EDURANT®

rilpivirine

AUSTRALIAN PRODUCT INFORMATION

1. NAME OF THE MEDICINE

Rilpivirine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EDURANT (rilpivirine) is available as 25 mg film-coated tablets. Each tablet contains rilpivirine hydrochloride equivalent to 25 mg rilpivirine.

Excipients with known effect

EDURANT tablets also contain lactose monohydrate. For a full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

EDURANT 25 mg tablets are white to off-white, film coated, round, biconvex, tablets of 6.4 mm, debossed with “TMC” on one side and “25” on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EDURANT, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with viral load ≤ 100,000 copies/mL at baseline.

This indication is based on Week 48 safety and efficacy analyses from 2 randomised double-blind, controlled Phase III trials in treatment-naïve adult patients and on Week 96 safety and efficacy analyses from the Phase IIb trial TMC278-C204 in treatment-naïve adult patients (see section 5.1 Pharmacodynamic Properties, Clinical Trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

The recommended dose of EDURANT in adults is one 25 mg tablet once daily taken orally with a meal (see section 5.2 Pharmacokinetic Properties).

Timing of dosing

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.

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 Interactions with Other Medicines and Other Forms of Interactions).

Method of administration

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

Special populations

Elderly

There is limited information regarding the use of EDURANT in patients >65 years of age (see sections 5.2 Pharmacokinetic Properties and 4.4 Special Warnings and Precautions for Use). No dose adjustment of EDURANT is required in elderly patients (see section 5.2 Pharmacokinetic Properties). EDURANT should be used with caution in this population (see sections 5.2 Pharmacokinetic Properties and 4.4 Special Warnings and Precautions for Use).

Paediatric population

The safety and efficacy of EDURANT in paediatric patients (<18 years of age) have not been established. Treatment with EDURANT is not recommended in these 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). Therefore, EDURANT is not recommended in patients with severe hepatic impairment. EDURANT should be used with caution in patients with moderate hepatic impairment (see sections 5.2 Pharmacokinetic Properties and 4.4 Special Warnings and Precautions for Use).

Renal impairment

Rilpivirine has mainly been studied in patients with normal renal function. No dose adjustment of EDURANT is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, EDURANT should be used with caution. In patients with severe renal impairment or end-stage renal disease, the combination of EDURANT with a strong CYP3A inhibitor (e.g., ritonavir-boosted HIV protease inhibitor) should only be used if the benefit outweighs the risk (see section 5.2 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. Alternatively switching to another ART regimen could be considered (see sections 5.2 Pharmacokinetic Properties, Pregnancy and postpartum and 4.6 Fertility, Pregnancy and Lactation, Use in pregnancy).

4.3 CONTRAINDICATIONS

Hypersensitivity to rilpivirine or to any of the excipients.

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 Interactions with Other Medicines and Other Forms of Interactions):

- 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 to 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 (18.2% with EDURANT versus 7.9% efavirenz arm) compared to patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/mL (5.7% with EDURANT versus 3.6% efavirenz arm). 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 treatment arms were observed from week 48 to week 96 (see section 5.1 Pharmacodynamic Properties, Clinical Trials). 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. More patients who failed virologically on EDURANT than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance. This information should be taken into consideration when initiating therapy with EDURANT (see section 5.1 Pharmacodynamic Properties, Clinical Trials).

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

Interactions with medicinal products

Caution should be given to prescribing rilpivirine with medicinal products that may reduce the exposure of rilpivirine. For information on interactions with medicinal products (see sections 4.3 Contraindications and 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including rilpivirine. 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 (see section 4.8 Adverse Effects (Undesirable Effects)). 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 Adverse Effects (Undesirable Effects)).

Hepatic impairment

No dose adjustment of EDURANT is required in patients with mild or moderate hepatic impairment but caution is advised in patients with moderate hepatic impairment. EDURANT has not been studied in patients with severe hepatic impairment. Therefore, EDURANT is not recommended in patients with severe hepatic impairment (see sections 5.2 Pharmacokinetic Properties and 4.2 Dose and Method of Administration). EDURANT should be used with caution in patients with moderate hepatic impairment (see sections 5.2 Pharmacokinetic Properties and 4.2 Dose and Method of Administration).

CYP3A metabolism

Rilpivirine is a CYP3A substrate. It is possible that different populations of patients have faster or slower rilpivirine metabolism because of the various isoenzymes within the CYP3A system.

Use in the elderly

There is limited information regarding the use of EDURANT in patients> 65 years of age (see section 5.2 Pharmacokinetic Properties). No dose adjustment of EDURANT is required in elderly patients. EDURANT should be used with caution in this population (see sections 5.2 Pharmacokinetic Properties and 4.2 Dose and Method of Administration).

Paediatric use

Treatment with EDURANT is not recommended in paediatric patients (<18 years of age) due to insufficient data in this patient population.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicinal products that affect rilpivirine exposure

Rilpivirine is primarily metabolised by cytochrome P450 CYP3A, and medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. 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 rilpivirine. Co-administration of EDURANT and medicinal products that inhibit CYP3A may result in increased plasma concentrations of rilpivirine.

Medicines that suppress gastric acid

Use of proton pump inhibitors is contraindicated as significant decreases in EDURANT plasma concentrations may occur (see section 4.3 Contraindications).

The combination of EDURANT and H_2-receptor antagonists or antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). 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 rilpivirine. H_2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after EDURANT and antacids should only be administered at least 2 hours before or at least 4 hours after EDURANT.

Medicinal products that are affected by the use of rilpivirine

EDURANT at a dose of 25 mg 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.

Interactions between rilpivirine and co-administered medicinal products are listed in the tables below (increase is indicated as "↑", decrease as "↓", no change as "↔", not applicable as "NA", once daily as "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 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 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 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.				

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
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					
Cabotegravir	30 mg q.d.	cabotegravir	↔	↔	↔
		rilpivirine	↔	↔	↓ 8%¥
	No dose adjustment is required when EDURANT is co-administered with cabotegravir.				
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.				

* 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 q.d.

¥ Reported as Ctau (observed concentration at end of dosing interval) instead of Cmin (observed minumumm concentration during the dosing interval)

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 singledose	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 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					

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
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 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 Troleandomycin	Concomitant use of EDURANT with clarithromycin, erythromycin and troleandomycinmay 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 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 2 hours before rilpivirine	rilpivirine	↓ 85%	↓ 76%	NA
	40 mg single dose taken 4 hours after rilpivirine	rilpivirine	↑ 21%	↑ 13%	NA

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
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*	60-100 mg 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*	0.035 mg q.d.	ethinylestradiol	↑ 17%	↔	↔
Norethindrone*	1 mg 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 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 rilpivirine 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 rilpivirine 25 mg 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 other medicinal products that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg q.d. and 300 mg q.d.) have been shown to prolong the QTc interval of the electrocardiogram (see section 5.1 Pharmacodynamic Properties). EDURANT at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. EDURANT should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 q.d.

Use in pregnancy - Category B1

There are no well controlled clinical or pharmacokinetic studies with rilpivirine in pregnant women. Placental transfer of rilpivirine or its metabolites from dam to fetus was demonstrated in rats. Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function. There was no clinically relevant 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 71 times higher than the exposure in humans at the recommended dose of 25 mg q.d.

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 Pharmacokinetic Properties, Pregnancy and postpartum).

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

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 Interactions with other medicines and other forms of interactions).

Use in lactation

It is not known whether rilpivirine is secreted in human milk. In nonclinical studies, rilpivirine was detected in the plasma of suckling rats following maternal dosing. 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 EFFECT ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse effects from clinical trials

The safety assessment is based on the 96 week 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 Pharmacodynamic Properties, Clinical Trials). The median duration of exposure for patients in the EDURANT and efavirenz arms 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 ECHO and THRIVE to 96 weeks, the most frequently reported ARs (≥ 2%) 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). Please note "transaminases increased" includes preferred terms "AST increased", "ALT increased", "Liver function test abnormal", "transaminases increased", "ALT abnormal", "hepatic enzyme increased" and hypertransaminasemia.

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) 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%).

The most common ARs were identified in the system organ classes (SOC) of nervous system disorders (25.7% in the EDURANT arm and 42.8% in the efavirenz arm), psychiatric disorders (23.6% in the EDURANT arm and 26.4% in the efavirenz arm) and gastrointestinal disorders (24.1% in the EDURANT arm and 22.1% in the efavirenz arm). The difference between EDURANT and the efavirenz arms observed in the SOC nervous system disorders was mainly due to the difference in dizziness experienced by patients.

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 rilpivirine

	Pooled data from the week 96 analysis of the Phase III ECHO and THRIVE trials	
System Organ Class (SOC) Adverse reaction, %	**rilpivirine + BR N=686**	**efavirenz + BR N=682**
Skin and subcutaneous tissue disorders	**2.3%**	**9.5%**
Rash*#	2.3%	9.5%
Psychiatric disorders	**9.3%**	**9.7%**
Depression	4.1%	3.2%
Insomnia	3.5%	3.5%
Abnormal dreams*†	1.6%	4.0%
Sleep disorders	1.3%	0.9%
Depressed mood	0.4%	0.3%
Nervous system disorders	**4.5%**	**10.7%**
Headache*	3.5%	3.8%

Dizziness*#	1.0%	6.7%
Somnolence	0.7%	1.3%
Gastrointestinal disorders	**3.8%**	**5.6%**
Abdominal pain	2.0%	1.9%
Nausea*	1.3%	2.8%
Vomiting	1.0%	2.1%
Abdominal discomfort	0.4%	0.1%
Metabolism and nutrition disorders	**1.2%**	**0.6%**
Decreased appetite	1.2%	0.6%
General disorders and administration site conditions	**1.6%**	**2.1%**
Fatigue	1.6%	2.1%
Investigations	**2.8%**	**4.0%**
Transaminases increased	2.8%	4.0%

BR=background regimen
N=total number of patients per treatment group
* Treatment comparison was pre-specified for these ARs (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, n/N (%)	DAIDS toxicity range	Pooled data from the week 96 analysis of the Phase III ECHO and THRIVE trials	
		rilpivirine + BR N=686	efavirenz + BR N=682
HEMATOLOGY			
Decreased hemoglobin	< 4.5 mmol/L < 74 g/L	1/685 (0.1%)	4/669 (0.6%)
Decreased platelet count	< 49999/mm^3 < 49999 x 10^9/L	1/684 (0.1%)	2/667 (0.3%)
Decreased white blood cell count	< 1499/mm^3 < 1.499 10^9/L	8/685 (1.2%)	7/669 (1.0%)
BIOCHEMISTRY			
Increased creatinine	> 1.8 x ULN	1/685 (0.1%)	1/670 (0.1%)
Increased AST	> 5.0 x ULN	16/685 (2.3%)	22/669 (3.3%)
Increased ALT	> 5.0 x ULN	11/685 (1.6%)	25/670 (3.7%)
Increased bilirubin	> 2.5 x ULN	5/685 (0.7%)	2/670 (0.3%)
Increased pancreatic amylase	> 2 x ULN	26/685 (3.8%)	32/670 (4.8%)
Increased lipase	> 3 x ULN	6/685 (0.9%)	11/670 (1.6%)
Increased total cholesterol (fasted)*	> 7.77 mmol/L > 300 mg/dL	1/685 (0.1%)	22/669 (3.3%)
Increased LDL cholesterol (fasted)*	≥ 4.91 mmol/L ≥ 191 mg/dL	10/685 (1.5%)	35/666 (5.3%)
Increased Triglycerides (fasted)*	≥ 8.49 mmol/L ≥ 751 mg/dL	4/685 (0.6%)	22/669 (3.3%)

BR=background regimen; ULN=upper limit of normal
N=number of patients 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 patients with results for the analyte.

Adrenal function

In the pooled Phase III trials, at Week 96, the overall mean change from baseline in basal cortisol was-19.1 nmol/L in the EDURANT group, and -0.6 nmol/L in the efavirenz group. At Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the EDURANT group (+18.4 ± 8.36 nmol/L) than in the efavirenz group (+54.1 ± 7.24 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 96 were within the normal range (>248nmol/L for basal and >500 nmol/L for stimulated values respectively). Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency.

Serum creatinine

In the pooled Phase III trials, serum creatinine increased minimally over 96 weeks of treatment with EDURANT. In the overall population, small mean increases from baseline in serum creatinine values were observed at the first on treatment assessment (week 2) for the rilpivirine-treated patients, which remained relatively stable until week 24 when further mean increases from baseline were observed until Week 96 (ranging from 5.3 µmol/L at week 2 to a maximum mean increase from baseline of 9.7 µmol/L at Week 96). For efavirenz-treated patients, serum creatinine values fluctuated around baseline up to Week 48 with a maximum mean increase from baseline of 3.5 µmol/L at Week 96. In patients who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in patients with normal renal function. These changes are not considered to be clinically relevant and no subject discontinued treatment due to increases in serum creatinine. Creatinine increases were comparable by background N(t)RTIs.

Serum lipids

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							
	rilpivirine + BR				**efavirenz + BR**			
	N	**Baseline**	**Week 96**		**N**	**Baseline**	**Week 96**	
Mean		**Mean (mmol/L)**	**Mean (mmol/L)**	**Mean change* (mmol/L)**		**Mean (mmol/L)**	**Mean (mmol/L)**	**Mean change* (mmol/L)**
Total cholesterol (fasted)†	546	4.2	4.3	0.1	507	4.1	4.8	0.7
HDL-cholesterol (fasted)†	545	1.1	1.2	0.1	505	1.0	1.3	0.3
LDL-cholesterol (fasted)†	543	2.5	2.5	0.0	503	2.5	2.8	0.4
Triglycerides (fasted)†	546	1.4	1.3	-0.1	507	1.5	1.6	0.1

N=number of patients 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

\# Excludes subjects who received lipid lowering agents during the treatment period

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) (see section 4.4 Special Warnings and Precautions for Use). 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

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 suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific antidote for overdose with EDURANT. Human experience of overdose with rilpivirine is limited. Treatment of overdose with rilpivirine consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

It is advisable to contact the Poison Information Centre (telephone 131126) for advice on the management of overdose.

PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type-1 (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.

Clinical trials

The evidence of efficacy of rilpivirine is based on the analyses of 96 week data from 2 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)] according to the time to loss of virologic response (TLOVR) algorithm was evaluated in patients receiving rilpivirine 25 mg q.d. in addition to a BR versus patients receiving efavirenz 600 mg q.d. in addition to a BR. The TLOVR imputation algorithm was used to define confirmed virologic response i.e., two consecutive viral load values below the threshold are needed to count as a response. Non-responders or failures were defined as those patients who never responded i.e. never achieved 2 consecutive viral load values of < 50 copies/mL, or who were a rebounder (patients responded, then has two consecutive viral load values above the threshold value of 50 copies/mL), or discontinued prematurely.

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 2 investigator-selected N(t)RTIs: tenofovir disoproxil fumarate plus emtricitabine or zidovudine plus lamivudine or abacavir plus lamivudine. In ECHO, randomisation was stratified by screening viral load. In THRIVE, randomisation was stratified by screening viral load and by N(t)RTI BR.

This analysis included 690 patients in ECHO (346 on rilpivirine and 344 on efavirenz, respectively) and 678 patients in THRIVE (340 on rilpivirine and 338 on efavirenz, respectively) who had completed 96 weeks of treatment or discontinued earlier.

In the pooled analysis for ECHO and THRIVE, demographics and baseline characteristics were balanced between the rilpivirine arm and the efavirenz arm. Table 6 displays selected demographic and baseline disease characteristics of the patients in the rilpivirine and efavirenz arms. 53.3% of patients in the rilpivirine arm and 48.2% of patients in the efavirenz arm were in the ≤ 100,000 copies/mL baseline viral load category. The proportion of patients with baseline viral load > 100,000 copies/mL was 46.7% and 51.8% in the rilpivirine arm and efavirenz arm, respectively.

Table 6: Demographic and baseline disease characteristics of antiretroviral treatment-naïve HIV-1 infected adult patients in the ECHO and THRIVE trials (pooled analysis)

	Pooled data from the ECHO and THRIVE trials	
	rilpivirine + 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 plasma HIV-1 RNA (range), copies/mL	90,450.0 (156 – 20,800,000)	104,500.0 (1,010 – 4,550,000)
Median baseline CD4+ cell count (range), x 10^6 cells/l	249 (1-888)	260 (1-1137)
Percentage of patients 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. Similar efficacy for rilpivirine was seen in each trial demonstrating non-inferiority to efavirenz, i.e. estimated treatment difference (95%CI) was -0.4 (-5.9; 5.2) and 3.5 (-1.7; 8.8) at week 48 (primary) and -3.2 (-9.4; 3.1) and 2.4 (-3.6; 8.4) at week 96, in ECHO and THRIVE respectively.

The response rate (confirmed undetectable viral load < 50 HIV-1 RNA copies/mL) at week 96 was comparable between the rilpvirine arm and the efavirenz arm (77.6% for both arms, estimated treatment difference [95%CI] is -0.4% [-4.6%; 3.8%]). The incidence of virologic failure was higher in the rilpivirine arm than the efavirenz arm at week 96 (11.5% for rilpvirine and 5.9% for efavirenz); 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 Randomized Treatment in the ECHO and THRIVE Trials (Pooled Analysis at Week 48 (primary) and Week 96; ITT-TLOVR[*])

	Outcome at Week 48		***Outcome at Week 96***	
n/N (%)	**rilpivirine + BR N=686**	**efavirenz + BR N=682**	**rilpivirine + BR N=686**	**efavirenz + BR N=682**
Confirmed Undetectable Viral Load (< 50 HIV-1 RNA copies/mL) [§#]	578/686 (84.3)	561/682 (82.3)	532/686 (77.6)	529/682 (77.6)
Virologic Failure[†]	62/686 (9.0)	33/682 (4.8)	(79/686) 11.5	40/682 (5.9)
Death	1/686 (0.1)	3/682 (0.4)	(1/686) 0.1	6/682 (0.9)
Discontinued due to adverse event (AE)	14/686 (2.0)	46/682 (6.7)	(26/686) 3.8	52/682 (7.6)
Discontinued for non-AE reason[¶]	31/686 (4.5)	39/682 (5.7)	(48/686) 7.0	55/682 (8.1)

N = number of patients per treatment group

* intent-to-treat time to loss of virologic response

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

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

† Includes patients 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

The mean change from baseline in CD4+ cell count was +192 x 10^6 cells/l in the rilpivirine arm and +176 x 10^6 cells/l in the efavirenz arm in the pooled analysis of the ECHO and THRIVE trials [estimated treatment difference (95% CI): 17.9 (2.1; 33.6)] at week 48. At week 96, the mean change from baseline in CD4+ cell count was +228 x 10^6 cells/l in the EDURANT arm (n=685) and +219 x 10^6 cells/l in the efavirenz arm (n=682) 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 96 weeks 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) at 48 weeks and at 96 weeks and virologic failure by baseline viral load, by baseline CD4 count, and by background NRTIs (pooled data from the ECHO and THRIVE trials)

	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)								
≤ 100,000	368	332 (90.2%)	330	276 (83.6%)	368	309 (84.0%)	329	263 (79.9%)
> 100,000	318	246 (77.4%)	352	285 (81.0%)	318	223 (70.1%)	353	266 (75.4%)
Virologic Failure[†] by baseline plasma viral load (copies/mL)								
≤ 100,000	368	14 (3.8%)	330	11 (3.3%)	368	21 (5.7%)	329	12 (3.6%)
> 100,000	318	48 (15.1%)	352	22 (6.3%)	318	58 (18.2%)	353	28 (7.9%)
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 patients per treatment group
n=number of observations
* Imputations according to the TLOVR algorithm.
† Includes patients 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).

At week 96, response rates (< 50 copies/mL [TLOVR]) in the pooled Phase III trial population were 84.0% in the EDURANT arm and 79.9% in the efavirenz arm in patients with a baseline viral load ≤ 100,000 copies/mL versus 70.1% and 75.4%, respectively, in patients with a baseline viral load > 100,000 copies/mL. The proportion of virologic failures according to TLOVR in the pooled Phase III trial population was 5.7% in the EDURANT arm and 3.6% in the efavirenz arm, for patients with a baseline viral load ≤ 100,000 copies/mL. The proportion of virologic failures was higher for patients with a baseline viral load > 100,000 copies/mL, especially in the EDURANT arm (18.2% EDURANT-treated patients vs. 7.9% efavirenz-treated patients).

The incidence of emergence of N(t)RTI and NNRTI RAMs in the virologic failures (according to the resistance analysis criteria) was lower in the ≤ 100,000 copies/mL category than in the > 100,000 copies/mL category. This difference was observed in both treatment groups but with a lower incidence of emerging mutations in the efavirenz arm. This difference in incidence of emerging mutations between treatment groups was greater for N(t)RTI mutations. At week 48, among patients with baseline viral load ≤ 100,000 copies/mL (16 patients in the rilpivirine arm and 12 patients in the efavirenz arm), 7 and 6 rilpivirine virologic failures and 2 and 5 efavirenz virologic failures had emerging N(t)RTI RAMs and NNRTI RAMs, respectively. Among patients with baseline viral load > 100,000 copies/mL (46 patients in the rilpivirine arm and 16 patients in the efavirenz arm), 35 and 33 rilpivirine virologic failures and 7 and 10 efavirenz virologic failures had emerging N(t)RTI RAMs and NNRTI RAMs, respectively. The less frequent emergence of N(t)RTI and NNRTI RAMs in the ≤ 100,000 copies/mL category, as compared to the > 100,000 copies/mL category of both treatment groups, as well as the lower incidence of emerging N(t)RTI mutations in efavirenz virologic failures as compared to rilpivirine virologic failures were confirmed in the week 96 pooled Phase III analyses.

Study TMC278-C204 was a randomised, active-controlled, Phase IIb trial in antiretroviral treatment-naïve HIV-1 infected adult patients consisting of 2 parts: an initial partially blinded dose-finding part [rilpivirine doses blinded] up to 96 weeks, followed by a long-term, open label

part. In the open label part of the trial, patients originally randomised to one of the 3 doses of rilpivirine were all treated with rilpivirine 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 2 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 rilpivirine 25 mg (N=93) compared to patients receiving efavirenz (N=89) was 76% and 71%, respectively. The mean increase from baseline in CD4+ counts was 146 x 10^6 cells/l in patients receiving rilpivirine 25 mg and 160 x 10^6 cells/l in patients receiving efavirenz.

Of those patients who were responders at week 96, 151/204 (74%) of patients receiving rilpivirine remained with undetectable viral load (< 50 HIV-1 RNA copies/mL) at week 240 compared to 51/63 (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. Out of 12 subjects completing the study, 10 were suppressed and the other 2 had increased viral load likely due to suboptimal adherence. 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.

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 to10,830 nM (920 to 3,970 ng/mL), treatment of HIV-2 infection with rilpivirine is not recommended in the absence of clinical data.

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

Rilpivirine showed additive antiviral activity in combination with the N(t)RTIs: abacavir, didanosine, emtricitabine, stavudine and tenofovir; the protease inhibitors: 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 patients

For the resistance analysis, a broader definition of virologic failure was used than in the primary efficacy analysis. The definition of virologic failure used in the efficacy analysis of the Phase III studies was based on the time to loss of virologic failure (TLOVR) algorithm (see section 5.1 Pharmacodynamic Properties, Clinical Trials).

The broader definition of virologic failure used in the resistance analysis of the Phase III studies included patients who were defined as rebounders (had 2 consecutive viral load measurements < 50 copies/mL, followed by 2 consecutive viral load values ≥ 50 copies/mL), patients who stopped treatment while not suppressed (had 2 consecutive viral load measurements < 50 copies/mL and stopped treatment with a last observed on-treatment viral load value of ≥ 50 copies/mL) or patients who never suppressed (no confirmed viral load measurements < 50 copies/mL and an increase in viral load ≥ 0.5 $\log_{10}$ copies/mL above the nadir, regardless of time of failure and reason for discontinuation).

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 as compared to 28 (of a total of 39) virologic failures in the efavirenz arm. 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, 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 the rilpivirine treatment, commonly in combination with the M184I substitution.

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

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

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, E138Q, E138R, 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 and L100I 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 patients

In the week 48 pooled analysis of the Phase III trials ECHO and THRIVE, 31 of the 62 patients 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 resistance analysis of the Phase III trials (ECHO and THRIVE), 42 out of 86 subjects with virologic failure on rilpivirine showed treatment-emergent resistance to rilpivirine

(genotypic analysis). In these patients, phenotypic cross-resistance to other NNRTIs was noted as follows: etravirine 32/42, efavirenz 30/42, and nevirapine 16/42. In patients with a baseline viral load ≤ 100,000 copies/mL, 9 out of 27 patients with virologic failure on rilpivirine showed treatment-emergent resistance to rilpivirine (genotypic analysis), with the following frequency of phenotypic cross-resistance: etravirine 4/9, efavirenz 3/9, and nevirapine 1/9. In rilpivirine virologic failures with resistance to rilpivirine (genotypic analysis), phenotypic cross-resistance to etravirine, efavirenz, and nevirapine was observed in, respectively, 28, 27, and 15 of 30 patients with baseline viral load > 100,000 copies/mL.

Effects on electrocardiogram

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

When supratherapeutic doses of 75 mg q.d. and 300 mg q.d. of rilpivirine were studied in healthy adults, the maximum mean time matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10.7 (15.3) and 23.3 (28.4) ms, respectively. Steady state administration of rilpivirine 75 mg q.d. and 300 mg 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 q.d. dose of rilpivirine.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy subjects and in adult antiretroviral treatment naïve HIV 1 infected patients. Exposure to rilpivirine was generally lower in HIV-1 infected patients than in healthy subjects.

Absorption

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4-5 hours. The absolute bioavailability of 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 (see section 4.2 Dose and Method of Administration).

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.

Metabolism

In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system. It is possible that different populations of patients have faster or slower rilpivirine metabolism because of the various isoenzymes within the CYP3A system.

Excretion

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

Additional information on special populations

Paediatric population

The pharmacokinetics of rilpivirine in paediatric patients (<18 years of age) have not been established.

Elderly

Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine pharmacokinetics are not different across the age range (18 to 78 years, with only 2 patients aged above 65 years) evaluated. No dose adjustment of rilpivirine is required in elderly patients. EDURANT should be used with caution in this population.

Gender

Population pharmacokinetic analysis in HIV infected patients showed no clinically relevant differences in the pharmacokinetics of rilpivirine 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

There is limited information regarding the use of EDURANT in patients with mild or moderate hepatic impairment, resulting in unexpected variability in the available data.

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 mean steady-state exposure to rilpivirine was higher in patients with mild hepatic impairment (27% higher for C_{max} and 47% higher for AUC) than in healthy controls. However, rilpivirine exposure in patients with moderate hepatic impairment (5% lower for C_{max} and 5% higher for AUC) was similar to healthy controls. The mean apparent elimination half-life of rilpivirine was longer in patients with mild (81 hours versus 61 hours respectively) and moderate (91 hours versus 56 hours, respectively) hepatic impairment compared to healthy controls. No dose adjustment is required in patients with mild hepatic impairment. No dose adjustment is suggested but caution is advised in patients with moderate hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child Pugh score C). Therefore, EDURANT is not recommended in patients with severe hepatic impairment (see sections 4.4 Special Warnings and Precautions for Use and 4.2 Dose and Method of Administration).

Hepatitis B and/or hepatitis C virus co infection

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

Renal impairment

The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. EDURANT has mainly been studied in patients with normal renal function. No dose adjustment is required for patients with mild or moderate renal impairment. In patients with severe renal impairment or end stage renal disease, EDURANT should be used with caution. In patients with severe renal impairment or end stage renal disease, the combination of EDURANT with a strong CYP3A inhibitor (e.g., ritonavir boosted HIV protease inhibitor) should only be used if the benefit outweighs the risk (see section 4.2 Dose and Method of Administration). As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

Carcinogenicity

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 q.d.).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate (each tablet contains 56 mg lactose monohydrate)

Croscarmellose sodium

Povidone

Polysorbate 20

Silicified microcrystalline cellulose (a combination of microcrystalline cellulose and silicon dioxide)

Magnesium stearate

Hypromellose

Titanium dioxide

Macrogol 3000

Glycerol triacetate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in the original bottle. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

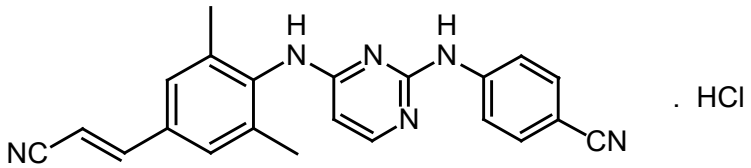
EDURANT tablets are provided in a high density polyethylene (HDPE) bottle with a polypropylene (PP) child resistant closure and induction seal liner. One bottle contains 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure:



. HCl

CAS No.: 700361-47-3

Molecular formula: $C_{22}H_{18}N_6.HCl$

Molecular weight: 402.88

The chemical name of rilpivirine is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino-2-pyrimidinyl]amino]benzonitrile monohydrochloride.

Rilpivirine hydrochloride is a white to off-white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range, its pKa is 5.6 (pyrimidine moiety) and log P between 1-octanol and a phosphate solution (pH 7.0) is 4.86 (at 21°C).

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113 Australia

NZ Office: Auckland New Zealand

9. DATE OF FIRST APPROVAL

23 December 2011

10. DATE OF REVISION

25 Aug 2023

Summary table of changes

Section	Summary of changes
4.4	Deletion of warning on fat redistribution
4.5	Inclusion of cabotegravir in drug interactions table (Table 1)
4.6	Update to pregnancy risk-benefit statement Deletion of statement on use of contraception in women of childbearing potential
4.8	Deletion of text defining laboratory abnormalities as Adverse Drug Reaction. Deletion of statement on lipodystrophy
5.2	Editorial correction to numbering of Pharmacokinetic Properties section from 5.3 to 5.2
4.2, 4.4, 4.5, 4.8, 5.1, 5.2	Editorial updates for additional clarity and readability