SCHEDULING STATUS **POM** **Rx Only**

BOTSWANA SCHEDULE: S2

NAMIBIA SCHEDULE: NS2

ZIMBABWE SCHEDULE: PP

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.
Excipients 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
White to off-white, film-coated, round, biconvex tablet, debossed with "TMC" on one side and "25" on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Adult Patients
EDURANT, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients.

Pediatric Patients (12 to 17 years of age)
EDURANT, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve pediatric patients 12 to less than 18 years of age with a viral load of ≤100000 HIV-1 RNA copies/mL.

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

4.2 Posology and method of administration
EDURANT must always be given in combination with other antiretroviral medicinal products.

Posology
Adults and Pediatric patients (12 to 17 years of age)
The recommended dose of EDURANT is one 25 mg tablet once daily taken orally with a meal (see sections 5.1 and 5.2).

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

Missed dose(s)
If the patient misses a dose of EDURANT within 12 hours of the time it is usually taken, the patient should take EDURANT with a meal as soon as possible and then take the next dose of EDURANT at the regularly scheduled time. 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.

Method of administration
EDURANT must be taken orally, once daily **with a meal** (see section 5.2).

Special populations

Pediatrics (12 to 17 years)

The recommended dose of EDURANT is one 25 mg tablet once daily taken orally with a meal (see *Pharmacokinetic properties*).

Pregnancy and Postpartum

The recommended dose of EDURANT in pregnant patients is one 25 mg tablet once daily taken orally with a meal. Lower exposures of rilpivirine were observed during pregnancy, therefore viral load should be monitored closely (see sections 4.6 and 5.2 - Additional information on special populations - Pregnancy and Postpartum).

Elderly (65 years of age and older)

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

Pediatric Population (less than 12 years of age)

The safety and efficacy of EDURANT in children less than 12 years have not been established (see section 5.2). Treatment with EDURANT is not recommended in children less than 12 years of age.

Hepatic impairment

No dose adjustment of EDURANT is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). EDURANT has not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see section 5.2).

Renal impairment

No dose adjustment of EDURANT is required in patients with renal impairment (see section 5.2).

4.3 Contraindications

Hypersensitivity to rilpivirine 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 glucocorticoid systemic dexamethasone, except as a single dose treatment
- St John's wort (*Hypericum perforatum*).

4.4 Special warnings and precautions for use

Transmission of HIV

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood or sexual contact. Appropriate precautions to prevent the transmission of HIV should continue to be employed.

Virologic failure and development of resistance

In the pooled analysis from the Phase III trials in adults through 96 weeks, patients treated with EDURANT with a baseline viral load >100000 HIV-1 RNA copies/ml had a greater risk of virologic failure compared to patients with a baseline viral load ≤100000 HIV-1 RNA copies/ml. The greater risk of virologic failure for patients in the EDURANT arm was observed in the first 48 weeks of these trials while low rates of virologic failure, similar between the treatment arms, were observed from week 48 to week 96 (see section 5.1). Patients with a baseline viral load >100000 HIV-1 RNA copies/ml who experienced virologic failure exhibited a higher rate of treatment emergent resistance to the NNRTI class. More patients who failed virologically on EDURANT than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance (see section 5.1).
No new information was identified in pediatric patients 12 to less 17 years in trial TMC278-C213.
This information should be taken into consideration when initiating therapy with EDURANT.

Interactions with medicinal products
Caution should be given to prescribing EDURANT with medicinal products that may reduce the exposure of rilpivirine.
For information on interactions with medicinal products (see section 4.5).

Immune reconstitution inflammatory syndrome
Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including EDURANT. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders such as Graves' disease and autoimmune hepatitis have also been reported to occur in the setting of immune reconstitution inflammatory syndrome; however, the time to onset is more variable, and these events can occur many months after initiation of treatment (see section 4.8).

Important information about some of the ingredients of EDURANT
EDURANT contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp 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, and medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine (see section 5.2). Co-administration of EDURANT and medicinal products that induce CYP3A may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of EDURANT. Co-administration of EDURANT and medicinal products that inhibit CYP3A may result in increased plasma concentrations of rilpivirine.
Co-administration of EDURANT 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
EDURANT at a dose of 25 mg daily (q.d.) is not likely to have a clinically relevant effect on the exposure of medicinal products metabolised by CYP enzymes.

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed below in Table 1 and Table 2, respectively.

Interaction table
Interactions between rilpivirine and co-administered medicinal products are listed in the tables 1 and 2 below (increase is indicated as "↑", decrease as "↓", no change as "↔", not applicable as "NA", once daily as "daily (q.d.)" and twice daily as "b.i.d.").

Table 1: Drug interactions – Rilpivirine co-administered with antiretroviral and antiviral medicinal products

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
HIV NUCLEOSIDE OR NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs/N[t]RTIs)					
Didanosine*#	400 mg daily (q.d.)	didanosine	↔	↑ 12 %	NA
		rilpivirine	↔	↔	↔
	No dose adjustment is required when EDURANT is co-administered with didanosine. Didanosine should be administered on an empty stomach and at least two hours before or at least four hours after EDURANT (which should be administered with a meal).				
Tenofovir disoproxil fumarate*#	300 mg daily (q.d.)	tenofovir	↑19 %	↑23 %	↑ 24 %
		rilpivirine	↔	↔	↔
	No dose adjustment is required when EDURANT is co-administered with tenofovir disoproxil fumarate.				

Other NRTIs (abacavir, emtricitabine, lamivudine, stavudine and zidovudine)	Based on the different elimination routes for rilpivirine and these other NRTIs, no clinically relevant drug-drug interactions are expected between these medicinal products and EDURANT.				
HIV NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)					
NNRTIs (delavirdine, efavirenz, etravirine, nevirapine)	It is not recommended to co-administer EDURANT with NNRTIs.				
HIV PROTEASE INHIBITORS (PIs) - with co-administration of low dose ritonavir					
Darunavir/ritonavir*#	800/100 mg daily (q.d.)	darunavir	↔	↔	↓ 11 %
		rilpivirine	↑ 79 %	↑ 130 %	↑ 178 %
	Concomitant use of EDURANT with darunavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when EDURANT is co-administered with darunavir/ritonavir.				
Lopinavir/ritonavir (soft gel capsules)*#	400/100 mg b.i.d.	lopinavir	↔	↔	↓ 11 %
		rilpivirine	↑29 %	↑ 52 %	↑74 %
	Concomitant use of EDURANT with lopinavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when EDURANT is co-administered with lopinavir/ritonavir.				
Other boosted PIs (atazanavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir, tipranavir/ritonavir)	Concomitant use of EDURANT with boosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). EDURANT is not expected to affect the plasma concentrations of co-administered PIs.				
HIV PROTEASE INHIBITORS (PIs) - without co-administration of low dose ritonavir					
Unboosted PIs (atazanavir, fosamprenavir, indinavir, nelfinavir)	Concomitant use of EDURANT with unboosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). EDURANT is not expected to affect the plasma concentrations of co-administered PIs.				
CCR5 ANTAGONISTS					
Maraviroc	No clinically relevant drug-drug interaction is expected when EDURANT is co-administered with maraviroc.				
HIV INTEGRASE STRAND TRANSFER INHIBITORS					
Raltegravir*	400 mg b.i.d.	raltegravir	↑ 10 %	↑ 9 %	↑ 27 %
		rilpivirine	↔	↔	↔
	No dose adjustment is required when EDURANT is co-administered with raltegravir.				
OTHER ANTIVIRAL AGENTS					
Ribavirin	No clinically relevant drug-drug interaction is expected when EDURANT is co-administered with ribavirin.				
Simeprevir*	150 mg once daily	simeprevir	↑ 10%	↔	↔
		rilpivirine	↔	↔	↑ 25%
	No dose adjustment is required for either drug when EDURANT is co-administered with simeprevir.				

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

\# This interaction study has been performed with a dose higher than the recommended dose for EDURANT assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of EDURANT 25 mg daily (q.d.)

Table 2: Drug interactions – Rilpivirine co-administered with non-antiretroviral medicinal products

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
ANTIARRHYTHMICS					
Digoxin*	0.5 mg single dose	digoxin	↔	↔	NA
	No dose adjustment is required when EDURANT is co-administered with digoxin.				

ANTIDIABETICS					
Metformin*	850 mg single dose	metformin	↔	↔	NA
	No dose adjustment is required when EDURANT is co-administered with metformin.				
ANTICONVULSANTS					
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	EDURANT should not be used in combination with these anticonvulsants as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT.				
AZOLE ANTIFUNGAL AGENTS					
Ketoconazole*#	400 mg daily (q.d.)	ketoconazole	↔	↓ 24 %	↓ 66 %
		rilpivirine	↑ 30 %	↑49 %	↑ 76 %
Fluconazole Itraconazole Posaconazole Voriconazole	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 when EDURANT is co-administered with azole antifungal agents.				
ANTIMYCOBACTERIALS					
Rifabutin*	300 mg q.d.†	rifabutin	↔	↔	↔
		25-*O*-desacetyl-rifabutin	↔	↔	↔
	300 mg q.d.	rilpivirine (25 mg q.d.)	↓ 31 %	↓ 42 %	↓ 48 %
	300 mg q.d.	rilpivirine (50 mg q.d.)	↑ 43 %	↑ 16 %	↔
			(as compared to 25 mg q.d. rilpivirine alone)		
	Concomitant use of EDURANT with rifabutin may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT. Throughout co-administration of EDURANT with rifabutin, the EDURANT dose should be increased from 25 mg once daily to 50 mg once daily. When rifabutin co-administration is stopped, the EDURANT dose should be decreased to 25 mg once daily.				
Rifampicin*#	600 mg daily (q.d.)	rifampicin	↔	↔	NA
		25-desacetyl-rifampicin	↔	↓ 9 %	NA
		rilpivirine	↓ 69 %	↓ 80 %	↓ 89 %
Rifapentine	EDURANT should not be used in combination with rifampicin or rifapentine as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT.				
MACROLIDE ANTIBIOTICS					
Clarithromycin Erythromycin	Concomitant use of EDURANT with clarithromycin or erythromycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.				
GLUCOCORTICOIDS					
Dexamethasone (systemic)	EDURANT should not be used in combination with systemic dexamethasone as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT. Alternatives should be considered, particularly for long-term use.				
PROTON PUMP INHIBITORS					
Omeprazole*#	20 mg daily (q.d.)	omeprazole	↓ 14 %	↓14 %	NA
		rilpivirine	↓ 40 %	↓40 %	↓ 33 %
Lansoprazole Rabeprazole Pantoprazole Esomeprazole	EDURANT should not be used in combination with proton pump inhibitors as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). This may result in loss of therapeutic effect of EDURANT.				
H_2-RECEPTOR ANTAGONISTS					
Famotidine*#	40 mg single dose taken 12 hours before rilpivirine	rilpivirine	↔	↓9 %	NA

	40 mg single dose taken two hours before rilpivirine	rilpivirine	↓ 85 %	↓ 76 %	NA
	40 mg single dose taken four hours after rilpivirine	rilpivirine	↑ 21 %	↑ 13 %	NA
Cimetidine Nizatidine Ranitidine	The combination of EDURANT and H_2-receptor antagonists should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). H_2-receptor antagonists should only be administered at least 12 hours before or at least four hours after EDURANT.				
ANTACIDS					
Antacids (e.g., aluminium or magnesium hydroxide, calcium carbonate)	The combination of EDURANT and antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). Antacids should only be administered either at least two hours before or at least four hours after EDURANT.				
NARCOTIC ANALGESICS					
Methadone*	60-100 mg daily (q.d.), individualised dose	R(-) methadone	↓ 14 %	↓ 16 %	↓ 22 %
		S(+) methadone	↓ 13 %	↓ 16 %	↓ 21 %
	No dose adjustments are required when initiating co-administration of methadone with EDURANT. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.				
HERBAL PRODUCTS					
St John's wort (*Hypericum perforatum*)	EDURANT should not be used in combination with products containing St John's wort (*Hypericum perforatum*) as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT.				
ANALGESICS					
Acetaminophen*# (paracetamol)	500 mg single dose	acetaminophen	↔	↔	NA
		rilpivirine	↔	↔	↑ 26 %
	No dose adjustment is required when EDURANT is co-administered with acetaminophen (paracetamol).				
ESTROGEN-BASED CONTRACEPTIVES					
Ethinylestradiol* Norethindrone*	0.035 mg daily (q.d.)	ethinylestradiol	↑ 17 %	↔	↔
	1 mg daily (q.d.)	norethindrone	↔	↔	↔
	No dose adjustment is required for the concomitant use of EDURANT and estrogen- and/or progesterone-based contraceptives.				
HMG CO-A REDUCTASE INHIBITORS					
Atorvastatin*#	40 mg daily (q.d.)	atorvastatin	↑ 35 %	↔	↓15 %
		rilpivirine	↓ 9 %	↔	↔
Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	No dose adjustment is required when EDURANT is co-administered with an HMG Co-A reductase inhibitor.				
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITOR					
Sildenafil*#	50 mg single dose	sildenafil	↔	↔	NA
		rilpivirine	↔	↔	↔
Vardenafil Tadalafil	No dose adjustment is required when EDURANT is co-administered with a PDE-5 inhibitor.				

*	The interaction between EDURANT and the drug 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 EDURANT assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of EDURANT 25 mg daily (q.d.)
†	This interaction study has been performed with a dose higher than the recommended dose for EDURANT.

QT prolonging drugs
There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicinal products that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg daily (q.d.) and 300 mg daily (q.d.)) have been shown to prolong the QTc interval of the electrocardiogram (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

Fertility
No human data on the effect of rilpivirine on fertility are available. In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg/kg/day, a dose of rilpivirine that showed maternal toxicity (see section 5.3). This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg daily (q.d.)

Pregnancy
There are no well controlled clinical or pharmacokinetic studies with EDURANT in pregnant women. Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function (see section 5.3). There was no teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg daily (q.d.) (see section 5.3).

To monitor maternal-fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry has been established (http://www.apregistry.com). This is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products. For rilpivirine, sufficient first trimester exposures are available to allow detection of at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

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). Virologic response was preserved throughout the trial period. 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 section 5.2 - Additional Information on Special Populations - Pregnancy and Postpartum).

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

Contraception in males and females
A trial to investigate the effect of EDURANT when co-administered with oral contraceptives demonstrated that EDURANT is unlikely to decrease the effectiveness of oral contraceptives. EDURANT and estrogen- and/or progesterone-based contraceptives can be used together without dose adjustments (see section 4.5).

Breast-feeding
It is not known whether rilpivirine is secreted in human milk. Because of both the potential for HIV transmission and the potential for adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving EDURANT.

4.7 Effects on ability to drive and use machines

EDURANT has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions from clinical trials

Throughout this section, adverse reactions are reported. Adverse reactions (AR's) are adverse events that were considered to be reasonably associated with the use of EDURANT based on the comprehensive assessment of the available adverse event information. A causal relationship with EDURANT cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse reactions from clinical trials in adult patients

The safety assessment is based on the week 96 pooled data from 1368 patients in the Phase III controlled trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) in antiretroviral treatment-naïve HIV-1 infected adult patients, 686 of whom received EDURANT (25 mg q.d.) (see section 5.1). The median duration of exposure for patients in the EDURANT and efavirenz arms was 104.3 and 104.1 weeks, respectively. Most ADRs occurred in the first 48 weeks of treatment.

In the Phase III controlled trials ECHO and THRIVE through 96 weeks, the most frequently reported adverse reactions (ARs) (>2 %) to EDURANT that were at least grade 2 in severity were depression, headache, insomnia, transaminases increased and rash (see Table 3 for the complete list of ARs).

The majority of the ARs reported during treatment with EDURANT 25 mg once daily were grade 1 to 2 in severity. Grade 3 or 4 ARs were reported in 3.6 % and 5.9 % of the EDURANT and efavirenz treated patients, respectively. The most common (reported in more than 1 patient in the EDURANT arm) reported grade 3 or 4 ARs were transaminases increased (1.6 % in the EDURANT arm and 2.9 % in the efavirenz arm), depression (0.7 % and 0.7 %, respectively), abdominal pain (0.4 % and 0.1 %, respectively), dizziness (0.3 % and 0.4 %, respectively) and rash (0.3 % and 0.6 %, respectively). 1.7 % of patients in the EDURANT arm discontinued treatment due to ARs compared to 4.0 % of patients in the efavirenz arm. In the EDURANT arm, all ARs leading to discontinuation had an incidence <0.5 %. In the efavirenz arm, the most common ARs leading to discontinuation were rash (1.5 %), transaminases increased (0.7 %), depression (0.6 %) and abnormal dreams (0.6 %).

ARs of at least moderate intensity (≥grade 2) reported in adult patients treated with EDURANT are summarised in Table 3. The ARs are listed by system organ class (SOC) and frequency.

Table 3: ARs of at least moderate intensity (≥ grade 2) reported in antiretroviral treatment-naïve HIV-1 infected adult patients treated with EDURANT

	Pooled data from the week 96 analysis of the Phase III ECHO and THRIVE trials		
System Organ Class (SOC) Adverse reaction, %	**EDURANT + BR N=686**	**Efavirenz + BR N=682**	**Treatment Difference (95 %CI)**
Metabolism and nutrition disorders			
Decreased appetite	1.2 %	0.6 %	0.6 (-0.4; 1.6)
Psychiatric disorders			
Depression	4.1 %	3.2 %	0.9 (-1.1; 2.8)
Insomnia	3.5 %	3.5 %	0 (-2.0; 1.9)
Abnormal dreams*†	1.6 %	4.0 %	-2.4 (-4.1; -0.6)
Sleep disorders	1.3 %	0.9 %	0.4 (-0.7; 1.5)
Depressed mood	0.4 %	0.3 %	0.1 (-0.5; 0.8)
Nervous system disorders			
Headache*	3.5 %	3.8 %	-0.3 (-2.3; 1.7)
Dizziness*#	1.0 %	6.7 %	-5.7 (-7.7; -3.7)
Somnolence	0.7 %	1.3 %	-0.6 (-1.7; 0.5)
Gastrointestinal disorders			
Abdominal pain	2.0 %	1.9 %	0.1 (-1.3; 1.6)
Nausea*	1.3 %	2.8 %	-1.5 (-3.0; 0)
Vomiting	1.0 %	2.1 %	-1.0 (-2.3; 0.3)
Abdominal discomfort	0.4 %	0.1 %	0.3 (-0.3; 0.9)
Skin and subcutaneous tissue disorders			
Rash*#	2.3 %	9.5 %	-7.2 (-9.7; -4.7)
General disorders and administration site conditions			
Fatigue	1.6 %	2.1 %	-0.4 (-1.9; 1.0)
Investigations			

Transaminases increased	2.8 %	4.0 %	-1.2 (-3.1; 0.7)

BR=background regimen; CI=confidence interval
N=total number of subjects per treatment group
* Treatment comparison was pre-specified for these ADRs (Fisher's Exact Test)
† p-value <0.01
# p-value <0.0001

No new AR terms were identified in adult patients in the Phase III ECHO and THRIVE trials between 48 weeks and 96 weeks nor in the Phase IIb TMC278-C204 trial through 240 weeks.

Laboratory abnormalities
Selected treatment emergent clinical laboratory abnormalities (grade 3 or grade 4), reported in EDURANT-treated patients, are shown in table 4.

Table 4: Selected treatment emergent laboratory abnormalities (grade 3 or grade 4) observed in antiretroviral treatment-naïve HIV-1 infected adult patients

Laboratory parameter abnormality, %	DAIDS toxicity range	Pooled data from the week 96 analysis of the Phase III ECHO and THRIVE trials	
		EDURANT + BR N=686	Efavirenz + BR N=682
HEMATOLOGY			
Decreased hemoglobin	<4.5 mmol/l <7.4 g/dl	0.1 %	0.6 %
Decreased platelet count	<49999/mm^3 <49999 x 10^9/l	0.1 %	0.3 %
Decreased white blood cell count	<1499/mm^3 <1.499 giga/l	1.2 %	1.0 %
BIOCHEMISTRY			
Increased creatinine	>1.8 x ULN	0.1 %	0.1 %
Increased AST	>5.0 x ULN	2.3 %	3.3 %
Increased ALT	>5.0 x ULN	1.6 %	3.7 %
Increased bilirubin	>2.5 x ULN	0.7 %	0.3 %
Increased pancreatic amylase	>2 x ULN	3.8 %	4.8 %
Increased lipase	>3 x ULN	0.9 %	1.6 %
Increased total cholesterol (fasted)*	>7.77 mmol/l >300 mg/dl	0.1 %	3.3 %
Increased LDL cholesterol (fasted)*	≥4.91 mmol/l ≥191 mg/dl	1.5 %	5.3 %
Increased triglycerides (fasted)*	≥8.49 mmol/l ≥751 mg/dl	0.6 %	3.3 %

BR=background regimen; ULN=upper limit of normal
N=number of subjects per treatment group
* p≤0.001 according to Fisher's Exact test (difference in grade 3 plus 4 abnormalities between the two treatment groups).
Note: Percentages were calculated for the number of subjects with results for the analyte.

Changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides are presented in table 5. The mean changes from baseline were smaller in the EDURANT arm versus the efavirenz arm. The impact of such findings has not been demonstrated.

Table 5: Lipid values, mean change from baseline

	Pooled data from the week 96 analysis of the Phase III ECHO and THRIVE Trials					
	EDURANT + BR N=686			Efavirenz + BR N=682		
	Baseline	Week 96		Baseline	Week 96	
Mean (95 % CI)	Mean (mg/dl)	Mean (mg/dl)	Mean change* (mg/dl)	Mean (mg/dl)	Mean (mg/dl)	Mean change* (mg/dl)
Total cholesterol (fasted)†	161	167	5	161	190	28
HDL-cholesterol	41	46	4	40	51	11

(fasted)†						
LDL-cholesterol (fasted)†	96	98	1	96	110	14
Triglycerides (fasted)†	124	117	-7	133	148	12

N=number of subjects per treatment group

* The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and week 96 values.

† p-value <0.001, Wilcoxon rank-sum test for treatment comparison of change from baseline

Adverse drug reactions from a clinical trial in pediatric patients (12 to 17 years)

The safety assessment is based on the Week 48 analysis of the single-arm, open-label Phase 2 trial, TMC278-C213, in which 36 antiretroviral treatment-naïve HIV-1 infected patients 12 17 years of age and weighing at least 32 kg received EDURANT (25 mg once daily) in combination with other antiretroviral medicinal products (see section 5.1, Clinical efficacy and safety). The median duration of exposure for patients was 63.5 weeks. There were no patients who discontinued treatment due to ARs. No new ARs were identified compared to those seen in adults.

Most ARs were Grade 1 or 2. The most common ARs (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.

Immune reconstitution inflammatory 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 (immune reconstitution inflammatory syndrome). Autoimmune disorders such as Graves' disease and autoimmune hepatitis have also been reported in the context of immune reconstitution inflammatory syndrome (see section 4.4).

Additional information on special populations

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

In patients co-infected with hepatitis B or C virus receiving EDURANT, the incidence of hepatic enzyme elevation was higher than in patients receiving EDURANT 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 to www.janssen.com.

4.9 Overdose

There is no specific antidote for overdose with EDURANT. Human experience of overdose with EDURANT is limited. Treatment of overdose with EDURANT 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. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose. 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:

A.20.2.8 Antiviral agents for systemic use, NNRTI (non-nucleoside reverse transcriptase inhibitor)

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 2510 to 10830 nM (920 to 3970 ng/ml), treatment of HIV-2 infection with EDURANT 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).

Rilpivirine showed additive antiviral activity in combination with the N(t)RTIs abacavir, didanosine, emtricitabine, stavudine and tenofovir; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; the NNRTIs efavirenz, etravirine and nevirapine; the fusion inhibitor enfuvirtide; and the entry inhibitor maraviroc. Rilpivirine shows additive to synergistic antiviral activity in combination with the NRTIs lamivudine and zidovudine, and the integrase inhibitor raltegravir.

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 amino acid substitutions 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 III trials, 62 (of a total of 72) virologic failures in the EDURANT arm had resistance data at baseline and time of failure. In this analysis the amino acid substitutions associated with NNRTI resistance that developed in at least two rilpivirine virologic failures were: V90I, K101E, E138K, E138Q, V179I, Y181C, V189I, H221Y, and F227C. The most common mutations were the same in the week 48 and week 96 analyses. In the trials, the presence of the substitutions 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 96 pooled resistance analysis, low rates of virologic failure, similar between the treatment arms, were observed from week 48 to week 96 (3.2 % in the EDURANT arm and 2.3 % in the efavirenz arm).

More patients who failed virologically on EDURANT than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance.

Considering all of the available *in vitro* and *in vivo* data, the following amino acid substitutions, when present at baseline, are likely to affect the activity of rilpivirine: K101E, K101P, E318A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, and M230L.

Cross-resistance
Site-directed NNRTI mutant virus
In a panel of 67 HIV-1 recombinant laboratory strains with one amino acid substitution 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 amino acid substitutions 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 andL100I resulted in a 7-fold reduced susceptibility to rilpivirine.

Recombinant clinical isolates
Rilpivirine retained sensitivity (FC≤BCO) against 62 % of 4786 HIV-1 recombinant clinical isolates resistant to efavirenz and/or nevirapine.

Treatment-naïve HIV-1 infected adult patients
In the week 48 pooled analysis of the Phase III trials ECHO and THRIVE, 31 of the 62 subjects with virologic failure on EDURANT with phenotypic resistance data lost susceptibility to rilpivirine. Of these, 28 were resistant to etravirine, 27 to efavirenz, and 14 to nevirapine. These cross-resistance findings were confirmed in the week 96 pooled analyses of the Phase III clinical trials.

In the week 96 pooled analyses, among virologic failures in the EDURANT arm with baseline viral load ≤100000 copies/ml and with resistance to rilpivirine, there were fewer patients with phenotypic cross-resistance than among those in the EDURANT arm with baseline viral load >100000 copies/ml. 3, 4 and 1 rilpivirine virologic failures with baseline viral load ≤100000 copies/ml and with resistance to rilpivirine (N=5) had cross-resistance to efavirenz, etravirine and nevirapine, respectively, compared to 27, 28, and 15 rilpivirine virologic failures with baseline viral load >100000 copies/ml (N=30), respectively.

Effects on QT/QTc interval and cardiac electrophysiology
The effect of EDURANT at the recommended dose of 25 mg daily (q.d.) 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 daily (q.d.) is not associated with a clinically relevant effect on QTc.

When supratherapeutic doses of 75 mg daily (q.d.) and 300 mg daily (q.d.) of EDURANT 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 EDURANT 75 mg daily (q.d.) and 300 mg daily (q.d.) 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 daily (q.d.) dose of EDURANT.

Clinical efficacy and safety
Treatment-naïve HIV-1 infected adult patients
The evidence of efficacy of EDURANT is based on the analyses of 96week data from two randomised, double-blinded, active-controlled, Phase III trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE). The trials were identical in design, with the exception of the background regimen (BR). At 96 weeks, the virologic response rate [confirmed undetectable viral load (<50 HIV-1 RNA copies/ml)] was evaluated in patients receiving EDURANT 25 mg daily (q.d.) in addition to a BR versus patients receiving efavirenz 600 mg daily (q.d.) in addition to a BR. Similar efficacy for EDURANT was seen in each trial demonstrating non-inferiority to efavirenz.

Antiretroviral treatment-naïve HIV-1 infected patients were enrolled who had a plasma HIV-1 RNA ≥5000 copies/ml and were screened for susceptibility to N(t)RTIs and for absence of specific NNRTI RAMs. In ECHO, the BR was fixed to the N(t)RTIs, tenofovir disoproxil fumarate plus emtricitabine. In THRIVE, the BR consisted of two 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 EDURANT arm and the efavirenz arm. Table 6 displays selected demographic and baseline disease characteristics of the patients in the EDURANT and efavirenz arms.

Table 6: Demographic and 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	
	EDURANT + BR N=686	**Efavirenz + BR N=682**
Demographic characteristics		
Median Age, years (range)	36 (18-78)	36 (19-69)
Sex		
Male	76 %	76 %
Female	24 %	24 %
Race		
White	61 %	60 %
Black/African American	24 %	23 %
Asian	11 %	14 %
Other	2 %	2 %
Not allowed to ask per local regulations	1 %	1 %
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 (1-1137)
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 7 below shows the efficacy results at 48 weeks and at 96 weeks for patients treated with EDURANT 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 EDURANT arm and the efavirenz arm. The incidence of virologic failure was higher in the EDURANT 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 EDURANT arm. Most of these discontinuations occurred in the first 48 weeks of treatment.

Table 7: Virologic Outcome of Randomised Treatment in the ECHO and THRIVE Trials in adults (Pooled Analysis at Week 48 (primary) and Week 96; ITT-TLOVR[*])				
	Outcome at Week 48		***Outcome at Week 96***	
%	**EDURANT + BR N=686**	**Efavirenz + BR N=682**	**EDURANT + BR N=686**	**Efavirenz + BR N=682**
Confirmed Undetectable Viral Load (<50 HIV-1 RNA copies/ml) [§#]	84.3	82.3	77.6	77.6
Virologic Failure[†]	9.0	4.8	11.5	5.9
Death	0.1	0.4	0.1	0.9
Discontinued due to adverse event (AE)	2.0	6.7	3.8	7.6
Discontinued for non-AE reason[¶]	4.5	5.7	7.0	8.1

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 48/96.

Predicted difference of response rates (95 % CI) at week 48: 1.6 % (-2.2 %; 5.3 %) and at week 96: 0 % (-4.6 %; 3.8 %); both p-values <0.0001 (non-inferiority at 12 % margin) from logistic regression model, including stratification factors and study.

† 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 x 10^6 cells/l in the EDURANT arm and +219 x 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)].

A subgroup analysis of the virologic response (<50 HIV-1 RNA copies/ml) at 48 and 96weeks and virologic failure by baseline viral load, CD4 count and by background NRTIs (pooled data from the ECHO and THRIVE trials) is presented in Table 8.

Table 8: Virologic response (<50 HIV-1 RNA copies/ml, ITT-TLOVR) and virologic failure by baseline viral load and by background NRTIs (Pooled analysis at Week 48 [primary] and Week 96 from the ECHO and THRIVE trials in adults)

	Outcome at Week 48				***Outcome at Week 96***			
	EDURANT + BR N=686		**Efavirenz + BR N=682**		**EDURANT + BR N=686**		**Efavirenz + BR N=682**	
	N	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Proportion of patients with HIV-1 RNA <50 copies/ml at week 48* and at week 96*by baseline plasma viral load (copies/ml)								
≤100000	368	332 (90.2 %)	330	276 (83.6 %)	368	309 (84.0 %)	329	263 (79.9 %)
>100000	318	246 (77.4 %)	352	285 (81.0 %)	318	223 (70.1 %)	353	266 (75.4 %)
>100000 to ≤500000	249	198 (79.5 %)	270	223 (82.6 %)	249	178 (71.5 %)	270	205 (75.9 %)
>500000	69	48 (69.6 %)	82	62 (75.6 %)	69	45 (65.2 %)	83	61 (73.5 %)
Virologic Failure† by baseline plasma viral load (copies/ml)								
≤100000	368	14 (3.8 %)	330	11 (3.3 %)	368	21 (5.7 %)	329	12 (3.6 %)
>100000	318	48 (15.1 %)	352	22 (6.3 %)	318	58 (18.2 %)	353	28 (7.9 %)
>100000 to ≤500000	249	33 (13.3 %)	270	13 (4.8 %)	249	43 (17.3 %)	270	18 (6.7 %)
>500000	69	15 (21.7 %)	82	9 (11.0 %)	69	15 (21.7 %)	83	10 (12.0 %)
Proportion of patients with HIV-1 RNA <50 copies/ml at week 48* and at week 96* by baseline CD4 count (x 10^6 cells/l)								
<50	34	20 (58.8 %)	36	29 (80.6 %)	34	19 (55.9 %)	36	25 (69.4 %)
≥50-<200	194	156 (80.4 %)	175	143 (81.7 %)	194	138 (71.1 %)	175	131 (74.9 %)
≥200-<350	313	272 (86.9 %)	307	253 (82.4 %)	313	252 (80.5 %)	307	244 (79.5 %)
≥350	144	130 (90.3 %)	164	136 (82.9 %)	144	123 (85.4 %)	164	129 (78.7 %)
Virologic Failure† by baseline CD4 count (x 10^6 cells/l)								
<50	34	6 (17.6 %)	36	1 (2.8 %)	34	6 (17.6 %)	36	4 (11.1 %)
≥50-<200	194	27 (13.9 %)	175	14 (8.0 %)	194	37 (19.1 %)	175	14 (8.0 %)

≥200-<350	313	21 (6.7 %)	307	14 (4.6 %)	313	26 (8.3 %)	307	15 (4.9 %)
≥350	144	8 (5.6 %)	164	4 (2.4 %)	144	10 (6.9 %)	164	7 (4.3 %)
Proportion of patients with HIV-1 RNA <50 copies/ml at week 48* and at week 96* by background N(t)RTI								
tenofovir disoproxil fumarate plus emtricitabine	550	459 (83.5 %)	546	450 (82.4 %)	550	423 (76.9 %)	546	422 (77.3 %)
zidovudine plus lamivudine	101	88 (87.1 %)	103	83 (80.6 %)	101	82 (81.2 %)	103	79 (76.7 %)
abacavir plus lamivudine	35	31 (88.6 %)	33	28 (84.8 %)	35	27 (77.1 %)	33	28 (84.8 %)

N=number of subjects per treatment group
n=number of observations

* Imputations according to the TLOVR algorithm.

† 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).

Study TMC278-C204 was a randomised, active-controlled, Phase IIb trial in antiretroviral treatment-naïve HIV-1 infected adult patients consisting of two parts: an initial partially blinded dose-finding part [EDURANT 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 EDURANT were all treated with EDURANT 25 mg once daily in addition to a BR, once the dose for the Phase III 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 two investigator-selected N(t)RTIs: zidovudine plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine.

Study TMC278-C204 enrolled 368 HIV-1 infected treatment-naïve adult patients who had a plasma HIV-1 RNA ≥5000 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 RAMs.

At 96 weeks, the proportion of patients with <50 HIV-1 RNA copies/ml receiving EDURANT 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 x 10^6 cells/l in patients receiving EDURANT 25 mg and 160 x 10^6 cells/l in patients receiving efavirenz.

Of those patients who were responders at week 96, 74 % of patients receiving EDURANT 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.

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). Virologic response was preserved throughout the trial period. 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.

Treatment-naïve HIV-1 infected pediatric patients (12 years to 17 years)

The pharmacokinetics, safety, tolerability and efficacy of EDURANT 25 mg once daily, in combination with an investigator-selected BR containing two NRTIs, was evaluated in trial TMC278-C213, a single-arm, open-label Phase 2 trial in antiretroviral treatment-naive HIV-1 infected pediatric subjects 12 to 17 years of age and

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/ml, and the median baseline CD4+ cell count was 414 x 10^6 cells/l (range: 25 to 983 x 10^6 cells/l).

The proportion of subjects with HIV-1 RNA <50 copies/ml at Week 48 (TLOVR) was 72.2 % (26/36). The proportion of responders was higher in subjects with a baseline viral load ≤100000 copies/ml (78.6 %, 22/28) as compared to those with a baseline viral load >100000 copies/ml (50.0 %, 4/8). The proportion of virological failures was 22.2 % (8/36). The proportion of virologic failures was lower in subjects with a baseline viral load ≤100000 copies/ml (17.9 %, 5/28) as compared to those with a baseline viral load >100000 copies/ml (37.5 %, 3/8). One subject discontinued due to an adverse event and 1 subject discontinued due to reasons other than an adverse event or virology failure. At Week 48, the mean increase in CD4+ cell count from baseline was 201.2 x 10^6 cells/l.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy subjects and in antiretroviral treatment-naïve HIV-1 infected patients 12 years of age and older. 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 four to five 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.

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

Pediatric population (12 to 17 years)

The pharmacokinetics of rilpivirine in antiretroviral treatment-naïve HIV-1 infected pediatric subjects 12 to 17 years of age receiving EDURANT 25 mg once daily were comparable to those in treatment- naïve HIV-1 infected adults receiving EDURANT 25 mg once daily. There was no impact of body weight on rilpivirine pharmacokinetics in pediatric subjects in trial TMC278-C213 (33 to 93 kg), similar to what was observed in adults.

Pediatrics (less than 12 years of age)

The pharmacokinetics of rilpivirine in pediatric patients less than 12 years of age have not been evaluated. Dosing recommendations for pediatric patients less than 12 years of age cannot be made due to insufficient data (see section 4.2).

Elderly (65 years of age and older)
Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine pharmacokinetics are not different across the age range (18 to 78 years) evaluated. No dose adjustment of EDURANT is required in elderly patients (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 eight patients with mild hepatic impairment (Child-Pugh score A) to eight matched controls, and eight patients with moderate hepatic impairment (Child-Pugh score B) to eight 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. No dose adjustment is required in patients with mild or moderate hepatic impairment. EDURANT has not been studied in patients with severe hepatic impairment (Child-Pugh score C) (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.

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 9). The decrease in unbound (i.e., 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 9: 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

Renal impairment
The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. Therefore, the impact of renal impairment on rilpivirine elimination is expected to be minimal. 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).

5.3 Preclinical safety data

General toxicology studies
Animal toxicology studies have been conducted with rilpivirine in mice, rats, rabbits, dogs and cynomolgus monkeys. The target organs and systems of toxicity were the adrenal cortex and the associated steroid biosynthesis (mouse, rat, dog, cynomolgus monkey), the reproductive organs (female mouse, male and female

dog), the liver (mouse, rat, dog), the thyroid and pituitary gland (rat), the kidney (mouse, dog), the hematopoietic system (mouse, rat, dog), and the coagulation system (rat).

Reproductive toxicology studies
In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg/kg/day, a dose of rilpivirine that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg daily (q.d.) 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 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 at the recommended dose of 25 mg daily (q.d.) In a pre- and post-natal development assessment in rats, rilpivirine had no effect on development of offspring during lactation or post-weaning when the mothers were dosed up to 400 mg/kg/day.

Carcinogenesis and mutagenesis
Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg/kg/day were administered to mice and doses of 40, 200, 500 and 1500 mg/kg/day were administered to rats. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in mice and rats. An increase in the incidences of follicular cell adenomas and/or carcinomas in the thyroid gland was observed in rats. Administration of rilpivirine did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in mice and rats are considered to be rodent-specific, associated with liver enzyme induction. A similar mechanism does not exist in humans; hence, these tumors are not relevant for humans. The follicular cell findings are considered to be rat-specific, associated with increased clearance of thyroxine and are not considered to be relevant for humans. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21-fold (mice) and 3-fold (rats), relative to those observed in humans at the recommended dose (25 mg daily (q.d.)).

Rilpivirine has tested negative in the *in vitro* Ames reverse mutation assay, *in vitro* chromosomal aberration assay in human lymphocyte and *in vitro* clastogenicity mouse lymphoma assay, tested in the absence and presence of a metabolic activation system. 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
Povidone K30
Polysorbate 20
Silicified microcrystalline cellulose
Magnesium stearate

Tablet coating
Lactose monohydrate
Hypromellose 2910 6 mPa.s
Titanium dioxide
Polyethylene glycol 3000
Triacetin

6.2 Incompatibilities
Not applicable.

6.3 Shelf-life
36 months

6.4 Special precautions for storage
Store below 30 °C in the original bottle in order to protect from light.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

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 International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium
Tel: +27 11 518 7000 (South Africa)
www.janssen.com

8. MARKETING AUTHORISATION NUMBERS

COUNTRY	NUMBER
Botswana	BOT 1703212
Ethiopia	4006/NMR/2017
Malawi	PMPB/PL437/1
Mozambique	
NAFDAC	B4-4149
Namibia	14/20.2.8/0025
Tanzania	TZ14H0270
Uganda	NDA/MAL/HDP/6257
Zambia	8942/14
Zimbabwe	2014/7.13/4960

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MANUFACTURED AND PACKED BY
Janssen-Cilag S.p.A
Via C.Janssen
Borgo S. Michele
04100 Latina
Italy

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