failure up to week 48 and 3 subjects discontinued beyond week 48. One subject discontinued due to an adverse event at week 48, and no additional subjects discontinued due to adverse events in the week 240 analysis.

Table 6: Virologic outcome in adolescent subjects in TMC278-C213 Cohort 1 **– week 48 and week 240 analysis; ITT-TLOVR***

	Week 48 N=36	**Week 240 N=32**
Response (confirmed < 50 HIV-1 RNA copies/ml)[§]	72.2% (26/36)	43.8% (14/32)
≤ 100,000	78.6% (22/28)	48% (12/25)
> 100,000	50% (4/8)	28.6% (2/7)
Non-response		
Virologic failure[±]		
Overall	22.2% (8/36)	50% (16/32)
≤ 100,000	17.9% (5/28)	48% (12/25)
> 100,000	37.5% (3/8)	57.1% (4/7)
Increase in CD4+ cell count (mean)	201.2×10^6 cells/l	113.6×10^6 cells/l

N=number of subjects per treatment group.

* Intent-to-treat time to loss of virologic response.

§ Subjects achieved virologic response (two consecutive viral loads < 50 copies/ml) and maintained it through week 48 and week 240.

± Virologic failure in efficacy analysis: includes subjects who were rebounder (confirmed viral load ≥ 50 copies/ml after being responder) or who were never suppressed (no confirmed viral load < 50 copies/ml, either ongoing or discontinued due to lack or loss of efficacy).

Treatment-naïve paediatric subjects 6 to less than 12 years of age

The pharmacokinetics, safety, tolerability and efficacy of rilpivirine weight-adjusted doses 12.5, 15 and 25 mg once daily, in combination with an investigator-selected BR containing two NRTIs, was evaluated in trial TMC278-C213 Cohort 2, a single-arm, open-label phase 2 trial in antiretroviral treatment-naïve HIV-1 infected paediatric subjects 6 to less than 12 years of age and weighing at least 17 kg. The week 48 analysis included 18 subjects, 17 (94.4%) subjects completed the 48-week treatment period, and 1 (5.6%) subject discontinued the study early due to reaching a virologic endpoint. The 18 subjects had a median age of 9.0 years (range 6 to 11 years) and the median weight at baseline was 25 kg (range 17 to 51 kg). 88.9 % were Black and 38.9% were female. The median baseline plasma viral load was 55 400 (range 567-149 000) copies/ml, and the median absolute baseline $CD4^+$ cell count was 432.5 × 10^6 cells/l (range 12-2 068 × 10^6 cells/l).

The number of subjects with HIV-1 RNA <50 copies/ ml at week 48 was 13/18 (72.2%), while 3/18 (16.7%) subjects had HIV-1 RNA≥50 copies/ml at week 48. Two subjects had missing viral load data at week 48 but remained on study. The viral load for these 2 subjects was <50 copies/ml, post-week 48. The median increase in CD4+ from baseline was 220 × 10^6 cells/l (range -520 to 635 x 10^6 cells/l) at week 48.

Virologically suppressed paediatric subjects 2 to less than 12 years of age

The pharmacokinetics, safety, tolerability and efficacy of rilpivirine weight-adjusted doses 12.5, 15 and 25 mg, in combination with an investigator-selected BR, was evaluated in TMC278HTX2002, a single-arm, open-label phase 2 trial in virologically suppressed HIV-1 infected paediatric subjects 2 to less than 12 years of age and weighing at least 10 kg. All participants completed the 48-week treatment.

The 26 subjects had a median age of 9.9 years, 61.5% male, 50% Black, 26.9% Asian and 23.1% White. The median weight at baseline was 28.1 kg (range 16 to 60 kg). Baseline plasma HIV-1 viral load was undetectable (<50 copies/ml) in 25 (96.2%) subjects and 1 (3.8%) subject had a baseline plasma viral load ≥50 copies/ml (125 copies/ml).The median absolute baseline CD4+ cell count was 881.5 × 10^6 cells/l (range 458 to 1327 × 10^6 cells/l).

All 26 subjects treated with rilpivirine (in combination with BR) were virologically suppressed (plasma viral load <50 copies/ml) at week 48. The median change in CD4+ cell count from baseline was - 27.5 × 10^6 cells/l (range -275 to 279× 10^6 cells/l) at week 48.

Pregnancy

Rilpivirine in combination with a background regimen was evaluated in a clinical trial of 19 pregnant women during the second and third trimesters, and postpartum. The pharmacokinetic data demonstrate that total exposure (AUC) to rilpivirine as a part of an antiretroviral regimen was approximately 30% lower during pregnancy compared with postpartum (6-12 weeks). The virologic response was generally preserved throughout the study: of the 12 subjects that completed the study, 10 subjects were

suppressed at the end of the study; in the other 2 subjects an increase in viral load was observed only postpartum, for at least 1 subject due to suspected suboptimal adherence. No mother to child transmission occurred in all 10 infants born to the mothers who completed the trial and for whom the HIV status was available. Rilpivirine was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of rilpivirine in HIV-1 infected adults (see sections 4.2, 4.4 and 5.2).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy subjects and in antiretroviral treatment-naïve and in virologically suppressed HIV-1 infected patients ≥6 years of age and weighing ≥ 16kg. Exposure to rilpivirine was generally lower in HIV-1 infected patients than in healthy subjects.

Absorption

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4-5 hours. The absolute bioavailability of EDURANT is unknown.

Effect of food on absorption

The exposure to rilpivirine was approximately 40% lower when EDURANT was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high-fat high-caloric meal (928 kcal). When EDURANT was taken with only a protein-rich nutritional drink, exposures were 50% lower than when taken with a meal. EDURANT **must be taken with a meal** to obtain optimal absorption. Taking EDURANT in fasted condition or with only a nutritional drink may result in decreased plasma concentrations of rilpivirine, which could potentially reduce the therapeutic effect of EDURANT (see section 4.2).

Distribution

Rilpivirine is approximately 99.7% bound to plasma proteins *in vitro*, primarily to albumin. The distribution of rilpivirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Biotransformation

In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system.

Elimination

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

Additional information on special populations

Paediatric population

The pharmacokinetics of rilpivirine in antiretroviral treatment-naïve or virologically suppressed HIV-1 infected paediatric patients aged 6 years to less than 18 years of age weighing at least 16 kg receiving the recommended weight-based dosing regimen of rilpivirine were comparable or higher (i.e., AUC is 39% higher, based on pharmacokinetic modeling) than. those obtained in treatment-naïve HIV-1 infected adult patients.

The pharmacokinetics of rilpivirine in paediatric patients less than 6 years of age or weighing less than 16 kg have not been evaluated in patients.

Older people

Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine pharmacokinetics are not different across the age range (18 to 78 years) evaluated, with only 3 subjects aged 65 years or older. No dose adjustment of EDURANT is required in older patients. EDURANT should be used with caution in this population (see section 4.2).

Gender

No clinically relevant differences in the pharmacokinetics of rilpivirine have been observed between men and women.

Race

Population pharmacokinetic analysis of rilpivirine in HIV infected patients indicated that race had no clinically relevant effect on the exposure to rilpivirine.

Hepatic impairment

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

No dose adjustment is suggested but caution is advised in patients with moderate hepatic impairment. EDURANT has not been studied in patients with severe hepatic impairment (Child-Pugh score C). Therefore, EDURANT is not recommended in patients with severe hepatic impairment (see section 4.2).

Hepatitis B and/or hepatitis C virus co-infection

Population pharmacokinetic analysis indicated that hepatitis B and/or C virus co-infection had no clinically relevant effect on the exposure to rilpivirine.

Renal impairment

The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. No dose adjustment is needed for patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, EDURANT should be used with caution, as plasma concentrations may be increased due to alteration of drug absorption, distribution and/or metabolism secondary to renal dysfunction. In patients with severe renal impairment or end-stage renal disease, the combination of EDURANT with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (see section 4.2).

Pregnancy and Postpartum

The exposure to total rilpivirine after intake of rilpivirine 25 mg once daily as part of an antiretroviral regimen was lower during pregnancy (similar for the 2nd and 3rd trimester) compared with postpartum (see Table 7). The decrease in unbound (ie, active) rilpivirine pharmacokinetic parameters during pregnancy compared to postpartum was less pronounced than for total rilpivirine.

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

Table 7: Pharmacokinetic Results of Total Rilpivirine After Administration of Rilpivirine 25 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

Pharmacokinetics of total rilpivirine (mean ± SD, t_{max}: median [range])	**Postpartum (6-12 Weeks) (n=11)**	**2nd Trimester of pregnancy (n=15)**	**3rd Trimester of pregnancy (n=13)**
C_{min}, ng/ml	84.0 ± 58.8	54.3 ± 25.8	52.9 ± 24.4
C_{max}, ng/ml	167 ± 101	121 ± 45.9	123 ± 47.5
t_{max}, h	4.00 (2.03-25.08)	4.00 (1.00-9.00)	4.00 (2.00-24.93)
AUC_{24h}, ng.h/ml	2714 ± 1535	1792 ± 711	1762 ± 662

5.3 Preclinical safety data

Repeated dose toxicity

Liver toxicity associated with liver enzyme induction was observed in rodents. In dogs, cholestasis-like effects were noted.

Reproductive toxicology studies

Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function. There was no teratogenicity with rilpivirine in rats and rabbits. The exposures (based on AUC) at the embryo-foetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans (minimum 12 years of age and weighing more than 32 kg) at the recommended dose of 25 mg once daily.

Carcinogenesis and mutagenesis

Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were greater than 12-fold (mice) and greater than 1.4-fold (rats), relative to the expected exposure in humans at a dose of 25 mg once daily. In rats, there were no drug-related neoplasms. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific.

Rilpivirine has tested negative in the absence and presence of a metabolic activation system in the *in vitro* Ames reverse mutation assay and the *in vitro* clastogenicity mouse lymphoma assay. Rilpivirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Croscarmellose sodium (E-468)

Povidone K30 (E-1201)

Polysorbate 20

Silicified microcrystalline cellulose (E-460)

Magnesium stearate (E-470b)

Tablet coating

Lactose monohydrate

Hypromellose 2910 6 mPa.s (E-464)

Titanium dioxide (E171)

Macrogol 3000

Triacetin (E-1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original bottle in order to protect from light. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

75 ml high density polyethylene (HDPE) bottle with a polypropylene (PP) child resistant closure and induction seal liner. Each carton contains one bottle of 30 tablets.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Janssen-Cilag Limited
50-100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00242/0678

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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