PROFESSIONAL INFORMATION INSERT

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

INTELENCE 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of INTELENCE contains 100 mg of etravirine.

Contains sugar: Each tablet contains 160 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white, oval tablet, debossed with “T125” on one side and “100” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INTELENCE, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients and antiretroviral treatmen-experienced children from 2 years of age and weighing at least 30 kg, including those with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance.

Treatment history and resistance testing should guide the use of INTELENCE.

In patients who have experienced virological failure on an NNRTI- and nucleoside or nucleotide reverse transcriptase inhibitor (N(t)RTI)-containing regimen, INTELENCE is not recommended for use in combination with N(t)RTIs only.

4.2 Posology and method of administration

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

Adults

The recommended dose of INTELENCE is 200 mg (two 100 mg tablets) taken orally twice daily (b.i.d.), following a meal.

Children and adolescents of at least 2 years of age and weighing at least 30 kg::

The recommended dose of INTELENCE is 200 mg (two 100 mg tablets) taken orally twice daily (b.i.d.), following a meal.

Special populations

Children (less than 2 years of age or weighing less than 30 kg)

Treatment with INTELENCE 100 mg tablet is not recommended in children less than 2 years of age or weighing less than 30 kg. The safety and efficacy in children weighing less than 30 kg has not been established with dosage forms available.

Elderly

Limited information is available in this population (*see section 4.4 and section 5*).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). The pharmacokinetics of INTELENCE have not been studied in patients with severe hepatic impairment (Child-Pugh score C) (*see section 4.4 and section 5*).

Renal impairment

No dose adjustment is required in patients with renal impairment (*see section 4.4 and section 5*).

Missed dose(s)

If the patient misses a dose of INTELENCE within 6 hours of the time it is usually taken, the patient should be told to take INTELENCE following a meal as soon as possible and then take the next dose of INTELENCE at the regularly scheduled time. If a patient misses a dose of INTELENCE by more than 6 hours of the time it is usually taken, the patient should be told not to take the missed dose and simply resume the usual dosing schedule.

Administration

Patients should be instructed to swallow the INTELENCE tablet(s) whole with a liquid such as water.

Patients who are unable to swallow the INTELENCE tablet(s) whole may disperse the tablet(s) in a glass of water. The patient should be instructed to do the following:

- place the tablet(s) in 5 mL (1 teaspoon) of water, or at least enough water to cover the medication,
- stir well for about 1 minute until the water looks milky,
- if desired, add up to 30 mL (2 tablespoons) more water or alternatively orange juice or milk (patients should not place the tablets in orange juice or milk without first adding water),

- drink it immediately,
- rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the patient takes the entire dose.

The use of warm (> 40°C) or carbonated beverages should be avoided.

In case of any doubt that a child will take the entire dose of the tablet(s) dispersed in water, treatment with another antiretroviral product needs to be considered.

For children who cannot swallow the tablet(s) whole, dispersion of the tablet(s) in water should only be considered if the child is likely to take the entire dose. The importance of consuming the entire dose needs to be highlighted to the child and their caregiver to avoid too low exposure and lack of virologic response.

It is recommended that INTELENCE tablet(s) dispersed in water be taken before other antiretroviral liquids that may need to be taken concomitantly.

4.3 Contraindications

Hypersensitivity to etravirine or to any of the excipients.

Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. INTELENCE should not be used in combination with carbamazepine, phenobarbital, or phenytoin as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE.

Posaconazole is a potent inhibitor of CYP3A4 and may increase plasma concentrations of INTELENCE. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A4. Concomitant systemic use of itraconazole or ketoconazole and INTELENCE may increase plasma concentrations of INTELENCE. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE.

Rifampicin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE should not be used in combination with rifampicin or rifapentine as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE.

INTELENCE should not be used concomitantly with products containing St. John's wort because co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE.

4.4 Special warnings and precautions for use

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 should continue to be employed.

Clinical studies are ongoing in HIV-1 infected children and adolescents.

Severe Skin and Hypersensitivity Reactions

Severe, potentially life-threatening and fatal skin reactions have been reported with INTELENCE; Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported. Hypersensitivity reactions including DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) have also been reported and were characterised by rash, constitutional findings and organ dysfunction, including hepatic failure.

Discontinue INTELENCE immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions,

conjunctivitis, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping INTELENCE treatment after the onset of severe rash may result in a life-threatening reaction.

Rash

Rash has been reported with INTELENCE. Most frequently, rash was mild to moderate, occurred in the second week of therapy and was infrequent after week 4. Rash was mostly self-limiting and generally resolved within 1 to 2 weeks on continued therapy. The incidence of rash was higher in females.

Elderly

Experience in geriatric patients is limited: In the Phase III trials, 6 patients aged 65 years or older and 53 patients aged 56 to 64 years received INTELENCE. The type and incidence of adverse events in patients > 55 years of age were similar to the ones in younger patients (*see section 4.2 and section 5.2*).

Patients with coexisting conditions

Liver disease

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). The pharmacokinetics of INTELENCE have not been studied in patients with severe hepatic impairment (Child-Pugh score C) (*see section 4.2 and section 5.2*).

Renal disease

Since the renal clearance of etravirine is negligible (< 1,2 %), a decrease in total body clearance is not expected in patients with renal impairment. No special precautions or dose adjustments are required in patients with renal impairment. As etravirine is highly bound to

plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (*see section 4.2 and section 5.2*).

Fat redistribution

Combination antiretroviral therapy (CART) has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age and with medicine-related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution (*see section 4.8*).

Immune reconstitution syndrome

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and Pneumocystis jiroveci pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary (*see section 4.8*).

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

Excipients

INTELENCE contains lactose (each tablet contains 160 mg lactose monohydrate) 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 INTELENCE.

4.5 Interaction with other medicines and other forms of interaction

Etravirine is a substrate and weak inducer of cytochrome P450 (CYP) 3A4 and a substrate and weak inhibitor of CYP2C9 and CYP2C19. Medicinal products that inhibit or induce CYP3A4, CYP2C9 and/or CYP2C19 may alter plasma concentrations of etravirine and may alter its therapeutic effect or adverse events profile.

Medicinal products that affect etravirine exposure

Etravirine is metabolised by CYP3A4, CYP2C9 and CYP2C19 followed by glucuronidation by uridine diphosphate glucuronosyl transferase (UDPGT). Medicinal products that induce CYP3A4, CYP2C9 or CYP2C19 may increase the clearance of etravirine resulting in lowered plasma concentrations of etravirine. Co-administration of INTELENCE and medicinal products that inhibit CYP3A4, CYP2C9 or CYP2C19 may decrease the clearance of etravirine and may result in increased plasma concentrations of etravirine.

Medicinal products that are affected by the use of etravirine

Etravirine is a weak inducer of CYP3A4. Co-administration of INTELENCE with medicinal products primarily metabolised by CYP3A4, such as clarithromycin, sildenafil and midazolam, may result in decreased plasma concentrations of such medicinal products, which could

decrease or shorten their therapeutic effects. Etravirine is a weak inhibitor of CYP2C9 and CYP2C19. Co-administration with medicinal products primarily metabolised by CYP2C9 or CYP2C19 may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect or adverse events profile.

Known and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in the tables below.

*Interaction table**

Interactions between etravirine and co-administered medicinal products are listed in the tables below (increase is indicated as "↑", decrease as "↓", no change as" ↔", not done as "ND", once daily as "q.d" and twice daily as "b.i.d").

Interactions with other medicines - Etravirine co-administered with antiretroviral medicinal products

Co-administered Medicinal Product	**Dose of Co-administered Medicinal Product (mg)**	**Medicinal Product Assessed**	**AUC**	**C_{min}**
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
NNRTIs	It is not recommended to co-administer INTELENCE with other NNRTIs			
Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)				
Didanosine	400 q.d.	didanosine etravirine	↔ ↔	ND ↔

	The combination of INTELENCE and didanosine can be used without dose adjustments. As didanosine is administered on an empty stomach, didanosine should be administered one hour before or two hours after INTELENCE (which should be administered following a meal).			
Tenofovir disoproxil fumarate	300 q.d.	tenofovir etravirine	↔ ↓ 19 %	↑ 19 % ↓ 18 %
	The combination of INTELENCE and tenofovir disoproxil fumarate can be used without dose adjustments.			
Other NRTIs	Based on the primarily renal elimination route for other NRTIs (e.g., abacavir, emtricitabine, lamivudine, stavudine and zidovudine), no medicine interactions are expected between these medicinal products and INTELENCE.			
Protease Inhibitors (PIs) – Unboosted (i.e. without co-administration of low-dose ritonavir)				
Atazanavir, unboosted	400 q.d.	atazanavir etravirine	↓ 17 % ↑ 50 %	↓ 47 % ↑ 58 %
	It is not recommended to co-administer unboosted atazanavir and INTELENCE.			
Ritonavir	Concomitant use of INTELENCE with full dose ritonavir (600 mg b.i.d) may cause a significant decrease in the plasma concentration of etravirine. This may result in loss of therapeutic effect of INTELENCE. It is not recommended to co-administer full dose ritonavir (600 mg b.i.d) with INTELENCE.			
Nelfinavir	Concomitant use of INTELENCE with nelfinavir may cause an increase in the plasma concentrations of nelfinavir.			
Fosamprenavir,	Concomitant use of INTELENCE with unboosted fosamprenavir may			

unboosted	cause an increase in the plasma concentrations of amprenavir.			
Other inboosted PIs	It is not recommended to co-administer INTELENCE with other unboosted PIs (including indinavir and saquinavir).			
Protease Inhibitors (PIs) - Boosted (with low dose ritonavir)				
Tipranavir/ ritonavir	500/200 b.i.d	tipranavir etravirine	↑ 18 % ↓ 76 %	↑ 24 % ↓ 82 %
	It is not recommended to co-administer tipranavir/ritonavir and INTELENCE.			
Fosamprenavir/ ritonavir	700/100 b.i.d	amprenavir etravirine	↑ 69 % ↔	↑ 77 % ↔
	Amprenavir and fosamprenavir/ritonavir may require dose adjustment when co-administered with INTELENCE.			
Atazanavir/ ritonavir	300/100 q.d.	atazanavir etravirine	↓ 14 % ↑ 30 %	↓ 38 % ↑ 26 %
	The combination of INTELENCE and atazanavir/ritonavir can be used without dose adjustments.			
Darunavir/ ritonavir	600/100 b.i.d	darunavir etravirine	↔ ↓ 37 %	↔ ↓ 49 %
	The combination of INTELENCE and darunavir/ritonavir can be used without dose adjustments.			
Lopinavir/ ritonavir (soft gel capsule)	400/100 b.i.d	lopinavir etravirine	↓ 20 % ↑ 17 %	↓ 8 % ↑ 23 %
	The combination of INTELENCE and lopinavir/ritonavir can be used without dose adjustments.			
Saquinavir/	1 000/100 b.i.d.	saquinavir	↔	↓ 20 %

ritonavir		etravirine	↓ 33 %	↓ 29 %
	The combination of INTELENCE and saquinavir/ritonavir can be used without dose adjustments.			
HIV PIs - Boosted (with cobicistat)				
Atazanavir /cobicistat, Darunavir /cobicistat	Co administration of INTELENCE with atazanavir/cobicistat or darunavir/cobicistat may decrease plasma concentrations of the PI and/or cobicistat, which may result in loss of therapeutic effect and development of resistance. Co administration of INTELENCE with atazanavir/cobicistat or darunavir/cobicistat is not recommended.			
Dual boosted Protease Inhibitors				
Lopinavir/ saquinavir/ ritonavir	400/800 to 1 000/100 b.i.d	lopinavir saquinavir etravirine	↓ 18 % ↓ 13 % ↔	↓ 24 % ↓ 13 % ↔
	The combination of INTELENCE and lopinavir/saquinavir/ritonavir can be used without dose adjustments.			
CCR5 Antagonists				
maraviroc	300 mg b.i.d.	maraviroc	↓ 53%	↓ 39%
		etravirine	↔	↔
	Concomitant use of INTELENCE with maraviroc may cause a significant decrease in the plasma concentration of maraviroc. When INTELENCE is co-administered with maraviroc in the absence of a potent CYP3A inhibitor (e.g., a boosted PI), the recommended dose of maraviroc is 600 mg b.i.d. No dose adjustment for INTELENCE is needed.			
Maraviroc / darunavir /	150/600/100 mg b.i.d.	maraviroc	↑ 3.1-fold*	↑ 5.3-fold*
		etravirine	↔	↔

ritonavir	When INTELENCE is co-administered with maraviroc in the presence of a potent CYP3A inhibitor (e.g., a boosted PI), refer to the applicable prescribing information of maraviroc for the recommended dose, treating INTELENCE as a CYP3A inducer (such as efavirenz). No dose adjustment for INTELENCE is needed. *compared to maraviroc 150 mg b.i.d.			
Fusion Inhibitors				
Enfuvirtide	90 b.i.d.	enfuvirtide etravirine*	ND ↔	ND ↔
	No interaction is expected for either INTELENCE or enfuvirtide when co-administered * based on population pharmacokinetic analysis			
Integrase Strand Transfer Inhibitors				
dolutegravir	50 mg q.d.	dolutegravir	↓ 71%	↓ 88%
		etravirine	↔	↔
Dolutegravir / darunavir / ritonavir	50 mg q.d. + 600/100 mg b.i.d.	dolutegravir	↓ 25%	↓ 37%
		etravirine	↔	↔
Dolutegravir / lopinavir/ ritonavir	50 mg q.d. + 400/100 mg b.i.d.	dolutegravir etravirine	↔ ↔	↑ 28% ↔
	Etravirine significantly reduced plasma concentrations of dolutegravir. Using cross-study comparisons to historical pharmacokinetic data for etravirine, dolutegravir did not appear to affect the pharmacokinetics of etravirine. The effect of etravirine on dolutegravir plasma concentrations was mitigated by co-administration of darunavir/ritonavir or			

	lopinavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir. Dolutegravir should only be used with INTELENCE when co-administered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir.			
Elvitegravir / ritonavir	150/100 mg q.d.	elvitegravir ritonavir etravirine	↔ ↔ ↔	ND ND ND
	The combination of INTELENCE and elvitegravir/ritonavir can be used without dose adjustments.			
Raltegravir	400 b.i.d	raltegravir etravirine	↓ 10 % ↔	↓ 34 % ↔
	The combination of INTELENCE and raltegravir can be used without dose adjustments.			

Interactions with other medicines - Etravirine co-administered with non-antiretroviral medicinal products

Co-administered Medicinal Product	**Dose of Co-administered Medicinal Product (mg)**	**Medicinal Product Assessed**	**AUC**	**C_{min}**
Antidysrhythmics				
digoxin	0,5 mg single dose	digoxin	↑ 18%	ND
		etravirine	↔	↔
	The combination of INTELENCE and digoxin can be used without dose adjustments. It is recommended that digoxin levels be monitored when digoxin is combined with INTELENCE.			

Amiodarone Bepridil Disopyramide Flecainide Lidocaine (systemic) Mexiletine Propafenone Quinidine	Concentrations of these antidysrhythmics may be decreased when co-administered with INTELENCE. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antidysrhythmics when co-administered with INTELENCE.
Anticoagulants	
Warfarin	Warfarin concentrations may be affected, causing likely increased anticoagulation activity, when co-administered with INTELENCE. It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with INTELENCE.
Anticonvulsants	
Carbamazepine Phenobarbital Phenytoin	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. INTELENCE should not be used in combination with carbamazepine, phenobarbital or phenytoin as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE (*see section 4.3*).
Antifungals	
Itraconazole Ketoconazole Posaconazole	Posaconazole is a potent inhibitor of CYP3A4 and may increase plasma concentrations of INTELENCE. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A4. Concomitant systemic use of

	itraconazole or ketoconazole and INTELENCE may increase plasma concentrations of INTELENCE. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE (*see section 4.3*).			
Fluconazole	200 q.a.m.	fluconazole etravirine	↔ ↑ 86 %	↔ ↑ 109 %
	The incidence of adverse events was similar in patients co-administering fluconazole and INTELENCE or placebo in the Phase III trials. The combination of INTELENCE and fluconazole can be used without dose adjustments.			
Voriconazole	200 b.i.d.	voriconazole etravirine	↑ 14 % ↑ 36 %	↑ 23 % ↑ 52 %
	The combination of INTELENCE and voriconazole can be used without dose adjustments.			
Anti-infectives				
Azithromycin	Based on the renal elimination pathway of azithromycin, no medicine interactions are expected between azithromycin and INTELENCE.			
Clarithromycin	500 b.i.d.	clarithromycin 14-hydroxy-clarithromycin etravirine	↓ 39 % ↑ 21 % ↑ 42 %	↓ 53 % ↔ ↑ 46 %
	Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-hydroxy-clarithromycin, were increased. Because 14-hydroxy-clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC), overall activity against this pathogen			

	may be altered; therefore, alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC.			
Antimalarials				
Artemether/Lumefantrine[1]	80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	artemether	↓ 38%	↓ 18%
		dihydroartemisinin	↓ 15%	↓ 17%
		lumefantrine	↓ 13%	↔
		etravirine	↔	↔
	No dose adjustment is needed for INTELENCE. Caution is warranted when co-administering INTELENCE and artemether/lumefantrine as it is unknown whether the decrease in exposure of artemether or its active metabolite, dihydroartemisinin, could result in decreased antimalarial efficacy.			
Rifampicin/ Rifampin/ Rifapentine	Rifampicin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE should not be used in combination with rifampicin or rifapentine as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE (*see section 4.3*).			
Rifabutin	300 q.d.	Rifabutin *25-O-*desacetylrifabutin etravirine	↓ 17 % ↓ 17 % ↓ 37 %	↓ 24 % ↓ 22 % ↓ 35 %
	The combination of INTELENCE and rifabutin can be used without dose adjustments.			
Antivirals				
Ribavirin	Based on the renal elimination pathway of ribavirin, no medicine interactions are expected between ribavirin and INTELENCE.			
Benzodiazepines				

Diazepam	Concomitant use of INTELENCE with diazepam may increase plasma concentrations of diazepam.			
Corticosteroids				
Dexamethasone (systemic)	Systemic dexamethasone induces CYP3A4 and can decrease etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE. Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for long-term use.			
Estrogen-based Contraceptives				
Ethinylestradiol Norethindrone	0.035 q.d. 1 q.d.	ethinylestradiol norethindrone etravirine	↑ 22 % ↔ ↔	↔ ↓ 22 % ↔
	The combination of estrogen- and/or progesterone-based contraceptives and INTELENCE can be used without dose adjustment.			
Hepatitis C Virus (HCV) Direct-Acting Antivirals (DAAs)				
daclatasvir	Co-administration of INTELENCE with daclatasvir may decrease daclatasvir concentrations. Increase the daclatasvir dose to 90 mg once daily.			
Elbasvir / grazoprevir	Co-administration of INTELENCE with elbasvir/grazoprevir may decrease elbasvir and grazoprevir concentrations, leading to reduced therapeutic effect of elbasvir/grazoprevir. It is not recommended to co-administer INTELENCE with elbasvir/grazoprevir.			
simeprevir	Concomitant use of INTELENCE with simeprevir may decrease plasma concentrations of simeprevir. It is not recommended to co-administer INTELENCE with simeprevir.			
boceprevir	800 mg t.i.d.	boceprevir	↑ 10%	↓ 12 %

		etravirine	↓ 23%	↓ 29 %
	The combination of INTELENCE and boceprevir can be used without dose adjustments. Caution should be applied if INTELENCE is co-administered with boceprevir and another medicine that potentially decreases etravirine plasma concentrations. Close monitoring for HIV and HCV virologic response is recommended. Please refer to the product information of the associated medications.			
ribavirin	Based on the renal elimination pathway of ribavirin, no medicine interactions are expected between ribavirin and INTELENCE.			
Herbal Products				
St John's wort *(Hypericum perforatum)*	INTELENCE should not be used concomitantly with products containing St. John's wort because co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE.			
HMG Co-A Reductase Inhibitors				
Atorvastatin	40 q.d.	atorvastatin 2-hydroxy-atorvastatin etravirine	↓ 37 % ↑ 27 % ↔	ND ND ↔
	Dose adjustment of atorvastatin may be necessary to tailor the clinical response when combined with INTELENCE.			
Fluvastatin Lovastatin	No interaction between pravastatin and INTELENCE is expected.			

Pravastatin Rosuvastatin Simvastatin	Lovastatin, rosuvastatin and simvastatin are CYP3A4 substrates and co-administration with INTELENCE may result in lower plasma concentrations of the HMG Co-A reductase inhibitor. Fluvastatin, rosuvastatin are metabolised by CYP2C9 and co-administration with INTELENCE may result in higher plasma concentrations of the HMG Co-A reductase inhibitor. Dose adjustments for these HMG Co-A reductase inhibitors may be necessary.			
H_2-Receptor Antagonists				
Ranitidine	150 b.i.d.	etravirine	↓ 14 %	ND
	INTELENCE can be co-administered with H_2-receptor antagonists without dose adjustments.			
Immunosuppressants				
Cyclosporine Sirolimus Tacrolimus	Co-administration with systemic immunosuppressants should be done with caution because plasma concentrations of cyclosporine, sirolimus or tacrolimus may be affected when co-administered with INTELENCE.			
Narcotic Analgesics				
Methadone	Individual dose ranging from 60 to 130 mg/day	R (-) methadone S (+) methadone etravirine	↔ ↔ ↔	↔ ↔ ↔
	No changes in methadone dosage were required based on clinical status during or after the period of INTELENCE co-administration.			
Phosphodiesterase type 5 (PDE-5) inhibitors				
Sildenafil Vardenafil Tadalafil	50 mg single dose	sildenafil N-desmethyl-sildenafil	↓ 57 % ↓ 41 %	ND ND
	Concomitant use of PDE-5 inhibitors with INTELENCE may require dose			

	adjustment of the PDE-5 inhibitor to attain the desired clinical effect.			
Platelet Aggregation Inhibitor				
clopidogrel	Activation of clopidogrel to its active metabolite may be decreased when clopidogrel is co-administered with INTELENCE. Alternatives to clopidogrel should be considered.			
Proton Pump Inhibitors				
Omeprazole	40 q.d.	etravirine	↑ 41 %	ND
	INTELENCE can be co-administered with proton pump inhibitors without dose adjustments.			
Selective Serotonin Reuptake Inhibitors (SSRIs)				
Paroxetine	20 q.d.	paroxetine etravirine	↔ ↔	↓ 13 % ↔
	INTELENCE can be co-administered with paroxetine without dose adjustments.			

* In medicine - medicine interaction studies, different formulations and/or doses of INTELENCE were used which led to similar exposures and, therefore, interactions relevant for one formulation are relevant for the other.

4.6 Fertility, pregnancy and lactation

Pregnancy

INTELENCE should not be used during pregnancy as safety and efficacy have not been demonstrated.

Women of childbearing potential

No human data on the effect of etravirine on fertility are available. In rats, there was no effect on mating or fertility with INTELENCE treatment.

Lactation

Etravirine is excreted in human breast milk. 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 INTELENCE.

4.7 Effects on ability to drive and use machines

No studies on the effects of INTELENCE on the ability to drive or operate machines have been performed. There is no evidence that INTELENCE may alter the patient's ability to drive and operate machines, however, the adverse reaction profile of INTELENCE should be taken into account (*see section 4.8*).

4.8 Undesirable effects

The safety assessment is based on all data from 1 203 patients in ongoing Phase III placebo-controlled trials DUET 1 and DUET 2 in antiretroviral treatment-experienced HIV-1 infected adult patients; 599 of whom received INTELENCE (200 mg b.i.d.) (see Pharmacodynamics properties). In these pooled trials, the median exposure for patients in the INTELENCE arm and placebo arm was 52,3 and 51,0 weeks, respectively.

The most frequent reported adverse reactions (ARs) that were at least grade 2 in severity were rash, diarrhoea, nausea and hypertriglyceridaemia.

Grade 3 and 4 ARs were reported in 22,2 % and 17,2 % of the INTELENCE and placebo treated patients, respectively. The most common reported grade 3 or 4 ARs were hypertriglyceridaemia (4,2 % in the INTELENCE arm and 2,3 % in the placebo arm) and hypercholesterolaemia (2,2 % in the INTELENCE arm and 2,3 % in the placebo arm), renal failure (2,0 % in the INTELENCE arm and 1,2 % in the placebo arm) and anaemia (1,7 % in

the INTELENCE arm and 1,3 % in the placebo arm). For treatment emergent clinical laboratory abnormalities (grade 3 or 4) reported in greater than or equal to 2 % of all INTELENCE treated patients, see table Treatment Emergent Laboratory Abnormalities. All other grade 3 and/or 4 ARs were reported in less than 1,5 % of the INTELENCE treated patients. 5,2 % of patients in the INTELENCE arm discontinued treatment due to ARs compared to 2,6 % of patients in the placebo arm. The most common AR leading to discontinuation was rash (2,2 % in the INTELENCE arm versus 0 % in the placebo arm).

Most frequently, rash was mild to moderate, occurred in the second week of therapy and was infrequent after week 4. Rash was mostly self-limiting and generally resolved within 1 to 2 weeks on continued therapy.

The incidence of rash was higher in women compared to men in the INTELENCE arm in the DUET trials (rash ≥ Grade 2 was reported in 9/60 [15,0 %] women versus 51/539 [9,5 %] men; discontinuations due to rash were reported in 3/60 [5,0 %] women versus 10/539 [1,9 %] men. In patients with a history of NNRTI- related rash, there was no apparent increased risk for the development of INTELENCE-related rash compared to patients without a history of NNRTI- related rash.

Adverse events in patients treated with INTELENCE in clinical studies are summarised in the table below. The adverse events are listed by system organ class (SOC) and frequency.

Adverse events at least possibly related in INTELENCE treated subjects. Adverse events appearing only in the placebo group are not shown in the table.

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).

Adverse reactions observed with etravirine in clinical trials		
System Organ Class (SOC)	**Frequency category**	**Adverse Reaction**
Blood and lymphatic system disorders	common	thrombocytopaenia, anaemia, decreased neutrophils
	uncommon	decreased white blood cell count
Immune system disorders	common	medicine hypersensitivity
	uncommon	immune reconstitution syndrome
Metabolism and nutrition disorders	common	diabetes mellitus, hyperglycaemia, hypercholesterolaemia, increased low density lipoprotein (LDL), hypertriglyceridaemia, hyperlipidaemia, dyslipidaemia, anorexia
Psychiatric disorders	common	anxiety, insomnia, sleep disorders
	uncommon	confusional state, disorientation, nightmares, nervousness, abnormal dreams
Nervous system disorders	very common	headache
	common	peripheral neuropathy, paraesthesia, hypoaesthesia, amnesia, somnolence
	uncommon	convulsion, syncope, tremor, hypersomnia, disturbance in attention
Eye disorders	common	blurred vision
Ear and labyrinth disorders	uncommon	vertigo
Cardiac disorders	common	myocardial infarction
	uncommon	atrial fibrillation, angina pectoris
Vascular disorders	common	hypertension
	rare	haemorrhagic stroke[a]
Respiratory, thoracic and mediastinal disorders	common	exertional dyspnoea
	uncommon	bronchospasm
Gastrointestinal disorders	very common	diarrhoea, nausea
	common	gastro-oesophageal reflux disease, vomiting, abdominal pain, abdominal

		distension, flatulence, gastritis, constipation, dry mouth, stomatitis, lipase increased, blood amylase increased
	uncommon	pancreatitis, haematemesis, retching
Hepatobiliary disorders	common	increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST)
	uncommon	hepatitis, hepatic steatosis, cytolytic hepatitis, hepatomegaly
Skin and subcutaneous tissue disorders	very common	rash
	common	lipohypertrophy, night sweats, dry skin, prurigo
	uncommon	angioneurotic oedema[a], swelling face, hyperhidrosis
	rare	Stevens-Johnson Syndrome[a], erythema multiforme[a]
	very rare	toxic epidermal necrolysis[a]
Renal and urinary disorders	common	renal failure, blood creatinine increased
Reproductive system and breast disorders	uncommon	gynaecomastia
General disorders and administration site conditions	common	fatigue
	uncommon	sluggishness
[a] These adverse reactions were observed in other clinical trials than DUET-1 and DUET-2.		

Laboratory abnormalities

Treatment emergent clinical laboratory abnormalities (grade 3 or 4), reported

in INTELENCE treated patients are shown in the table below.

Treatment emergent Grade 3 to 4 laboratory abnormalities reported

Pooled DUET 1 and DUET 2 trials			
Laboratory Parameter Preferred term n (%)	**DAIDS Toxicity range**	**Placebo DUET**	**TMC125 DUET**
GENERAL BIOCHEMISTRY			

PANCREATIC AMYLASE		**57 (9,4)**	**53 (8,9)**
Grade 3	> 2 to 5 x ULN	51 (8,4)	44 (7,4)
Grade 4	> 5 x ULN	6 (1,0)	9 (1,5)
LIPASE		**16 (2,6)**	**20 (3,4)**
Grade 3	> 3 to 5 x ULN	13 (2,2)	12 (2,0)
Grade 4	> 5 x ULN	3 (0,5)	8 (1,3)
CREATININE		**10 (1,7)**	**12 (2,0)**
Grade 3	1,9 to 3.4 x ULN	9 (1,5)	12 (2,0)
Grade 4	> 3,4 x ULN	1 (0,2)	0 (0)
GENERAL HAEMATOLOGY			
WHITE BLOOD CELL COUNT		**26 (4,3)**	**12 (2,0)**
Grade 3	1 to 1,499 x 10^9/l	22 (3,6)	6 (1,0)
Grade 4	< x 10^9/l	4 (0,7)	6 (1,0)
HAEMATOLOGY DIFFERENTIAL COUNTS			
NEUTROPHILS		**45 (7,5)**	**30 (5,1)**
Grade 3	0,5 to 0,749 x 10^9/l 500 to 749/mm^3	26 (4,3)	21 (3,5)
Grade 4	< 0,5 x 10^9/l < 500/mm^3	19 (3,1)	9 (1,5)
LIPIDS AND GLUCOSE			
TRIGLYCERIDES		**35 (5,8)**	**55 (9,2)**
Grade 3	8,49 to 13,56 mmol/l 751 to 1 200 mg/dl	24 (4,0)	34 (5,7)
Grade 4	> 13,56 mmol/l > 1 200 mg/dl	11 (1,8)	21 (3,5)

TOTAL CHOLESTEROL		**32 (5,3)**	**48 (8,1)**
Grade 3	> 7,77 mmol/l > 300 mg/dl	32 (5,3)	48 (8,1)
LOW DENSITY LIPOPROTEIN CALCULATED		**39 (6,6)**	**42 (7,2)**
Grade 3	> 4,9 mmol/l > 190 mg/dl	39 (6,6)	**42 (7,2)**
HYPERGLYCAEMIA		**14 (2,3)**	**21 (3,5)**
Grade 3	13,89 to 27.75 mmol/l 251 to 500 mg/dl	13 (2,2)	21 (3,5)
Grade 4	> 27,75 mmol/l > 500 mg/dl	1 (0,2)	0 (0)
LIVER FUNCTION			
ALANINE AMINO TRANSFERASE		**12 (2,0)**	**22 (3,7)**
Grade 3	5,1 to 10 x ULN	10 (1,7)	16 (2,7)
Grade 4	> 10 x ULN	2 (0,3)	6 (1,0)
ASPARTATE AMINO TRANSFERASE		**12 (2,0)**	**19 (3,2)**
Grade 3	5,1 to 10 x ULN	10 (1,7)	16 (2,7)
Grade 4	> 10 x ULN	2 (0,3)	3 (0,5)

ULN = Upper Limit of Normal

Lipodystrophy

Combination antiretroviral therapy 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*).

Immune Reconstitution Syndrome

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

Additional information on special populations

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

In the pooled analysis for DUET-1 and DUET-2, the safety profile in co-infected subjects (n=139) was comparable between the INTELENCE arm and the placebo arm. Among co-infected patients, grade 3 or 4 elevations in AST developed in 9,7 % of the 72 patients in the INTELENCE arm and in 6 % of the 67 patients in the placebo arm, and grade 3 or grade 4 elevations in ALT developed in 11,1 % of patients in the INTELENCE arm and in 7,5 % of patients in the placebo arm. Among co-infected patients, 1,4 % of those treated with INTELENCE and 3,0 % in the placebo arm discontinued because of liver or biliary system disorders. Standard clinical monitoring of patients with chronic hepatitis is considered adequate.

Adverse reactions from clinical trials with paediatric patients (1 year to less than 18 years of age):

The safety assessment in children and adolescents is based on two single-arm trials. PIANO is a Phase 2 trial in which 101 antiretroviral treatment-experienced HIV-1 infected paediatric

patients 6 years to less than 18 years of age received INTELENCE in combination with other antiretroviral agents. TMC125-C234/IMPAACT P1090 is a Phase 1/2 trial in which 26 antiretroviral treatment-experienced HIV-1 infected paediatric patients aged 1 year to less than 6 years received INTELENCE in combination with other antiretroviral agents. The frequency, type and severity of adverse reactions in paediatric patients were comparable to those observed in adults. Rash was reported more frequently in female subjects than in male subjects (rash ≥ Grade 2 was reported in 13/64 [20,3 %] females versus 2/37 [5,4 %] males; discontinuations due to rash were reported in 4/64 [6,3 %] females versus 0/37 [0 %] males). Most often, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy. Rash was mostly self-limiting and generally resolved within 1 week on continued therapy.

Postmarketing data

System Organ Class	Adverse Reaction
Immune system disorders	Hypersensitivity reactions, including DRESS [(Drug Rash with Eosinophilia and Systemic Symptoms) have been reported and were characterised by rash, constitutional findings, and infrequently organ dysfunction, including hepatic failure.]
Musculoskeletal and connective tissue disorders	Rhabdomyolysis

In a pharmacovigilance postmarketing epidemiologic study to define the long-term safety profile of etravirine in HIV 1 infected children and adolescents receiving etravirine with other HIV 1 antiretrovirals (N=182), Stevens Johnson Syndrome was reported at a higher incidence (1 %) than has been reported in adult clinical trials (< 0,1 %).

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

There is no specific antidote for overdose with INTELENCE. Treatment of overdose with INTELENCE consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Since etravirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Etravirine is a NNRTI of human immunodeficiency virus type 1 (HIV-1). Etravirine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. Etravirine can bind in at least 2 conformationally distinct modes. In vitro, within a given binding mode, torsional flexibility of etravirine permits access to numerous conformational variants, while the design of etravirine permits significant repositioning and reorientation (translation and

rotation) within the pocket. Etravirine does not inhibit the human DNA polymerases α, β and γ.

Antiviral activity in vitro

Etravirine exhibits activity against laboratory strains and clinical isolates of wild type HIV-1 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC50 values ranging from 0,9 nM to 5,5 nM (i.e. 0,4 to 2,4 ng/ml).

Etravirine demonstrates antiviral activity in vitro against a broad panel of HIV-1 group M (subtype A, B, C, D, E, F, G) and group O primary isolates with EC50 values ranging from 0,7 nM to 21,7 nM. These EC50 values are well below the 50 % cellular toxicity concentration range of 15 µM to > 100 µM.

The EC50 value of etravirine for HIV-1 increases by a median factor of 5,8 in the presence of human serum.

No antagonism is observed between etravirine and any of the studied antiretrovirals. Etravirine shows additive antiviral activity in combination with the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir and saquinavir; the N(t)RTIs zalcitabine, didanosine, stavudine, abacavir and tenofovir; the NNRTIs efavirenz, delavirdine and nevirapine and the fusion inhibitor enfuvirtide. Etravirine shows additive to synergistic antiviral activity in combination with the NRTIs emtricitabine, lamivudine and zidovudine.

Resistance

The amino acid substitutions, which led to the highest resistance to etravirine in cell culture are Y181I (13-fold change in EC50 value) and Y181V (17-fold change in EC50 value). The

antiviral activity of etravirine in cell culture against 24 HIV-1 strains with multiple amino acid substitutions associated with resistance to N(t)RTIs and/or PIs is comparable to that observed against wild type HIV-1.

In the Phase III trials, mutations that developed most commonly in patients with virologic failure to the INTELENCE-containing regimen were V179F, V179I, Y181C and Y181I which usually emerged in a background of multiple other NNRTI resistance-associated mutations (RAMs). In all the trials conducted with INTELENCE in HIV-1 infected patients, the following mutations emerged most commonly: L1001, E138G, V179F, V179I, Y181C and H221Y.

Cross-resistance

Limited cross-resistance between etravirine and efavirenz was observed in vitro in 3 of the 65 site directed HIV-1 mutant strains containing an NNRTI resistance associated mutation. For the other strains, the amino acid positions associated with decreased susceptibility to etravirine and efavirenz were different. Etravirine retains an EC50 value < 10 nM against 83 % of 6 171 clinical isolates resistant to delavirdine, efavirenz and/or nevirapine. The treatment of patients with delavirdine, efavirenz or nevirapine following virologic failure of an etravirine-containing regimen is not recommended.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

The pharmacokinetic properties of etravirine have been evaluated only in adult healthy subjects and in adult treatment-experienced HIV-1 infected patients. Exposure to etravirine was lower in HIV-1 infected patients than in healthy subjects.

Absorption

As an intravenous formulation of etravirine is unavailable, the absolute bioavailability of INTELENCE is unknown. After oral administration with food, the maximum plasma concentration of etravirine is generally achieved within 4 hours. In healthy subjects, the absorption of etravirine is not affected by co-administration of oral ranitidine or omeprazole, medicines that are known to increase gastric pH.

Effect of food on absorption

The exposure to etravirine is similar when taken following a standard normal caloric meal (561 kcal) or high-fat high caloric meal (1 160 kcal). When compared to administration following a standard normal caloric meal, exposures decreased when etravirine was taken before a standard normal caloric meal (17 %), following a croissant (20 %), or fasted (51 %). Therefore, to achieve optimal exposure, INTELENCE should be taken following a meal.

Distribution

Etravirine is approximately 99,9 % bound to plasma proteins, primarily to albumin (99,6 %) and α1-acid glycoprotein (97,66 % to 99,02 %) in vitro. The distribution of etravirine into compartments other than plasma (e.g. cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Metabolism

In vitro experiments with human liver microsomes (HLMs) indicate that etravirine primarily undergoes oxidative metabolism by the hepatic cytochrome CYP450 (CYP3A) system and, to a lesser extent, by the CYP2C family followed by glucuronidation.

Elimination

After administration of radiolabelled 14C-etravirine dose, 93,7 % and 1,2 % of the radioactivity could be retrieved in faeces and urine, respectively. Unchanged etravirine accounted for 81,2 % to 86,4 % of the administered dose in faeces. Unchanged etravirine was not detected in urine. The terminal half-life of etravirine was approximately 30 to 40 hours.

SPECIAL POPULATIONS

Children and adolescents (1 year to less than 18 years of age)

The pharmacokinetics of etravirine in 122 treatment-experienced HIV-1-infected paediatric patients, 1 year to less than 18 years of age, showed that the administered weight-based dosages resulted in etravirine exposure comparable to that in adults receiving INTELENCE 200 mg twice daily.

The pharmacokinetic parameters for etravirine (AUC_{12h} and C_{0h}) are summarized in the table below.

Pharmacokinetic parameters for etravirine in treatment-experienced HIV-1-infected paediatric patients 1 year to less than 18 years of age (PIANO [48 Weeks analysis, population PK] and TMC125-C234/IMPAACT P1090 [48 week analysis])

Study	**PIANO**	**TMC125-C234/ IMPAACT P1090**	**TMC125-C234/ IMPAACT P1090**
Age Range (years)	**(6 years to less than 18 years)**	**(2 years to less than 6 years) Cohort I**	**(1 year to less than 2 years old) Cohort II**
Parameter	**Etravirine** N=101	**Etravirine** N=15	**Etravirine** N=6
AUC_{12h} (ng•h/mL)			

Geometric Mean ± Standard Deviation	3729 ± 4305	3824 ± 3613	3328 ± 3138
Median (Range)	4560 (62 - 28865)	3709 (1221-12999)	3390 (1148 - 9989)
C_{0h} (ng•h/mL)			
Geometric Mean ± Standard Deviation	205 ± 342	203 ± 280	193 ± 186
Median (Range)	287 (2 - 2276)	180 (54 - 908)	147 (0[a] - 503)

Children (less than 1 year of age)

No data are available for children less than 1 year of age.

Elderly

Population pharmacokinetic analysis in HIV infected patients showed that etravirine pharmacokinetics are not considerably different in the age range (18 to 77 years) evaluated (*see section 4.2 and section 4.4*).

Hepatic impairment

Etravirine is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with mild (Child-Pugh score A) hepatic impairment to 8 matched controls and 8 patients with moderate (Child-Pugh score B) hepatic impairment to 8 matched controls, the multiple dose pharmacokinetic disposition of etravirine was not altered in patients with mild to moderate hepatic impairment. No dosing adjustment is required in patients with mild or moderate hepatic impairment. INTELENCE has not been studied in patients with severe hepatic impairment (Child-Pugh score C) (*see section 4.2 and section 4.4*).

Hepatitis B and/or hepatitis C virus co-infection

Population pharmacokinetic analysis of the clinical trials showed reduced clearance for INTELENCE in HIV-1 infected patients with hepatitis B and/or C virus co-infection. Based

upon the safety profile (see section 4.8), no dose adjustment is necessary in patients co-infected with hepatitis B and/or C virus, with mild to moderate hepatic impairment.

Renal impairment

The pharmacokinetics of etravirine have not been studied in patients with renal insufficiency. Results from a mass balance study with radioactive 14C-etravirine showed that < 1,2 % of the radioactivity of the administered dose of etravirine is excreted in the urine. No unchanged medicine was detected in urine so the impact of renal impairment on etravirine elimination is expected to be minimal. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (*see section 4.2 and section 4.4*).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

croscarmellose sodium

hypromellose

lactose monohydrate

magnesium stearate

microcrystalline cellulose

Contains sugar: Lactose monohydrate 160 mg

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.

Keep the bottle tightly closed in order to protect from moisture.

Do not remove the desiccant pouches.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

120 tablets are packed in a white, high density polyethylene container sealed with a polypropylene child resistant closure with an induction seal liner, together with 3 desiccant silica gel pouches and 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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