PROFESSIONAL INFORMATION INSERT

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

EDURANT 25 mg (film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of EDURANT contains 25 mg rilpivirine as rilpivirine hydrochloride.

Contains sugar: Each film-coated tablet contains 56,113 mg lactose monohydrate.

For a 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 medicines, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients.

Paediatric Patients (12 to less than 18 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 paediatric patients 12 to less than 18 years of age with a viral load of ≤ 100000 HIV-1 RNA copies/mL.

4.2 Posology and method of administration

EDURANT must always be given in combination with other antiretroviral medicinal products.

Adults and paediatric patients (12 to less than 18 years of age)

The recommended dose of EDURANT is 25 mg once-daily taken orally with a meal.

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.

Pregnancy and Postpartum

The recommended dose of EDURANT in pregnant patients is one 25 mg tablet once daily taken orally with a meal. Lower exposure of rilpivirine was observed during pregnancy, therefore viral load should be monitored closely.

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.

Special populations

Paediatrics (less than 12 years of age)

The safety and efficacy of EDURANT in children less than 12 years of age have not been proven. Treatment with EDURANT is not recommended for use in children less than 12 years of age.

Elderly (65 years of age and older)

No dose adjustment of EDURANT is required in elderly patients.

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).

Renal impairment

No dose adjustment of EDURANT is required in patients with renal impairment.

4.3 Contraindications

Hypersensitivity to rilpivirine or to any of the excipients of EDURANT.

It is not recommended that EDURANT be co-administered with other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) e.g. delavirdine, efavirenz, etravirine, nevirapine (see *section 4.5 INTERACTIONS*).

EDURANT should not be used in combination with carbamazepine, oxcarbazepine, phenobarbital, phenytoin and dexamethasone (except as a single-dose treatment) as co-administration may cause significant decreases in rilpivirine plasma concentrations due to the induction of CYP3A enzymes. This may result in loss of therapeutic effect of EDURANT.

Rifabutin, rifampicin and rifapentine are potent inducers of CYP3A enzymes. EDURANT should not be used in combination with these medicines as co-administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of EDURANT.

EDURANT should not be used concomitantly with products containing St. John's Wort (*Hypericum perforatum*) because co-administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of EDURANT.

The proton-pump inhibitors (PPIs) lanzoprazole, omeprazole, rabeprazole, pantoprazole and esomeprazole should not be administered concomitantly with EDURANT as this may result in significant decreases in rilpivirine plasma concentration due to gastric pH increase. This may result in loss of therapeutic effect of EDURANT.

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, other bodily secretion, 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 through 96 weeks, patients treated with EDURANT with a baseline viral load > 100 000 HIV-1 RNA copies/mL had a greater risk of virologic failure compared to patients with a baseline viral load ≤ 100 000 HIV-1 RNA copies mL.

The greater risk of virologic failure for patients in regimens containing EDURANT was observed in the first 48 weeks of these trials while a low rate of virologic failure was observed from week 48 to week 96.

Patients with a baseline viral load > 100 000 HIV-1 RNA copies/ mL who experienced virologic failure exhibited a higher rate of treatment-emergent resistance to the NNRTI class. Patients who failed virologically on EDURANT developed lamivudine/emtricitabine-associated resistance. This information should be taken into consideration when initiating therapy with EDURANT.

No new information was identified in paediatric patients 12 to less than 18 years.

Interaction with other medicines

Caution should be given to prescribing EDURANT with other medicines that may reduce

the exposure of rilpivirine (see *section 4.5 INTERACTIONS*).

Fat redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "Cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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 systems respond 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 UNDESIRABLE EFFECTS*).

Excipients

EDURANT contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia,

Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take EDURANT.

4.5 Interaction with other medicines and other forms of interaction

Medicines that affect rilpivirine exposure:

Rilpivirine is primarily metabolised by cytochrome P450 (CYP3A), and medicines that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Co-administration of EDURANT and medicines that induce CYP3A may result in decreased plasma concentrations of rilpivirine (exposure) which could potentially reduce the therapeutic effect of EDURANT. Co-administration of EDURANT and medicines that inhibit CYP3A may result in increased plasma concentrations of rilpivirine.

Co-administration of EDURANT with medicines that increase gastric pH such as PPI's, may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of EDURANT.

Medicines that are affected by the use of rilpivirine

EDURANT at a dose of 25 mg q.d. (once daily) is not likely to have a clinically relevant effect on the exposure of medicines metabolised by CYP enzymes.

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

Interaction table

Interactions between rilpivirine and co-administered medicines are listed in Table 1 and

Table 2 below (increase is indicated as "↑", decrease as "↓", no change as "↔", not applicable as "NA").

Table 1: Medicine interactions - Rilpivirine co-administered with antiretroviral and antiviral medicines					
Co-administered medicine	**Dose of co-administered medicine**	**Medicine assessed**	**C_{max}**	**AUC**	**C_{min}**
HIV NUCLEOSIDE OR NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs/N[t]RTIs)					
Didanosine*#	400 mg daily	didanosine	↔	↑ 12 %	NA
		rilpivirine	↔	↔	↔
	No dose-adjustment is required when EDURANT is co-administered with didanosine. As didanosine is administered on an empty stomach, didanosine should be administered at least one hour before or two hours after EDURANT (which should be administered with a meal).				
Tenofovir disoproxil fumarate*#	300 mg daily	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 interactions are expected between these medicines 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	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	400/100 mg twice daily	lopinavir	↔	↔	↓ 11 %
		rilpivirine	↑ 29 %	↑ 52 %	↑ 74 %

capsules)*#	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 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 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 medicine was evaluated in a clinical study. All other medicine 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 medicine. The dosing recommendation is applicable to the recommended dose of EDURANT 25 mg daily.

Table 2: Medicine interactions - Rilpivirine co-administered with non-antiretroviral medicines					
Co-administered medicine	**Dose of co-administered medicine**	**Medicine 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 (see CONTRAINDICATIONS).				
AZOLE ANTIFUNGAL AGENTS					
Ketoconazole*#	400 mg daily	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 daily±	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)		
	EDURANT should not be used in combination with rifabutin 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. 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	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 (see CONTRAINDICATIONS).				
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 (see CONTRAINDICATIONS).				
PROTON PUMP INHIBITORS					
Omeprazole*#	20 mg daily	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 (see CONTRAINDICATIONS).				
H_2-RECEPTOR ANTAGONISTS					
Famotidine*#	40 mg single dose taken 12 hours before rilpivirine	rilpivirine	↔	↓ 9 %	NA
	40 mg single dose taken 2 hours before rilpivirine	rilpivirine	↓ 85 %	↓ 76 %	NA
	40 mg single dose taken 4 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 4 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 2 hours before or at least 4 hours after EDURANT.				
NARCOTIC ANALGESICS					
Methadone*	60 mg to 100 mg daily, 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 (see CONTRAINDICATIONS).				
ANALGESICS					
Acetaminophen*# (paracetamol)	500 mg single dose	acetaminophen	↔	↔	NA
		rilpivirine	↔	↔	↑ 26 %

	No dose-adjustment is required when EDURANT is co-administered with acetaminophen (paracetamol).				
OESTROGEN-BASED CONTRACEPTIVES					
Ethinyloestradiol* Norethindrone*	0,035 mg daily	ethinyloestradiol	↑ 17 %	↔	↔
	1 mg daily	norethindrone	↔	↔	↔
	No dose-adjustment is required for the concomitant use of EDURANT and oestrogen-and/or progesterone-based contraceptives.				
HMG CO-A REDUCTASE INHIBITORS					
Atorvastatin*#	40 mg daily	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 medicine was evaluated in a clinical study. All other 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 medicine. The dosing recommendation is applicable to the recommended dose of EDURANT 25 mg daily.
†	This interaction study has been performed with a dose higher than the recommended dose for EDURANT.

QT prolonging medicines

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicines that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, supratherapeutic doses of rilpivirine have been shown to prolong the QTc interval of the electrocardiogram (see *section 5 Pharmacodynamic Properties*). EDURANT should be used with caution when co-administered with medicines with a known risk of Torsade de Pointes.

4.6 Fertility, pregnancy, and lactation

Safety in lactation has not been established.

Women of childbearing potential

Adequate contraception is recommended for women of childbearing potential when taking EDURANT.

Contraception in 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 oestrogen and/or progesterone based contraceptives can be used without dose adjustments.

Pregnancy

There are no well controlled clinical or pharmacokinetic studies with EDURANT in pregnant women.

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.

Breastfeeding

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.

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. 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 once daily.

4.7 Effects on ability to drive and use machines

EDURANT may influence the ability to drive and use machines.

Dizziness and somnolence have been reported with the use of EDURANT.

4.8 Undesirable effects

The safety assessment is based on the week 96 pooled data from 1 368 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 daily). The median duration of exposure for patients was 104.3 and 104.1 weeks, respectively. Most adverse reactions (ARs) occurred in the first 48 weeks of treatment.

In the phase III controlled trials, the most frequently reported adverse reactions (ARs) (≥ 2 %) that were at least grade 2 in severity, were depression, insomnia, headache, rash, abnormal dreams, nausea and dizziness (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. The most commonly reported grade 3 or 4 ARs were transaminases increased, depression, abdominal pain, dizziness and rash. All ARs leading to discontinuation had an incidence < 0,5 %.

Clinical 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. Selected treatment emergent laboratory abnormalities, considered as ARs, are included in Table 4.

Adverse reactions are listed by system organ class and frequency. The following terms and frequencies are applied: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

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 clinical trials
System Organ Class (SOC) **Adverse reaction, Frequency**	**EDURANT + BR** **N=686**
Metabolism and nutrition disorders	
Decreased appetite	Common
Psychiatric disorders	
Depression	Common
Insomnia	Very common
Abnormal dreams	Common
Sleep disorders	Common
Depressed mood	Common

Nervous system disorders	
Headache	Very common
Dizziness	Very common
Somnolence	Common
Gastrointestinal disorders	
Abdominal pain	Common
Nausea	Very common
Vomiting	Common
Abdominal discomfort	Common
Skin and subcutaneous tissue disorders	
Rash	Common
General disorders and administration site conditions	
Fatigue	Common
Investigations	
Transaminases increased	Very common

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); considered as ARs, 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 clinical trials
		EDURANT + BR N=686
HAEMATOLOGY		
Decreased haemoglobin	< 4.5 mmol/L < 7.4 g/dL	0.1%
Decreased platelet count	< 49999/mm^3 < 49999 x 10^9/L	0.1%
Decreased white blood cell count	< 1499/mm^3 < 1.499 giga/L	1.2%
BIOCHEMISTRY		
Increased creatinine	> 1.8 x ULN	0.1%
Increased AST	> 5.0 x ULN	2.3%
Increased ALT	> 5.0 x ULN	1.6%
Increased bilirubin	> 2.5 x ULN	0.7%
Increased pancreatic amylase	> 2 x ULN	3.8%
Increased lipase	> 3 x ULN	0.9%
Increased total cholesterol (fasted)*	> 7.77 mmol/L > 300 mg/dL	0.1%
Increased LDL cholesterol (fasted)*	≥ 4.91 mmol/L ≥ 191 mg/dL	1.5%
Increased triglycerides (fasted)*	≥ 8.49 mmol/L ≥ 751 mg/dL	0.6%

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 n 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 impact of such findings has not been demonstrated.

Table 5: Lipid values, mean change from baseline	
	Pooled data from the clinical trials

	EDURANT+ BR **N = 686**		
	Baseline	**Week 96**	
Mean (95 % CI)	**Mean** **(mmol/l)**	**Mean** **(mmol/l)**	**Mean change*** **(mmol/l)**
Total cholesterol (fasted)†	8.9	9.3	0.3
HDL-cholesterol (fasted)†	2.3	2.6	0.2
LDL-cholesterol (fasted)†	5.3	5.4	0.1
Triglycerides (fasted)†	6.9	6.5	-0.4

N = number of subjects per treatment group; BR = background regimen

* 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 reactions from a clinical trial in paediatric patients (12 to 17 years of age)

The safety assessment is based on the Week 48 analysis of the single-arm, open-label Phase II trial, TMC278-C213, in which 36 antiretroviral treatment-naïve HIV 1 infected patients 12 to 17 years of age and weighing at least 32 kg received EDURANT (25 mg once daily) in combination with other antiretroviral medicinal products. 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 ARs of transaminase increased were reported.

Lipodystrophy

Combination antiretroviral therapy (CART) has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see *section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

Additional information on special populations

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

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. 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 medicine product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via “6.04 Adverse Drug Reaction Reporting Form” found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/index/8

4.9 Overdose

Symptoms

There is no specific antidote for overdose with EDURANT. Human experience of overdose with EDURANT is limited.

Treatment

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

Rilpivirine is a diarylpyrimidine NNRTI of HIV. 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 5 220 nM (920 to 1 910 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 1,0 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. Rilpivirine also 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 EC50 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 rilpivirine 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 2 rilpivirine virologic failures were: V90I, K101E, E138K, E138Q, V179I Y181C, V189I and 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).

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, E138A E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V 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 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 48 pooled analysis of the phase III trials ECHO and THRIVE, 31 of the 62 subjects with virologic failure on rilpivirine 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 ≤ 100,000 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 > 100,000 copies/mL. 3, 4 and 1 rilpivirine virologic failures with baseline viral load ≤ 100,000 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 > 100,000 copies/mL (N = 30), respectively.

Effects on QTc interval

The effect of rilpivirine at the recommended dose of 25 mg 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. Rilpivirine, at the recommended dose of 25 mg daily, is not associated with a clinically relevant effect on QTc interval.

When supratherapeutic doses of 75 mg daily and 300 mg daily of rilpivirine were studied in healthy adults there was a dose related QTcF prolongation. 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 daily and 300 mg 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 daily dose of rilpivirine.

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 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 4 to 5 hours. The absolute bioavailability of rilpivirine is unknown.

Effect of food on absorption

The exposure to rilpivirine was approximately 40 % lower when rilpivirine was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high fat high caloric meal (928 kcal). When rilpivirine 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 (CYP3A) 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.

SPECIAL POPULATIONS

Paediatrics (17 years of age and younger)

The pharmacokinetics of rilpivirine in antiretroviral treatment naïve HIV-1 infected paediatric subjects 12 to less than 18 years of age receiving EDURANT 25 mg once daily were comparable to those in treatment-naive HIV-1 infected adults receiving EDURANT 25 mg once daily. There was no impact of body weight on rilpivirine pharmacokinetics in paediatric subjects in trial C213 (33 to 93 kg), similar to what was observed in adults.

The pharmacokinetics of rilpivirine in paediatric patients less than 12 years of age are under investigation. Dosing recommendations for paediatric patients less than 12 years of age cannot be made due to insufficient data *(see section 4.2 POSOLOGY AND METHOD OF ADMINISTRATION).*

Elderly (65 years of age and older)

Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine pharmacokinetics is not different across the age range (18 to 78 years) evaluated. No dose adjustment is required in elderly patients.

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. No dose adjustment is required in patients with mild or moderate hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child-Pugh score C).

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 has 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium

Lactose monohydrate (Each film-coated tablet contains 56,113 mg lactose monohydrate.)

Magnesium stearate

Polysorbate 20

Povidone K30

Silicified microcrystalline cellulose

Tablet coating

Hypromellose 2910 6 mPa.s

Lactose monohydrate

Polyethylene glycol 3000

Titanium dioxide

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C in the original bottle in order to protect from light.

Keep the bottle tightly closed.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

30 tablets are packed into a white, high density polyethylene bottle sealed with a polypropylene child-resistant closure with an induction seal liner. The bottle is packed into an outer cardboard carton together with a leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

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9 DATE OF FIRST AUTHORISATION

Date of registration: 05 December 2013

10 DATE OF REVISION OF THE TEXT

19 June 2023