PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrINTELENCE®

etravirine tablets

tablets, 25 mg, 100 mg, 200 mg, oral

Human Immunodeficiency Virus (HIV) non-nucleoside reverse transcriptase inhibitor

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9
www.janssen.com/canada

Date of Initial Authorization:
March 27, 2008

Date of Revision:
October 14, 2022

Submission Control Number: 264392

RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.4 Administration	10/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

INTELENCE® (etravirine), in combination with other antiretroviral agents, is indicated for:

- the treatment of human immunodeficiency virus type 1 (HIV-1) infection in treatment-experienced adult and pediatric (from 6 to <18 years of age) patients who have failed prior therapy and have HIV-1 strains resistant to multiple antiretroviral agents, including NNRTIs (see 4 DOSAGE AND ADMINISTRATION).

The adult indication is based on safety and efficacy data at 48 weeks from two Phase III, double-blinded, placebo-controlled trials in treatment-experienced patients who had a least one NNRTI resistance-associated mutation and multiple primary protease inhibitor mutations (see 14 CLINICAL TRIALS for description of studies).

1.1 Pediatrics

Pediatrics (<6 years of age)
The safety and efficacy of Intelence in pediatric patients <6 years of age have not been established. Treatment with Intelence is not indicated for pediatric patients younger than 6 (see 7 WARNINGS AND PRECAUTIONS and 10.3 Pharmacokinetics)

Pediatrics (from 6 to <18 years of age)
Intelence, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced pediatric patients 6 years to <18 years of age, including those with NNRTI resistance.

This indication is based on 24-week analyses of a single-arm, on-going Phase II trial evaluating safety, PK, and antiretroviral activity in Intelence in antiretroviral treatment-experienced pediatric subjects 6 years to less than 18 years of age. The results of 48 weeks analysis were similar to those of 24 weeks (see 7 WARNINGS AND PRECAUTIONS, 4 DOSAGE AND ADMINISTRATION, and 10 CLINICAL PHARMACOLOGY).

1.2 Geriatrics

Geriatrics (>65 years of age)
Clinical studies of Intelence did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised when administering Intelence in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy (see 7 WARNINGS AND PRECAUTIONS, 4 DOSAGE AND ADMINISTRATION, and 10 CLINICAL PHARMACOLOGY).

2 CONTRAINDICATIONS

- Co-administration of Intelence is contraindicated with the combination ombitasvir/paritaprevir/ritonavir and with drugs containing dasabuvir (see 9 DRUG INTERACTIONS)
- Intelence (etravirine) is contraindicated in patients who are hypersensitive to etravirine or to any ingredient in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The following points should be considered when initiating therapy with Intelence:

- Do not use Intelence with only N[t]RTIs in the setting of previous NNRTI failure. This is based on an analysis of an exploratory Phase 2 clinical trial in patients who had experienced virologic failure on an NNRTI- and N[t]RTI-containing regimen (See 14 CLINICAL TRIALS for Description of Studies).
- The use of other active antiretroviral agents with Intelence is associated with an increased likelihood of treatment response.
- Treatment history and, when available, resistance testing, should guide the use of Intelence.
- The safety and efficacy of Intelence have not been established in treatment-naive adult/pediatric patients.
- Intelence must always be given in combination with other antiretroviral medicinal products.
- It is recommended that the dosage of Intelence be taken following a meal. The type of food does not affect the exposure to etravirine.
- Patients should be instructed to swallow the tablet(s) whole with a liquid such as water (see 4.4 Administration).

4.2 Recommended Dose and Dosage Adjustment

Adults
The recommended oral dose of Intelence tablets is 200 mg (one 200 mg tablet or two 100 mg tablets) taken twice daily (b.i.d.) following a meal (see 10.3 Pharmacokinetics).

Geriatric Patients
In general, caution should be exercised in the administration of Intelence in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy (see 1 INDICATIONS, 7 WARNINGS AND PRECAUTIONS and 10.3 Pharmacokinetics).

Pediatric Patients
Treatment-Experienced Pediatric Patients (from 6 to <18 years of age)
The recommended dose of Intelence for pediatric patients (6 years to <18 years of age and weighing at least 16 kg (35.2 lbs)) is based on body weight (see table below). Intelence tablet(s) should be taken orally, following a meal.

Table 1: Recommended dose of Intelence for pediatric patients 6 years to less than 18 years of age

Weight (kg)	Dose
≥16 to <20 kg	100 mg b.i.d.
≥20 to <25 kg	125 mg b.i.d.
≥25 to <30 kg	150 mg b.i.d.
≥30 kg	200 mg b.i.d.

Children (<6 years of age)
The safety and efficacy of Intelence in pediatric patients <6 years of age have not yet been established. Treatment with Intelence is not recommended in children younger than 6 (see 1 INDICATIONS, 7 WARNINGS AND PRECAUTIONS and 10.3 Pharmacokinetics).

Pregnancy
No dose adjustment is required during pregnancy and postpartum. Given the increased etravirine exposure during pregnancy, caution should be applied for those pregnant patients that require concomitant medications or have comorbidities that may further increase etravirine exposure.

Hepatic Impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment.
The pharmacokinetics of Intelence has not been studied in patients with severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, **Hepatic/Biliary/Pancreatic**, and 10.3 Pharmacokinetics, **Special Populations and Conditions**, **Hepatic insufficiency**).

Renal Impairment
No dose adjustment is required in patients with renal impairment (see 7 WARNINGS AND PRECAUTIONS, **Renal** and 10.3 Pharmacokinetics, **Special Populations and Conditions**, **Renal Insufficiency**).

4.4 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 liquid 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 grapefruit juice, warm liquids (>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.

4.5 Missed Dose

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.

5 OVERDOSAGE

There is no specific antidote for overdose with Intelence. Human experience of overdose with Intelence is limited. 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 be beneficial in significant removal of the active substance.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	tablet, 25 mg	colloidal andydrous silica, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.
Oral	tablet, 100 mg	colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.
Oral	tablet, 200 mg	colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, and silicified microcrystalline cellulose.

Intelence 25 mg tablets

Intelence tablets are supplied as white to off-white oval, scored tablets containing 25 mg of etravirine.

Each tablet is debossed with “T125” on one side. Intelence 25 mg tablets are packaged in bottles in the following configuration: 25 mg tablets—bottles of 120. Each bottle contains 2 desiccant pouches.

Intelence 100 mg tablets

Intelence tablets are supplied as white to off-white oval tablets containing 100 mg of etravirine.

Each tablet is debossed with “T125” on one side and “100” on the other side. Intelence 100 mg tablets are packaged in bottles in the following configuration: 100 mg tablets—bottles of 120. Each bottle contains 3 desiccant pouches.

Intelence 200 mg tablets

Intelence 200 mg tablets are available as white to off-white, biconvex, oblong tablets containing 200 mg of etravirine.

Each tablet is debossed with “T200” on one side. Intelence 200 mg tablets are packaged in bottles in the following configuration: 200 mg tablets—bottles of 60. Each bottle contains 3 desiccant pouches.

7 WARNINGS AND PRECAUTIONS

General

Patients with hereditary problems of lactose intolerance should not take this medicine.

Carcinogenesis and Mutagenesis

Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. A statistically significant increase in the incidences of hepatocellular adenomas and carcinomas was observed in treated female mice. Administration of etravirine did not cause a statistically significant increase in the incidence of tumors in female or male rats. The relevance of the findings in mice to humans is not known. At the highest tested doses, the systemic exposures (based on AUC) to etravirine were lower than those in humans at the clinical therapeutic dose (200 mg b.i.d) with animal versus human AUC ratios being 0.6 (mice) and between 0.2 and 0.7 (rats) (see 16 NON-CLINICAL TOXICOLOGY, **Carcinogenicity** and **Genotoxicity**).

Etravirine 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 presence and absence of the metabolic activation system. Etravirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice (see 16 NON-CLINICAL TOXICOLOGY, **Carcinogenicity** and **Genotoxicity**).

Endocrine and Metabolism

Serum Lipids and Blood Glucose
Serum lipids and blood glucose may increase during antiretroviral therapy. Disease control and lifestyle changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

Hepatic/Biliary/Pancreatic

Hepatic Impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. The pharmacokinetics of Intelence have not been studied in patients with severe hepatic impairment (see 4.2 Recommended Dosage and Dosage Adjustment, **Hepatic Impairment** and 10 CLINICAL PHARMACOLOGY, **Special Populations and Conditions**, **Hepatic Insufficiency**).

Pancreatitis
Pancreatitis has been reported infrequently (<1%) during clinical trials with Intelence. In the placebo-controlled Phase III DUET-1 and DUET-2 trials, the rate of clinical pancreatitis was similar in patients receiving Intelence 4/599 (0.7%) and placebo 2/604 (0.3%). Pancreatitis has been reported in one healthy volunteer (1/1093, 0.09%).

In the DUET trials asymptomatic Grade 3 or 4 increases in serum amylase levels were observed in a similar number of patients treated with Intelence (7.5%) and placebo (7.9%) (see 8 ADVERSE REACTIONS, **Laboratory Abnormalities**). Grade 3 or 4 elevated lipase levels were reported in 2.7% patients receiving Intelence compared to 1.7% of patients receiving placebo.

Immune

Immune Reconstitution
Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including Intelence. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP and TB), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, and autoimmune hepatitis, polymyositis and Guillain-Barré syndrome) 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 and sometimes there can be an atypical presentation.

Renal

Renal Impairment
Since the renal clearance of etravirine is minimal (<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 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, **Special Populations and Conditions**, **Renal Insufficiency**).

Skin

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking Intelence (etravirine). During both clinical development and postmarket, cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme have been reported. In a postmarketing epidemiologic study in HIV-1 infected children and adolescents

receiving Intelence along with other antiretrovirals, Stevens Johnson Syndrome was reported at a higher incidence (1%) than has been reported in adult clinical trials (< 0.1%). Hypersensitivity reactions including DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) have also been reported and were characterized by rash, constitutional findings, and infrequently 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, facial edema, 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.

In Phase III clinical trials, Grade 3 and 4 rashes were reported in 1.3% of subjects receiving Intelence compared to 0.2% of placebo subjects. A total of 2% of HIV-1-infected patients receiving Intelence discontinued from Phase III trials due to rash. 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 (see 8 ADVERSE REACTIONS).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies with etravirine in pregnant women. Studies in animals have not shown evidence of developmental toxicity or effect on reproductive function and fertility (see 16 NON-CLINICAL TOXICOLOGY, **Reproductive and Developmental Toxicity**).

Intelence (200 mg b.i.d.), was evaluated in combination with other antiretroviral agents in an open-label study of 15 pregnant women during the second and third trimesters of pregnancy and postpartum. Etravirine pharmacokinetic data are available for 13 women in the second trimester, 10 women in the third trimester and 10 women postpartum. The exposure to total etravirine was generally higher during pregnancy compared with postpartum, and less so for unbound etravirine exposure. Given the increased etravirine exposure during pregnancy, caution should be applied for those pregnant patients that require concomitant medications or have comorbidities that may further increase etravirine exposure (see 10 CLINICAL PHARMACOLOGY, **Special Populations and Conditions**, **Pregnancy and Postpartum**). There were no relevant clinical findings in the mothers or in the newborns in this trial.

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

Antiretroviral Pregnancy Registry: *To monitor maternal-fetal outcomes of pregnant women exposed to Intelence, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.*

7.1.2 Breast-feeding

Etravirine is excreted in human breast milk. Because of both the potential for HIV transmission and the potential for adverse events in nursing infants, mothers should be instructed not to breast-feed if they are receiving Intelence.

7.1.3 Pediatrics

The safety assessment in children and adolescents is based on the Week 24 analysis of the single arm, Phase II PIANO trial in which 101 antiretroviral treatment-experienced HIV-1 infected pediatric subjects 6 years to less than 18 years of age and weighing at least 16 kg (35.2 lbs), received Intelence in combination with other antiretroviral agents (see 8 ADVERSE REACTIONS).

The safety and effectiveness of Intelence in pediatric patients less than 6 years of age or in treatment-naive patients have not been established.

7.1.4 Geriatrics

There were insufficient numbers of subjects aged 65 and over in the clinical studies to determine whether they respond differently from younger subjects. In general, caution should be exercised when administering Intelence in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety assessment is based on all data from 1203 patients in the ongoing Phase III placebo-controlled trials in antiretroviral treatment-experienced HIV-1-infected adult patients [DUET-1 (TMC125-C206) and DUET-2 (TMC125-C216)], 599 of whom received Intelence (etravirine), 200 mg b.i.d. In these pooled trials, the median exposure for subjects in the Intelence arm and placebo arm was 52.3 and 51.0 weeks, respectively.

In total, 79.3% and 73.0% of the adult subjects experienced adverse drug reactions (ADRs; i.e., adverse events considered related to Intelence) with Intelence and placebo, respectively. The majority of the ADRs reported during treatment with Intelence were Grade 1 to 2 in severity. Grade 3 or 4 ADRs were reported in 22.2% and 17.2% of the Intelence- and placebo-treated subjects. The most commonly reported Grade 3 or 4 ADRs were hypertriglyceridemia (4.2% in the Intelence arm and 2.3% in the placebo arm), hypercholesterolemia (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 anemia (1.7% in the Intelence arm and 1.3% in the placebo arm). ADRs were reported as SAEs in 6.8% and 8.3% of subjects treated with Intelence and placebo, respectively. ADRs that led to permanent discontinuation of the investigational medication were reported in 5.2% of the Intelence-treated subjects and in 2.6% of the placebo-treated subjects. The most commonly reported ADRs (any grade) with Intelence identified from the pooled DUET trials were rash (any type), reported by 19.2% of Intelence-treated subjects and by 10.9% of placebo-treated subjects, diarrhea (18.0% and 23.5%), and nausea (14.9% and 12.8%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse drug reactions (ADRs) of moderate intensity or greater (≥Grade 2) and reported in ≥1% of adult subjects treated with Intelence (200 mg b.i.d.) in the DUET-1 and DUET-2 trials are presented in Table 2. Laboratory abnormalities considered ADRs are included in Table 4.

Table 2: Treatment-Emergent Adverse Reactions[1] of at Least Moderate Intensity (Grades 2-4) in ≥1% of Adult Subjects in the Intelence Treatment Groups

System Organ Class, Preferred Term, %	DUET-1 and DUET-2 Trials	
	Intelence + BR N=599	Placebo + BR N=604
Blood and Lymphatic System Disorders		
Anemia	4.0%	3.8%
Thrombocytopenia	1.3%	1.5%
Cardiac Disorders		
Myocardial infarction	1.3%	0.3%
Gastrointestinal Disorders		
Diarrhea	7.0%	11.3%
Nausea	5.2%	4.8%
Abdominal pain	3.5%	3.1%
Vomiting	2.8%	2.8%
Gastroesophageal reflux disease	1.8%	1.0%
Flatulence	1.5%	1.0%
Gastritis	1.5%	1.0%
General Disorders and Administration Site Conditions		
Fatigue	3.5%	4.6%
Metabolism and Nutrition Disorders		
Hypertriglyceridemia	6.3%	4.3%
Hypercholesterolemia	4.3%	3.6%
Hyperlipidemia	2.5%	1.3%
Hyperglycemia	1.5%	0.7%
Diabetes mellitus	1.3%	0.2%
Nervous System Disorders		
Peripheral neuropathy	3.8%	2.0%
Headache	3.0%	4.5%
Psychiatric Disorders		
Insomnia	2.7%	2.8%
Anxiety	1.7%	2.6%
Renal and Urinary Disorders		
Renal failure	2.7%	2.0%
Skin and Subcutaneous Tissue Disorders		
Rash	10.0%	3.5%
Lipohypertrophy	1.0%	0.3%
Night sweats	1.0%	1.0%

System Organ Class, Preferred Term, %	DUET-1 and DUET-2 Trials	
	Intelence + BR N=599	Placebo + BR N=604
Vascular Disorders		
Hypertension	3.2%	2.5%

N = total number of subjects per treatment group
BR = background regimen
1. Includes adverse reactions at least possibly, probably, or very likely related to the drug

Skin Rash
The most frequently reported adverse drug reaction of at least Grade 2 in severity in the Phase III studies was rash (10%). Stevens-Johnson syndrome, severe hypersensitivity reaction, and erythema multiforme were reported in <0.1% of adult subjects during clinical development with Intelence. A total of 2% of HIV-1-infected subjects receiving Intelence discontinued from Phase III trials due to rash. In general, rash was mild to moderate, macular to maculopapular or erythematous, occurred primarily in the second week of therapy and was infrequent after Week 4. Rash generally resolved within 1-2 weeks on continued therapy. In Phase III studies, the incidence of rash was higher in women compared to men in the Intelence arm (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). Patients with a history of NNRTI-related rash did not appear to be at increased risk for the development of Intelence-related rash compared to patients without a history of NNRTI-related rash. See Table 3 for a summary of rash events.

Table 3: Rash (Any Type) – Week 48 DUET Analysis

Rash Summary, n (%)	Placebo N=604	Pooled DUET Trials N=599
Rash (any type)	**66 (10.9)**	**115 (19.2)**
Grade 1	46 (7.6)	61 (10.2)
Grade 2	21 (3.5)	52 (8.7)
Grade 3	0	8 (1.3)
Onset in days, median	50.0	14.0
Duration in days, median	26.0	15.0
Leading to permanent stop	**0**	**13 (2.2)**
Vesicular Rash	**1 (0.2)**	**0**

N = number of subjects, n = number of subjects with observations

8.2.1 Clinical Trial Adverse Reactions - Pediatrics

Clinical Trial Experience in Pediatric Patients (6 years to <18 years)

The safety assessment in children and adolescents is based on the Week 24 analysis of the single arm, Phase II PIANO trial (TMC125-C213) in which 101 antiretroviral treatment-experienced HIV-1 infected pediatric subjects 6 years to <18 years of age and weighing at least 16 kg (35.2 lbs), received Intelence in combination with other antiretroviral agents (see 14 CLINICAL TRIALS). The frequency, type and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults. Adverse Reactions with at least Grade 2 in severity and occurred more than 2% in pediatric subjects were rash (14.9%), diarrrhea (5.9%), vomiting (4.0%), headache (4.0%), bronchospasm (3.0%), and hypercholesterolemia

(3.0%). 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). Rash was mostly mild to moderate and self-limiting, of macular/papular type, and occurred in the second week of therapy. Rash was generally resolved within 1 week on continued therapy. Rash including serious (Grade 3 or 4) events and discontinuations were more frequently observed in female subjects compared to male subjects. The safety profile for subjects who completed 48 weeks of treatment was similar to the safety profile of subjects who completed 24 weeks of treatment.

8.3 Less Common Clinical Trial Adverse Reactions

Treatment-emergent adverse drug reactions in the DUET-1 and DUET-2 trials (n=599) occurring in less than 1% of adult patients receiving Intelence (200 mg b.i.d.), and of at least moderate intensity (≥Grade 2) are listed below by body system:

Cardiac disorders: angina pectoris, atrial fibrillation

Ear and labyrinth disorders: vertigo

Eye disorders: blurred vision

Gastrointestinal disorders: abdominal distension, constipation, dry mouth, hematemesis, pancreatitis, retching, stomatitis

General disorders and administration site conditions: sluggishness

Hepatobiliary disorders: cytolytic hepatitis, hepatic steatosis, hepatitis, hepatomegaly

Immune system disorders: drug hypersensitivity, immune reconstitution inflammatory syndrome

Metabolism and nutrition disorders: anorexia, dyslipidemia

Nervous system disorders: convulsion, disturbance in attention, hypoesthesia, syncope, amnesia, hypersomnia, paraesthesia, somnolence, tremor

Psychiatric disorders: abnormal dreams, confusional state, disorientation, nervousness, nightmares, sleep disorders

Reproductive system and breast disorders: gynecomastia

Respiratory, thoracic and mediastinal disorders: bronchospasm, exertional dyspnea

Skin and subcutaneous tissue disorders: dry skin, hyperhidrosis, prurigo, swelling face

Additional ADRs observed in other trials occurring in less than 1% of patients receiving Intelence (200 mg b.i.d.), and of at least moderate intensity (≥ Grade 2) are listed below by body system:

Metabolism and nutrition disorders: acquired lipodystrophy

Nervous system disorders: haemorrhagic stroke

Skin and subcutaneous tissue disorders: angioneurotic edema, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis

Additional ADRs of at least moderate intensity observed in other trials were acquired lipodystrophy, angioneurotic edema, erythema multiforme and haemorrhagic stroke, each reported in no more than 0.5% of subjects. Stevens-Johnson syndrome has been reported rarely (<0.1%) during clinical development with Intelence.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Treatment-emergent clinical laboratory abnormalities (Grade 3 or 4) observed in adult patients and reported in greater than or equal to 2% of Intelence-treated subjects are presented in the table below. All other Grade 3 or 4 abnormal laboratory parameters were observed in less than 2% of the Intelence-treated subjects.

Table 4: Treatment Emergent Grade 3 to 4 Laboratory Abnormalities Reported in ≥2% of Adult Subjects

	Pooled DUET-1 and DUET-2 Trials	
Laboratory Parameter Preferred Term, n (%)	**Intelence + BR N=599**	**Placebo + BR N=604**
GENERAL BIOCHEMISTRY		
Pancreatic amylase	**53 (8.9)**	**57 (9.4)**
Grade 3	44 (7.4)	51 (8.4)
Grade 4	9 (1.5)	6 (1.0)
Creatinine	**12 (2.0)**	**10 (1.7)**
Grade 3	12 (2.0)	9 (1.5)
Grade 4	0 (0)	1 (0.2)
Lipase	**20 (3.4)**	**16 (2.6)**
Grade 3	12 (2.0)	13 (2.2)
Grade 4	8 (1.3)	3 (0.5)
GENERAL HEMATOLOGY		
White blood cell count	**12 (2.0)**	**26 (4.3)**
Grade 3	6 (1.0)	22 (3.6)
Grade 4	6 (1.0)	4 (0.7)
HEMATOLOGY DIFFERENTIAL COUNTS		
Neutrophils	**30 (5.1)**	**45 (7.5)**
Grade 3	21 (3.5)	26 (4.3)
Grade 4	9 (1.5)	19 (3.1)
LIPIDS AND GLUCOSE		
Total cholesterol	**48 (8.1)**	**32 (5.3)**
Grade 3	48 (8.1)	32 (5.3)
Low density lipoprotein	**42 (7.2)**	**39 (6.6)**
Grade 3	42 (7.2)	39 (6.6)
Elevated glucose levels	**21 (3.5)**	**14 (2.3)**
Grade 3	21 (3.5)	13 (2.2)
Grade 4	0 (0)	1 (0.2)
Triglycerides	**55 (9.2)**	**35 (5.8)**
Grade 3	34 (5.7)	24 (4.0)

	Pooled DUET-1 and DUET-2 Trials	
Laboratory Parameter Preferred Term, n (%)	**Intelence + BR N=599**	**Placebo + BR N=604**
Grade 4	21 (3.5)	11 (1.8)
HEPATIC PARAMETERS		
Alanine amino transferase	**22 (3.7)**	**12 (2.0)**
Grade 3	16 (2.7)	10 (1.7)
Grade 4	6 (1.0)	2 (0.3)
Aspartate amino transferase	**19 (3.2)**	**12 (2.0)**
Grade 3	16 (2.7)	10 (1.7)
Grade 4	3 (0.5)	2 (0.3)

BR = Background regimen

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 adult subjects (139) was generally comparable between subjects receiving Intelence and subjects receiving placebo. There was a higher incidence of hepatic and biliary system disorders in co-infected subjects treated with Intelence (12.5% of 72 subjects) compared to co-infected subjects in the placebo group (9.0% of 67 subjects). No specific pattern or type of event was observed.

Among co-infected subjects:

- Grade 3 or 4 elevations in AST developed in 9.7% of subjects in the Intelence arm compared to 6.0% of subjects in the placebo arm;

- Grade 3 or 4 elevations in ALT developed in 11.1% of subjects in the Intelence arm compared to 7.5% of subjects in the placebo arm;

- Grade 3 or 4 elevations in bilirubin developed in 5.7% of subjects in the Intelence arm compared to 1.5% of subjects in the placebo arm.

8.5 Post-Market Adverse Reactions

Immune system disorders: Immune reconstitution inflammatory syndrome, Severe hypersensitivity reactions including DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) with cases of hepatic failure (see 7 WARNINGS AND PRECAUTIONS, **Immune**).

Skin and subcutaneous tissue disorders: Fatal cases of toxic epidermal necrolysis (see 7 WARNINGS AND PRECAUTIONS, **Skin**).

Musculoskeletal and connective tissue disorders: Myopathy, Rhabdomyolysis

Post Marketing Studies in Pediatric Patients:

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%).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Etravirine is metabolized by cytochrome CYP3A4, CYP2C9 and CYP2C19 followed by glucuronidation of the metabolites by uridine diphosphate glucuronosyltransferase (UDPGT). Therefore, co-administration of Intelence with drugs that induce or inhibit CYP3A, CYP2C9, or CYP2C19 may result in altered plasma concentrations of etravirine and alter the therapeutic effect or adverse reaction profile of Intelence.

Etravirine is an inducer of CYP3A4, and an inhibitor of CYP2C9, CYP2C19 and P-glycoprotein. Therefore, co-administration of drugs that are substrates of CYP3A4, CYP2C9, CYP2C19 or that are transported by the P-glycoprotein with Intelence may result in altered plasma concentrations and alter the therapeutic effect or adverse reaction profile of the co-administered drug(s).

9.4 Drug-Drug Interactions

Co-adminitstration of Intelence is contraindicated with the combination ombitasvir/paritaprevir/ritonavir and with drugs containing dasabuvir because decrease in exposure (CYP3A induction by etravirine) may lead to a potential loss of therapeutic activity of ombitasvir/paritaprevir/ritonavir or dasabuvir (see 2 CONTRAINDICATIONS).

Drugs that are not recommended for co-administration with Intelence are included in Table 5. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 5: Drugs That Should Not Be Co-administered With Intelence

Concomitant Drug Class: Drug Name	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
efavirenz nevirapine delavirdine rilpivirine	Combining two NNRTIs has not been shown to be beneficial. Concomitant use of Intelence with efavirenz or nevirapine may cause a decrease in the plasma concentrations of etravirine and loss of therapeutic effect of Intelence. Intelence and other NNRTIs should not be co-administered. Combining two NNRTIs has not been shown to be beneficial. Intelence and delavirdine or rilpivirine should not be co-administered.
HIV-Antiviral Agents: HIV Protease Inhibitors (PIs)—Unboosted (i.e., without co-administration of low-dose ritonavir)	
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.

Concomitant Drug Class: Drug Name	Clinical Comment
atazanavir nelfinavir indinavir	Concomitant use of Intelence without co-administration of low-dose ritonavir may cause a significant alteration in the plasma concentrations of the PI. Intelence should not be co-administered with PIs without low-dose ritonavir.
HIV-Antiviral Agents: HIV Protease Inhibitors (PIs)—Boosted (with co-administration of low-dose ritonavir)	
fosamprenavir/ritonavir	An increase of 69% for amprenavir exposure was observed when fosamprenavir/ritonavir was co-administered in the presence of etravirine. Appropriate doses of the combination of Intelence and fosamprenavir/ritonavir have not been established. Intelence and fosamprenavir/ritonavir should not be co-administered.
tipranavir/ritonavir	Concomitant use of Intelence with tipranavir/low-dose ritonavir may cause a significant decrease in the plasma concentration of etravirine and loss of therapeutic effect of Intelence. Tipranavir/low-dose ritonavir and Intelence should not be co-administered.
HIV-Antiviral Agents: HIV Protease Inhibitiors (PIs) – Boosted (with co-administration of 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.
Hepatitis C Virus (HCV) Direct-Acting Antivirals:	
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.
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 and loss of therapeutic effect of Intelence.

Concomitant Drug Class: Drug Name	Clinical Comment
Antimycobacterials: rifampin	Rifampin is a potent inducer of CYP450 enzymes. Intelence should not be used in combination with rifampin as co-administration may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of 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 and loss of therapeutic effect of Intelence.

Established and other potentially significant drug interactions with Intelence are included in Table 6. These recommendations are based on either drug interaction studies or predicated interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)		
didanosine[1]	↔ etravirine ↔ didanosine	No dose adjustments for Intelence and didanosine are needed when co-administered. 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[1]	↓ etravirine ↔ tenofovir	No dose adjustments for Intelence and tenofovir disoproxil fumarate are needed when co-administered.
Other NRTIs: Based on the primarily renal elimination route for other NRTIs (e.g., abacavir, emtricitabine, lamivudine, stavudine, and zidovudine), no drug interactions are expected between these drugs and Intelence.		
HIV-Antiviral Agents: Protease Inhibitors (PIs)—Boosted (with co-administration of low-dose ritonavir)		
atazanavir/ritonavir	↔ etravirine ↓ atazanavir	Concomitant use of Intelence with atazanavir/ritonavir may decrease, in some cases significantly, the C_{min} of atazanavir. Caution should be exercised when Intelence is co-administered with atazanavir/ritonavir. Close monitoring for HIV virologic response is recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
darunavir/ritonavir[1]	↓ etravirine ↔ darunavir	The mean systemic exposure (AUC) of etravirine was reduced by 37% when Intelence was co-administered with darunavir/ritonavir. However, the combination of darunavir/ritonavir and etravirine was used safely and effectively in the Phase III trials, therefore, no dose adjustments for Intelence and darunavir/ritonavir are needed when co-administered.
lopinavir/ritonavir (soft gel capsule)[1]	↑ etravirine ↓ lopinavir	The mean systemic exposure (AUC) of etravirine after co-administration of Intelence with lopinavir/ritonavir is anticipated to be about 85% higher than the mean AUC of etravirine observed in the Phase III trials[2]. The amount of safety data at these increased etravirine exposures is limited, therefore, Intelence and lopinavir/ritonavir should be co-administered with caution.
lopinavir/ritonavir (tablet)[1]	↔ lopinavir ↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced by approximately 35% after co-administration with lopinavir/ritonavir. This reduction is similar to the reduction in the mean systemic exposure of etravirine in the presence of darunavir/ritonavir observed in Phase III trials, therefore Intelence can be co-administered with the tablet formulation of lopinavir/ritonavir without dose adjustments.
saquinavir/ritonavir[1]	↓ etravirine ↔ saquinavir	The mean systemic exposure (AUC) of etravirine was reduced by about 33% after co-administration of Intelence and saquinavir/ritonavir. The reduction in the mean systemic exposures of etravirine in the presence of saquinavir/ritonavir is similar to the reduction in mean systemic exposures of etravirine in the presence of darunavir/ritonavir, therefore, no dose adjustments for Intelence and saquinavir/ritonavir are needed when co-administered.
HIV-Antiviral Agents: Dual Boosted HIV Protease Inhibitors		
lopinavir/saquinavir/ ritonavir[1]	↔ etravirine ↓ lopinavir ↓ saquinavir	No dose adjustments for Intelence and lopinavir/saquinavir/ritonavir are needed when co-administered.

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
CCR5 Antagonists		
maraviroc	↔ etravirine ↓ maraviroc	Concomitant use of Intelence with maraviroc may cause a significant decrease (53%) in the plasma concentration of maraviroc. When Intelence is co-administered with maraviroc in the absence of a potent CYP3A4 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/ ritonavir	↔ etravirine ↑ maraviroc	When Intelence is co-administered with maraviroc in the presence of a potent CYP3A inhibitor (e.g., a boosted PI), the recommended dose of maraviroc is 150 mg b.i.d. No dose adjustment of Intelence is needed.
HIV-Antiviral Agents: Fusion Inhibitors		
enfuvirtide	↔ etravirine ↔ enfuvirtide	No interaction is expected for either Intelence or enfuvirtide when co-administered.
HIV-Antiviral Agents: Integrase Strand Transfer Inhibitors		
dolutegravir	↔ etravirine ↓ dolutegravir	Intelence significantly reduced plasma concentrations of dolutegravir. Using cross-study comparisons to historical pharmacokinetic data for Intelence, dolutegravir did not appear to affect the pharmacokinetics of Intelence.
dolutegravir/darunavir /ritonavir	↔ etravirine ↓ dolutegravir	The effect of Intelence 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.
dolutegravir/lopinavir /ritonavir	↔ etravirine ↔ dolutegravir	

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
raltegravir[1]	↔ etravirine ↓ raltegravir	No dose adjustment s for Intelence and raltegravir are needed when co-administered.
Other Agents		
Antiarrhythmics: amiodarone bepridil disopyramide flecainide lidocaine (systemic) mexiletine propafenone quinidine	↓ antiarrhythmics	Concentrations of these antiarrhythmics may be decreased when co-administered with Intelence. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with Intelence.
digoxin	↑ digoxin ↔ etravirine	No dose adjustments for Intelence and digoxin are needed when co-administered. It is recommended that digoxin levels be monitored when digoxin is combined with Intelence.
Anticoagulants: warfarin	↑ warfarin	Warfarin concentrations may be affected when co-administered with Intelence. Co-administration of Intelence and warfarin is anticipated to cause an increase in warfarin exposures, while etravirine exposures are not expected to change. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with Intelence.

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
Anti-infectives: azithromycin	↔ etravirine ↔ azithromycin	Based on the renal elimination pathway of azithromycin, no drug interactions are expected between azithromycin and Intelence.
clarithromycin[1]	↑ etravirine ↓ clarithromycin ↑ 14-OH-clarithromycin	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	↔ etravirine ↓ artemether ↓ dihydroartemisinin ↓ lumefantrine	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.
Antifungals: fluconazole	↔ fluconazole ↑ etravirine ↑ voriconazole	The plasma concentrations of Intelence are increased when co-administered with fluconazole (a potent inhibitor of CYP2C9) or with voriconazole, (a substrate and inhibitor of CYP3A, CYP2C9 and CYP2C19). The mean systemic exposure (AUC) of etravirine after co-administration of Intelence with fluconazole or voriconazole in the absence of a boosted HIV protease inhibitor is anticipated to be about 194% and 114% higher, respectively, as compared to the mean AUC of etravirine observed in Phase III trials[2]. There is limited safety data on these increased etravirine exposures. Therefore Intelence and either fluconazole or voriconazole should be co-administered with caution. Dose adjustments for voriconazole may be necessary depending on other co-administered drugs.
Itraconazole posaconazole ketoconazole	↑ etravirine ↓ itraconazole ↔ posaconazole ↓ ketoconazole	Posaconazole is a potent inhibitor of CYP3A and may increase plasma concentrations of etravirine. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of itraconazole or ketoconazole and Intelence may increase plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by Intelence. Dose adjustments for itraconazole or ketoconazole may be necessary depending on other co-administered drugs.

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
Antimycobacterials: rifabutin[1]	↓ etravirine ↓ rifabutin ↓ 25-O-desacetylrifabutin	The combination of Intelence and rifabutin should be used with caution due to the risk of decrease in etravirine and rifabutin exposures. If Intelence is co-administered with darunavir/ritonavir, saquinavir/ritonavir or the tablet formulation of lopinavir/ritonavir, then rifabutin should not be co-administered due to the potential for significant reductions in etravirine exposure.
Benzodiazepines: diazepam	↑ diazepam	Concomitant use of Intelence with diazepam may increase plasma concentrations of diazepam. A decrease in diazepam dose may be needed.
Corticosteroids: dexamethasone (systemic)	↓ etravirine	Systemic dexamethasone induces CYP3A 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[1] norethindrone[1]	↔ etravirine ↑ ethinylestradiol ↔ norethindrone	No dose adjustments for Intelence and estrogen and/or progesterone based contraceptives are needed when co-administered.
Hepatitis C Virus (HCV) Direct-Acting Antivirals: daclatasvir ribavirin	↓ daclatasvir	Co-administration of Intelence with daclatasvir may decrease daclatasvir concentrations. Increase the daclatasvir dose to 90 mg once daily. Based on the renal elimination pathway of ribavirin, no drug interactions are expected between ribavirin and Intelence.
HMG-CoA Reductase Inhibitors: atorvastatin[1]	↔ etravirine ↓ atorvastatin ↑ 2-OH-atorvastatin	Atorvastatin plasma concentrations are decreased 37% and plasma concentrations of the active metabolite, 2-hydroxy-atorvastatin, are increased by 27% when combined with Intelence. Dose adjustment of atorvastatin may be necessary to tailor the clinical response when combined with Intelence.

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
fluvastatin lovastatin pravastatin rosuvastatin simvastatin	↔ etravirine ↑ fluvastatin ↓ lovastatin ↔ pravastatin ↔ rosuvastatin ↓ simvastatin	No interaction between pravastatin and Intelence is expected. Lovastatin, rosuvastatin, and simvastatin are CYP3A substrates and co-administration with Intelence may result in lower plasma concentrations of the HMG-CoA reductase inhibitor. Fluvastatin and rosuvastatin are metabolized by CYP2C9. Co-administration of fluvastatin with Intelence may result in higher plasma concentrations of the HMG-CoA reductase inhibitor. Dose adjustments for fluvastatin may be necessary. No interaction between rosuvastatin and Intelence is expected.
H_2-Receptor Antagonists: ranitidine[1]	↓ etravirine	No dose adjustment of Intelence is needed when co-administered with H_2 receptor antagonists.
Immunosuppressants: cyclosporine sirolimus tacrolimus	↓ 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[1]	↔ etravirine ↔ R(-) methadone ↔ S(+) methadone	Intelence and methadone may be co-administered without dose adjustments, however, clinical monitoring for withdrawal symptoms is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Phosphodiesterase Type 5 (PDE-5) Inhibitors: sildenafil[1] vardenafil tadalafil	↓ sildenafil ↓ N-desmethyl-sildenafil	Sildenafil plasma concentrations are decreased by 57% and plasma concentrations of the active metabolite, N-desmethyl-sildenafil, are decreased by 41% when combined with Intelence. 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 Inhibitors: 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[1]	↑ etravirine	No dose adjustment of Intelence is needed when co-administered with proton pump inhibitors.
Selective Serotonin Reuptake Inhibitors (SSRIs): paroxetine[1]	↔ etravirine ↔ paroxetine	No dose adjustment of Intelence is needed when co-administered with paroxetine.

↑ = increases, ↓ = decreases, ↔ = no change

1. The interaction between Intelence and the drug was evaluated in a clinical trial. All other drug interactions shown are predicted.
2. The expected increase in systemic exposure of etravirine when co-administered with either lopinavir/ritonavir tablet (~85%), fluconazole (~194%) or voriconazole (~114%) is theoretical and is based on comparisons of etravirine exposures from drug-drug interaction studies to those in the pivotal Phase III trials (in which darunavir/ritonavir was co-administered as part of the background regimen).

Drug interaction studies were performed with etravirine and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of etravirine on the AUC, C_{max}, and C_{min} values are summarized in Table 7 and Table 8. Different formulations and/or doses were used which led to similar exposures and, therefore, interactions relevant for one formulation are relevant for the other.

Table 7: Drug Interactions: Pharmacokinetic Parameters for Etravirine in the Presence of Co-administered Drugs[1]

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	PK	Mean Ratio of Etravirine Pharmacokinetic Parameters 90% CI; No Effect = 1.00		
				C_{max}	AUC	C_{min}
Co-Administration With Protease Inhibitors (PIs)						
atazanavir	400 mg q.d.	14	↑	1.47 (1.36-1.59)	1.50 (1.41-1.59)	1.58 (1.46-1.70)
atazanavir/ ritonavir[3]	300/100 mg q.d.	14	↑	1.30 (1.17-1.44)	1.30 (1.18-1.44)	1.26 (1.12-1.42)
darunavir/ ritonavir	600/100 mg b.i.d.	14	↓	0.68 (0.57-0.82)	0.63 (0.54-0.73)	0.51 (0.44-0.61)
fosamprenavir/ ritonavir	700/100 mg b.i.d.	8	↔	N.A.	N.A.	N.A.
lopinavir/ ritonavir (soft gel capsule)	400/100 mg b.i.d.	13	↑	1.15 (0.94-1.41)	1.17 (0.96-1.43)	1.23 (0.98-1.53)
lopinavir/ritonavir (tablet)	400/100 mg b.i.d.	16	↓	0.70 (0.64-0.78)	0.65 (0.59-0.71)	0.55 (0.49-0.62)
ritonavir	100 mg single dose	18	↔	1.00 (0.89-1.12)	1.03 (0.91-1.17)	N.A.
ritonavir	600 mg b.i.d.	11	↓	0.68 (0.55-0.85)	0.54 (0.41-0.73)	N.A.
saquinavir/ ritonavir	1000/100 mg b.i.d.	14	↓	0.63 (0.53-0.75)	0.67 (0.56-0.80)	0.71 (0.58-0.87)
tipranavir/ ritonavir	500/200 mg b.i.d.	19	↓	0.29 (0.22-0.40)	0.24 (0.18-0.33)	0.18 (0.13-0.25)
Co-Administration with Dual Boosted Protease Inhibitors (PIs)						
lopinavir/ saquinavir/ ritonavir	400 mg/800-1000 mg/100 mg b.i.d.	11	↔	N.A.	N.A.	N.A.
Co-Administration With Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
didanosine	400 mg q.d.	15	↔	1.16 (1.02-1.32)	1.11 (0.99-1.25)	1.05 (0.93-1.18)
tenofovir disoproxil fumarate	300 mg q.d.	23	↓	0.81 (0.75-0.88)	0.81 (0.75-0.88)	0.82 (0.73-0.91)
Co-Administration With CCR5 Antagonists						

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	PK	Mean Ratio of Etravirine Pharmacokinetic Parameters 90% CI; No Effect = 1.00		
				C_{max}	AUC	C_{min}
maraviroc	300 mg b.i.d.	14	↔	1.05 (0.97-1.17)	1.06 (0.99-1.14.)	1.08 (0.98-1.19)
Co-Administration With Fusion Inhibitors						
enfuvirtide	90 mg b.i.d.	261	↔[2]	N.A.	N.A.	N.A.
Co-Administration With Integrase Strand Transfer Inhibitors						
raltegravir	400 mg b.i.d.	19	↔	1.04 (0.97-1.12)	1.10 (1.03-1.16)	1.17 (1.10-1.26)
Co-Administration With Other Drugs						
atorvastatin	40 mg q.d.	16	↔	0.97 (0.93-1.02)	1.02 (0.97-1.07)	1.10 (1.02-1.19)
boceprevir	800 mg t.i.d.	20	↓	0.76 (0.68-0.85)	0.77 (0.66-0.91)	0.71 (0.54-0.95)
clarithromycin	500 mg b.i.d.	15	↑	1.46 (1.38-1.56)	1.42 (1.34-1.50)	1.46 (1.36-1.58)
ethinylestradiol/ norethindrone	0.035 mg q.d./ 1 mg q.d.	16	↔	N.A.	N.A.	N.A.
fluconazole	200 mg q.a.m.	16	↑	1.75 (1.60-1.91)	1.86 (1.73-2.00)	2.09 (1.90-2.31)
methadone	Individual dose regimen ranging from 60 to 130 mg/day	16	↔	N.A.	N.A.	N.A.
omeprazole	40 mg q.d.	18	↑	1.17 (0.96-1.43)	1.41 (1.22-1.62)	N.A.
paroxetine	20 mg q.d.	16	↔	1.05 (0.96-1.15)	1.01 (0.93-1.10)	1.07 (0.98-1.17)
Ranitidine	150 mg b.i.d.	18	↓	0.94 (0.75-1.17)	0.86 (0.76-0.97)	N.A.
Rifabutin	300 mg q.d.	12	↓	0.63 (0.53-0.74)	0.63 (0.54-0.74)	0.65 (0.56-0.74)
voriconazole	200 mg b.i.d.	16	↑	1.26 (1.16-1.38)	1.36 (1.25-1.47)	1.52 (1.41-1.64)

CI = Confidence Interval; N = maximum number of subjects with data; N.A. = not available; ↑ = increases; ↓ = decreases; ↔ = no change; q.d. = once daily; b.i.d. = twice daily; t.i.d. = three times daily; q.a.m. = once daily in the morning

1. In drug-drug 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.
2. Based on population pharmacokinetic analysis
3. The systemic exposure of etravirine when co-administered with atazanavir/ritonavir in HIV infected patients is similar to exposures of etravirine observed in the Phase III trials after co-administration of Intelence and darunavir/ritonavir (as part of the background regimen).

Table 8: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Etravirine[1]

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	PK	Mean Ratio of Co-administered Drug Pharmacokinetic Parameters 90% CI; No effect = 1.00		
				C_{max}	AUC	C_{min}
Co-Administration With Protease Inhibitors (PIs)						
atazanavir	400 mg q.d.	14	↓	0.97 (0.73-1.29)	0.83 (0.63-1.09)	0.53 (0.38-0.73)
atazanavir/ ritonavir	300/100 mg q.d.	13	↓	0.97 (0.89-1.05)	0.86 (0.79-0.93)	0.62 (0.55-0.71)
darunavir/ ritonavir	600/100 mg b.i.d.	15	↔	1.11 (1.01-1.22)	1.15 (1.05-1.26)	1.02 (0.90-1.17)
fosamprenavir/ ritonavir	700/100 mg b.i.d.	8	↑	1.62 (1.47-1.79)	1.69 (1.53-1.86)	1.77 (1.39-2.25)
lopinavir/ ritonavir (soft gel capsule)	400/100 mg b.i.d.	14	↓	0.85 (0.62-1.05)	0.80 (0.49-1.07)	0.92 (0.15-1.68)
lopinavir/ritonavir (tablet)	400/100 mg b.i.d.	16	↔	0.89 (0.82-0.96)	0.87 (0.83-0.92)	0.80 (0.73-0.88)
lopinavir/ saquinavir/ ritonavir	400 mg b.i.d./ 800-1000 mg b.i.d./ 100 mg b.i.d.	11	↓ LPV	0.84 (0.74-0.95)	0.82 (0.70-0.96)	0.76 (0.54-1.08)
		11	↓ SQV	0.85 (0.61-1.19)	0.87 (0.62-1.21)	0.87 (0.60-1.28)
saquinavir/ ritonavir	1000/100 mg b.i.d.	15	↔	1.00 (0.70-1.42)	0.95 (0.64-1.42)	0.80 (0.46-1.38)
tipranavir/ ritonavir	500/200 mg b.i.d.	19	↑	1.14 (1.02-1.27)	1.18 (1.03-1.36)	1.24 (0.96-1.59)
Co-Administration With CCR5 Antagonists						
maraviroc	300 mg b.i.d.	10	↓	0.40 (0.28-0.57)	0.47 (0.38-0.58)	0.61 (0.53-0.71)
maraviroc/darunavir/ ritonavir *compared to maraviroc 150 mg b.i.d.	150 mg/600 mg/100 mg b.i.d.	10	↑	1.77* (1.20-2.60)	3.10* (2.57-3.74)	5.27* (4.51-6.15)
Co-Administration With Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
didanosine	400 mg q.d.	14	↔	0.91 (0.58-1.42)	0.99 (0.79-1.25)	N.A.
tenofovir disoproxil fumarate	300 mg q.d.	19	↔	1.15 (1.04-1.27)	1.15 (1.09-1.21)	1.19 (1.13-1.26)
Co-Administration With Integrase Strand Transfer Inhibitors						
dolutegravir	50 mg q.d.	16	↓	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
dolutegravir (when co-administered with darunavir/ritonavir)	50 mg q.d./ 600/100 mg b.i.d.	9	↓	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
dolutegravir (when	50 mg q.d./	8	↔	1.07	1.11	1.28

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	PK	Mean Ratio of Co-administered Drug Pharmacokinetic Parameters 90% CI; No effect = 1.00		
				C_{max}	AUC	C_{min}
co-administered with lopinavir/ritonavir)	400/100 mg b.i.d.			(1.02 to 1.13)	(1.02 to 1.20)	(1.13 to 1.45)
raltegravir	400 mg b.i.d.	19	↓	0.89 (0.68-1.15)	0.90 (0.68-1.18)	0.66 (0.34-1.26)
Co-Administration With Other Drugs						
atorvastatin	40 mg q.d.	16	↓	1.04 (0.84-1.30)	0.63 (0.58-0.68)	N.A.
2-hydroxy-atorvastatin		16	↑	1.76 (1.60-1.94)	1.27 (1.19-1.36)	N.A.
boceprevir	800 mg t.i.d.	20	↑	1.10 (0.94-1.29)	1.10 (0.94-1.28)	0.88 (0.66-1.17)
clarithromycin	500 mg b.i.d.	15	↓	0.66 (0.57-0.77)	0.61 (0.53-0.69)	0.47 (0.38-0.57)
14-hydroxy-clarithromycin		15	↑	1.33 (1.13-1.56)	1.21 (1.05-1.39)	1.05 (0.90-1.22)
digoxin	0.5 mg single dose	16	↑	1.19 (0.96-1.49)	1.18 (0.90-1.56)	N.A.
ethinyl estradiol	0.035 mg q.d.	16	↑	1.33 (1.21-1.46)	1.22 (1.13-1.31)	1.09 (1.01-1.18)
norethindrone	1 mg q.d.	16	↔	1.05 (0.98-1.12)	0.95 (0.90-0.99)	0.78 (0.68-0.90)
fluconazole	200 mg q.a.m.	15	↔	0.92 (0.85-1.00)	0.94 (0.88-1.01)	0.91 (0.84-0.98)
R(-) methadone	Individual dose regimen ranging from 60 to 130 mg/day	16	↔	1.02 (0.96-1.09)	1.06 (0.99-1.13)	1.10 (1.02-1.19)
S(+) methadone		16	↔	0.89 (0.83-0.97)	0.89 (0.82-0.96)	0.89 (0.81-0.98)
paroxetine	20 mg q.d.	16	↔	1.06 (0.95-1.20)	1.03 (0.90-1.18)	0.87 (0.75-1.02)
rifabutin	300 mg q.d.	12	↓	0.90 (0.78-1.03)	0.83 (0.75-0.94)	0.76 (0.66-0.87)
25-*O*-desacetylrifabutin	300 mg q.d.	12	↓	0.85 (0.72-1.00)	0.83 (0.74-0.92)	0.78 (0.70-0.87)
sildenafil	50 mg single dose	15	↓	0.55 (0.40-0.75)	0.43 (0.36-0.51)	N.A.
N-desmethyl-sildenafil		15	↓	0.75 (0.59-0.96)	0.59 (0.52-0.68)	N.A.
voriconazole	200 mg b.i.d.	14	↑	0.95	1.14	1.23

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	PK	Mean Ratio of Co-administered Drug Pharmacokinetic Parameters 90% CI; No effect = 1.00		
				C_{max}	AUC	C_{min}
				(0.75-1.21)	(0.88-1.47)	(0.87-1.75)

CI = Confidence Interval; N = number of subjects with data; N.A. = not available; ↑ = increases; ↓ = decreases; ↔ = no change; q.d. = once daily ; b.i.d. = twice daily; t.i.d. = three times daily; q.a.m. = once daily in the morning

1. In drug-drug 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.

9.5 Drug-Food Interactions

The systemic exposure (AUC) to etravirine was decreased by about 50% when Intelence was administered under fasting conditions, as compared to when Intelence was administered following a meal. Therefore, Intelence should always be taken following a meal. The caloric and fat content of the meal is irrelevant.

Grapefruit or grapefruit juice can inhibit CYP3A enzyme activity and should be avoided with Intelence.

9.6 Drug-Herb Interactions

Concomitant use of Intelence and St. John's Wort (*Hypericum perforatum*), or products containing St. John's Wort, is not recommended. Co-administration of etravirine with St. John's Wort may cause significant decreases in etravirine plasma concentrations, which may result in loss of therapeutic effect of Intelence (see 9.4 Drug-Drug Interactions, Table 5).

Interactions with other herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Etravirine is a non-nucleoside reverse transcriptase inhibitor (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 two conformationally distinct modes. Within a given binding mode, torsional flexibility of etravirine permits access to numerous conformational variants, while the compact 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.

Decreases in plasma viral load were typically observed as early as 1–2 days after the start of Intelence administration in monotherapy trials.

Resistance

Development of resistance against etravirine *in vitro* typically required multiple NNRTI-resistances associated mutations (RAMs) of which the following were observed most frequently: L100I, E138K, E138G, V179I, Y181C and M230I.

In the Phase III trials, DUET-1 and DUET-2, mutations that developed most commonly in subjects with virologic failure to the Intelence-containing regimen were V179F, V179I and Y181C, generally within a background of other NNRTI RAMs (see 15 MICROBIOLOGY **Resistance in treatment-experienced subjects**).

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. Cross-resistance to delavirdine, efavirenz and/or nevirapine is expected after virologic failure with an etravirine-containing regimen for the virologic failure isolates. Therefore, the treatment of patients with delavirdine, efavirenz or nevirapine following virologic failure of an etravirine-containing regimen is not recommended (see 15 MICROBIOLOGY, **Cross-Resistance *In Vitro***).

10.3 Pharmacokinetics

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

Table 9: Population Pharmacokinetic Estimates of Etravirine 200 mg b.i.d. in HIV-1-Infected Adult Subjects[1] (Integrated Data from Phase III DUET Trials at Week 48)

Parameter	Etravirine 200 mg b.i.d. N=575
AUC_{12h} (ng•h/mL)	
Geometric Mean ± Standard Deviation	4552 ± 4710
Median (Range)	4380 (458-59084)
C_{0h} (ng/mL)	
Geometric Mean ± Standard Deviation	297±391
Median (Range)	298 (2-4852)

1. PK values are about 30% higher in healthy volunteers
All HIV-infected subjects enrolled in Phase III clinical trials received darunavir/ritonavir 600/100 mg b.i.d. as part of their background regimen. Therefore, the pharmacokinetic parameter estimates in Table 1 account for reductions in the pharmacokinetic parameters of etravirine due to co-administration of Intelence with darunavir/ritonavir.

When Intelence was administered for 8 days to healthy volunteers, the increase in exposure to etravirine was generally dose proportional between total daily doses of 200 and 400 mg, and the total exposure to etravirine was similar irrespective of whether the total daily dose was administered in a once-daily or twice-daily regimen.

Absorption

Maximum etravirine plasma concentrations are generally attained by 4 hours following single or multiple oral doses of 100 mg to 400 mg. Dose-proportional pharmacokinetics were observed

for daily doses from 200-400 mg and steady-state plasma concentrations were reached in approximately 7 days.

The population pharmacokinetics derived geometric mean (SD) C_{0h} and AUC_{12h} for etravirine in 574 HIV-1-infected patients receiving Intelence is 4531.53 (±4543.69) ng.h/mL and 296.74 (±377.52) ng/mL, respectively.

An intravenous formulation of etravirine is unavailable: thus, 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, drugs that are known to increase gastric pH.

Effect of food on oral absorption
The exposure to etravirine is similar when taken following a standard normal caloric meal (561 kcal) or high-fat high caloric meal (1160 kcal). When compared to administration following a standard normal caloric meal, exposure to etravirine was decreased by 51% in fasted conditions. Therefore, to achieve optimal exposure, Intelence should be taken following a meal. The caloric and fat content of the meal is irrelevant. (See 4 DOSAGE AND ADMINISTRATION and 9 DRUG INTERACTIONS; 9.5 Drug-Food Interactions).

Distribution
Etravirine is approximately 99.9% bound to plasma proteins, primarily to albumin (99.6%) and alpha1-acid glycoprotein (94.48-97.66%) *in vitro*. The distribution of etravirine into compartments other than plasma (e.g. cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

In rats, the highest concentrations of radiolabelled etravirine and its metabolites were measured in the gastrointestinal tract, liver and adrenal gland and the lowest levels were associated with blood, plasma, brain, lung and bone. There was no evidence of undue retention or accumulation. The elimination of radioactivity was complete in rats within 96 hours of etravirine oral administration.

In pregnant rats, there was distribution of radiolabelled etravirine and its metabolites to the placenta, vagina, uterus, mammary glands and fetus. Total radioactivity levels in placenta and fetus were about twice the levels observed in maternal blood.

Metabolism
In vitro experiments with human liver microsomes (HLMs) indicate that etravirine primarily undergoes oxidative metabolism by CYP3A, CYP2C9 and CYP2C19 enzymes. The major metabolites, formed by methyl hydroxylation of the dimethylbenzonitrile moiety, were at least 90% less active than etravirine against wild-type HIV in cell culture.

Etravirine is not a substrate for P-glycoprotein in *in vitro* studies. Etravirine is an inhibitor of P-glycoprotein *in vitro* with a 50% inhibitory concentration (IC_{50}) value of 10,500 ng/mL for the probe paclitaxel. This value is approximately 20-fold higher than the average maximum plasma concentration observed in HIV-1 infected patients and is unlikely to have a clinically relevant

impact. The extent of first-pass metabolism of etravirine has not been evaluated due to the absence of a suitable intravenous formulation. Etravirine has no pharmacologically active metabolites in the presence of NNRTI-resistant strains of HIV. No dose-dependent changes in metabolism have been observed for etravirine over the daily dose range of 200-400 mg.

Elimination
The terminal elimination half-life of etravirine is approximately 30-40 hours. After administration of a radiolabelled ^{14}C-etravirine dose, 93.7% and 1.2% of the administered radioactivity could be retrieved in feces and urine, respectively. Unchanged etravirine accounted for 81.2%-86.4% of the administered dose in feces while no unchanged etravirine could be detected in urine.

After administration of a radiolabelled ^{14}C-etravirine dose in human subjects, 93.7% and 1.2% of the administered dose of ^{14}C-etravirine could be retrieved in feces and urine, respectively. Unchanged etravirine accounted for 81.2% to 86.4% of the administered dose in feces. Unchanged etravirine was not detected in urine.

Effects on Electrocardiogram
In a randomized, double-blind, active- and placebo-controlled crossover study, 41 healthy male and female volunteers were administered Intelence 200 mg b.i.d., Intelence 400 mg q.d., placebo and moxifloxacin 400 mg. After 8 days of dosing, etravirine did not prolong the QT interval. The placebo-adjusted mean maximum increases in QTcF from baseline after 200 mg b.i.d. and 400 mg q.d. of etravirine were 0.1 msec and -0.2 msec, respectively, and 10.1 msec for moxifloxacin 400 mg q.d. No subject in any group had an increase in QTcF of $\geq$60 msec. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec.

Special Populations and Conditions

- **Pediatrics**

The pharmacokinetics of etravirine in 101 treatment-experienced HIV-1-infected pediatric subjects, 6 years to <18 years of age and weighing at least 16 kg (35.2 lbs), showed that the administered weight-based dosages resulted in etravirine exposure comparable to that in adults receiving Intelence 200 mg twice daily (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY) when administered at a dose corresponding to 5.2 mg/kg twice daily. The population pharmacokinetic estimates for etravirine AUC_{12h} and C_{0h} are summarized in the table below.

Table 10: Population Pharmacokinetic Estimates for Etravirine (all doses combined) in Treatment-Experienced HIV-1-Infected Pediatric Subjects 6 years to <18 years of age (PIANO 24 and 48 weeks analysis)

	Outcome at Week 24	***Outcome at Week 48***
Parameter	N = 101	N = 101
AUC_{12h} (ng•h/mL)		
Geometric Mean ± Standard Deviation	3742 ± 4314	3729 ± 4305
Median (Range)	4499 (62 - 28865)	4560 (62 – 28865)
C_{0h} (ng/mL)		
Geometric Mean ± Standard Deviation	205 ± 342	205 ± 342

Median (Range)	287 (2 - 2276)	287 (2 - 2276)

The pharmacokinetics of etravirine in pediatric patients (<6 years of age) are under investigation. There are insufficient data at this time to recommend a dose in pediatric patients <6 years of age.

- **Geriatrics**

Population pharmacokinetic analysis in HIV-infected subjects showed that etravirine pharmacokinetics are not considerably different in the age range (18 to 77 years) evaluated (see 7.1.4 Geriatrics).

- **Sex**

A limited number of women were included in studies. The pharmacokinetics of etravirine in HIV-1-infected patients appears to be similar between men and women. The pharmacokinetics of etravirine in HIV-1-infected patients appears to be similar between men and women.

- **Pregnancy and Breast-feeding**

The total etravirine exposure after intake of Intelence 200 mg b.i.d. as part of an antiretroviral regimen was generally higher during pregnancy compared with postpartum (see Table 11). The differences were less pronounced for unbound etravirine exposure.
In women receiving Intelence 200 mg b.i.d., higher mean values for C_{max}, AUC_{12h} and C_{min} were observed during pregnancy compared to postpartum. During the 2nd and 3rd trimester of pregnancy mean values of these parameters were comparable.

Table 11: Pharmacokinetic results of total etravirine after administration of etravirine 200 mg b.i.d. as part of an antiretroviral regimen, during the 2nd trimester of pregnancy, the 3rd trimester of pregnancy, and postpartum.

Pharmacokinetics of etravirine (mean ± SD, median)	**Intelence 200 mg b.i.d. postpartum**	**Intelence 200 mg b.i.d. 2nd trimester**	**Intelence 200 mg b.i.d. 3rd trimester**
N	10	13	10[1]
C_{min}, ng/mL	269 ± 182 284	383 ± 210 346	349 ± 103 371
C_{max}, ng/mL	569 ± 261 528	774 ± 300 828	785 ± 238 694
AUC_{12h}, h*ng/mL	5004 ± 2521 5246	6617 ± 2766 6836	6846 ± 1482 6028

1. n=9 for AUC12h

Each subject served as her own control, and with an intra-individual comparison, the total etravirine C_{min}, C_{max} and AUC_{12h} values were 1.2-, 1.4- and 1.4-fold higher, respectively, during the 2nd trimester of pregnancy as compared to postpartum, and 1.1-, 1.4- and 1.2-fold higher, respectively, based during the 3rd trimester of pregnancy as compared to postpartum.

- **Ethnic Origin**

Population pharmacokinetic analysis of etravirine in HIV-infected patients indicated that race had no apparent effect on the exposure to etravirine.

- **Hepatic Insufficiency**

Hepatic Impairment

Etravirine is primarily metabolized and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment to 8 matched controls and 8 patients with moderate 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 (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

Hepatitis B or Hepatitis C Virus Co-infection
Population pharmacokinetic analysis of the DUET-1 and DUET-2 trials showed reduced clearance for Intelence in HIV-1-infected subjects with hepatitis B and/or C virus co-infection. Based upon the safety profile, no dose adjustment is necessary in patients co-infected with hepatitis B and/or C virus.

- **Renal Insufficiency**

The pharmacokinetics of etravirine have not been studied in patients with renal insufficiency. Results from a mass balance study with radioactive ^{14}C-etravirine showed that <1.2% of the administered dose of etravirine is excreted in the urine. No unchanged drug 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 hemodialysis or peritoneal dialysis (see 7 WARNINGS AND PRECAUTIONS, **Renal** and 4 DOSAGE AND ADMINISTRATION, **Recommended Dose and Dosage Adjustment**, **Renal Impairment**).

11 STORAGE, STABILITY AND DISPOSAL

Store Intelence tablets between 15–30°C. Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant pouches.

Keep out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:
etravirine

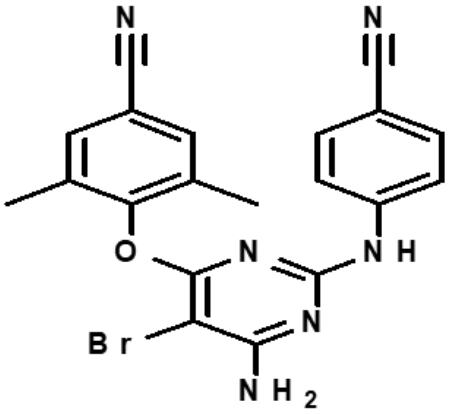
Chemical name:
4-[[6-amino-5-bromo-2-[(4-cyanophenyl)-amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile

Molecular formula and molecular mass:

Molecular formula: $C_{20}H_{15}BrN_6O$

Molecular mass: 435.28

Structural formula:



Physicochemical properties:

Etravirine is a white to slightly yellowish-brown powder with a solubility in water of <0.001 g/100 mL at 20°C.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment-Experienced Adult Patients

Trials TMC125-C206(DUET) and TMC125-216(DUET-2)

The evidence of efficacy of INTELENCE® (etravirine) is based on the analyses of 48-week data from 2 randomized, double-blinded, placebo-controlled, Phase III trials DUET-1 and DUET-2. These trials were identical in design, and similar efficacy for Intelence was seen in each trial. The results below are pooled data from the two trials.

Treatment-experienced HIV-1-infected adult subjects who had plasma HIV-1 RNA >5000 copies/mL and had 1 or more NNRTI resistance-associated mutations at screening or from prior genotypic analysis (i.e., archived resistance) were enrolled. These subjects also had 3 or more of the following primary PI mutations: D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, V82A/F/L/S/T, I84V, N88S, or L90M at screening, and were on a stable antiretroviral regimen for at least 8 weeks. Randomization was stratified by the intended use of enfuvirtide in the BR, previous use of darunavir/ritonavir, and screening viral load. This analysis included 612 subjects in DUET-1 and 591 subjects in DUET-2 who had completed 48 weeks of treatment or discontinued earlier.

At 48 weeks, the virologic response rate was evaluated in subjects receiving Intelence (200 mg b.i.d.) in addition to a BR versus subjects receiving placebo in addition to a BR. The BR consisted of darunavir/ritonavir 600/100 mg b.i.d. and at least 2 other investigator-selected antiretroviral drugs (N[t]RTIs with or without enfuvirtide).

45.6% of subjects in the Intelence arm and 46.9% of subjects in the placebo arm used enfuvirtide in the underlying antiretroviral therapy. 25.5% of subjects in the Intelence arm used enfuvirtide for the first time (*de novo*), compared with 26.5% of subjects in the placebo arm. 20.0% of subjects in the Intelence arm re-used enfuvirtide, compared with 20.4% of subjects in the placebo arm. Virologic response was defined as achieving a confirmed undetectable viral load (<50 HIV-1 RNA copies/mL).

In the pooled analysis for DUET-1 and DUET-2, demographics and baseline characteristics were balanced between the Intelence arm and the placebo arm. Table 12 describes the demographic and baseline disease characteristics of the subjects in the Intelence arm and subjects in the placebo arm.

Table 12: Demographic and Baseline Disease Characteristics of Adult Subjects in the DUET-1 and DUET-2 Trials (Pooled Analysis)

	Pooled DUET Trials		DUET–1		DUET–2	
	Placebo N = 604	Intelence N = 599	Placebo N = 308	Intelence N = 304	Placebo N = 296	Intelence N = 295
Demographic Characteristics						

	Pooled DUET Trials		DUET–1		DUET–2	
	Placebo N = 604	**Intelence N = 599**	**Placebo N = 308**	**Intelence N = 304**	**Placebo N = 296**	**Intelence N = 295**
Median Age, years (range)	45 (18-72)	46 (18-77)	45 (18-72)	45 (18-67)	45 (20-69)	46 (31-77)
Sex						
Male	89%	90%	86%	87%	92%	94%
Female	11%	10%	14%	13%	8%	6%
Race						
White	70%	70%	65%	65%	76%	77%
Black	13%	13%	12%	13%	14%	13%
Hispanic	12%	11%	14%	14%	10%	8%
Asian	1%	1%	1%	1%	0%	2%
Other	4%	4%	8%	7%	0%	1%
Baseline Disease Characteristics						
Median Baseline Plasma HIV-1 RNA (range), log_{10}copies/mL	4.8 (2.2-6.5)	4.8 (2.7-6.8)	4.9 (2.4-6.5)	4.8 (2.7-6.2)	4.8 (2.2-6.3)	4.8 (3.0-6.8)
Percentage of Subjects with Baseline Viral Load:						
<30,000 copies/mL	28.8%	27.5%	27.3%	26.6%	30.4%	28.5%
≥30,000 and <100,000 copies/mL	35.3%	34.4%	31.8%	34.2%	38.9%	34.6%
≥100,000 copies/mL	35.9%	38.1%	40.9%	39.1%	30.7%	36.9%
Median Baseline CD4+ Cell Count (range), 10^6 cells/L	109 (0–912)	99 (1–789)	109 (1–694)	99 (1–789)	108 (0–912)	100 (1–708)
Percentage of Subjects with Baseline CD4+ Cell Count:						
<50 cells/mm^3	34.7%	35.6%	36.5%	34.7%	32.8%	36.6%
≥50 and <200 cells/mm^3	34.5%	34.8%	33.9%	34.0%	35.1%	35.6%
≥200 cells/mm^3	30.8%	29.6%	29.7%	31.4%	32.1%	27.8%
Median (range) Number of PI Mutations[1]	4 (8)	4 (0-7)	4 (8)	4 (0-7)	4 (0-8)	4 (0-7)
Percentage of Subjects with Previous Use of NNRTIs:						
0	7.9%	8.2%	6.5%	6.9%	9.5%	9.5%
1	46.7%	46.9%	48.4%	50.0%	44.9%	43.7%
>1	45.4%	44.9%	45.1%	43.1%	45.6%	46.8%

	Pooled DUET Trials		DUET–1		DUET–2	
	Placebo N = 604	Intelence N = 599	Placebo N = 308	Intelence N = 304	Placebo N = 296	Intelence N = 295
Percentage of Subjects with Previous Use of the Following NNRTIs:						
Efavirenz	72.5%	70.3%	73.7%	72.4%	71.3%	68.1%
Nevirapine	58.6%	57.1%	58.4%	56.9%	58.8%	57.3%
Delavirdine	12.6%	13.7%	13.0%	8.2%	12.5%	19.3%
Median (range) Number of NNRTI RAMs[2]:	2 (0-7)	2 (0-7)	2 (0-7)	2 (0-7)	2 (0-6)	2 (0-6)
Median Fold Change of the Virus for the Following NNRTIs:						
Delavirdine	26.1	27.3	32.3	27.1	23.0	27.5
Efavirenz	45.4	63.9	72.8	99.8	25.0	39.9
Etravirine	1.5	1.6	1.4	1.6	1.7	1.6
Nevirapine	74.0	74.3	73.7	74.3	74.3	77.3
Percentage of Subjects with Previous Use of Enfuvirtide	42.2%	39.6%	34.4%	30.6%	50.3%	48.8%
Percentage of Subjects with a Phenotypic Sensitivity Score (PSS) for the background therapy[3] of:						
0	16.2%	17.0%	16.4%	17.3%	16.1%	16.7%
1	38.7%	36.5%	35.1%	38.2%	42.5%	34.7%
2	27.8%	26.9%	31.8%	23.6%	23.6%	30.3%
≥3	17.3%	19.7%	16.8%	20.9%	17.7%	18.4%

RAMs = Resistance-Associated Mutations
FC = fold change in EC_{50}

1. IAS-USA primary PI mutations [August/September 2007], D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, L76V,V82A/F/L/S/T, I84V, N88S, L90M
2. Tibotec NNRTI RAMs [June 2008]: A98G, V90I, L100I, K101E/H/P/Q, K103H/N/S/T, V106A/M/I, V108I, E138A/G/K/Q, V179D/E/F/G/I/T, Y181C/I/V, Y188C/H/L, V189I, G190A/C/E/Q/S, H221Y, P255H, F227C/L, M230I/L, P236L, K238N/T, Y318F
3. The PSS was calculated for the background therapy (as determined on Day 7). Percentages are based on the number of subjects with available phenotype data. For fusion inhibitors (enfuvirtide), subjects were considered resistant if the drug was used in previous therapy up to baseline. Intelence is not included in this calculation.

Study results

Table 13 below presents the efficacy results at 48 weeks for adult patients in the Intelence arm and patients in the placebo arm from the pooled DUET-1 and DUET-2 trials.

At Week 24 a statistically significant interaction (p=0.0064, Breslow-Day test) between treatment and enfuvirtide use was seen. The interaction effect was still significant at Week 48 (p=0.1279). Therefore, the primary analysis at Week 48 was performed for each enfuvirtide stratum: “Re-Used/Not Used Enfuvirtide” [patients re-using or not using enfuvirtide] and “De novo Enfuvirtide use”.

Table 13: Outcomes of Treatment at Week 48 of the DUET-1[2] and DUET-2[2] Trials (pooled analysis)

Outcomes	De Novo Enfuvirtide use		Re-Used/Not Used Enfuvirtide	
	Placebo + BR N=159	Intelence + BR N=153	Placebo + BR N=445	Intelence + BR N=446
Virologic Responders				
Viral Load <50 HIV-1 RNA copies/mL[1]	93 (58.5%)	109 (71.2%)[†]	147 (33.0%)	254 (57.0%)[†]
Viral Load <400 HIV-1 RNA copies/mL[1]	110 (69.2%)	125 (81.7%)	176 (39.6%)	303 (67.9%)
Mean change from baseline in log10 HIV-1 RNA	-2.22 (0.11)	-2.60 (0.10)	-1.23 (0.07)	-2.13 (0.07)*
Mean change from baseline in CD4 cell count	111.4 (9.3)	134.5 (10.0)	59.2 (5.0)	85.7 (5.0)
Virologic Failures	52 (32.7)	30 (19.6)	248 (55.7)	147 (33.0)
Viral Load ≥50 HIV-1 RNA copies/mL	17 (10.7%)	16 (10.5%)	30 (6.7%)	50 (11.2%)
Death	4 (2.5%)	4 (2.6%)	16 (3.6%)	7 (1.6%)
Discontinuation due to Adverse Event	3 (1.9%)	7 (4.6%)	11 (2.5%)	24 (5.4%)
Discontinuation due to Other Reasons	7 (4.4%)	3 (2.0%)	23 (5.2%)	14 (3.1%)

[1] Imputations according to the TLOVR algorithm
NS: p>0.05, *: p<0.0001; p-values Intelence vs. placebo

BR – background regimen consisting of DRV/rtv + minimum of 2 commercially available ARVs consisting of NRTI(s) with or without ENFUVIRTIDE

1. p-value vs. placebo from CMH test controlling for previous DRV use and baseline viral load
2. DUET 1 & 2 are ongoing 96-week clinical trials.

At Week 48, AIDS-defining illness or death occurred in 5.8% of Intelence-treated subjects and 9.8% of placebo-treated subjects.

The proportion of virologic responders (viral load <50 HIV-1 RNA copies/mL) by the Phenotypic Sensitivity Score (PSS) of the background therapy, including enfuvirtide, is shown in Table 14.

Table 14: Virologic Response (Viral Load <50 HIV-1 RNA copies/mL) at Week 48 by Phenotypic Sensitivity Score (PSS) in the Non-Viral Failure Excluded Population of TMC125-C206 and TMC125-C216 Trials (Pooled Analysis)

	Intelence + BR N=539	Placebo + BR N=536
PSS[1]		
0	46% (40/87)	6% (5/83)
1	63% (125/200)	32% (64/201)
2	79% (114/145)	62% (97/156)
≥ 3	78% (83/107)	75% (72/96)

1. In the calculation of the PSS, darunavir was counted as a sensitive antiretroviral if the FC ≤ 10; enfuvirtide was counted as a sensitive antiretroviral if it had not been used previously. Intelence was not included in this calculation.

Trial TMC125-C227

Trial TMC125-C227 was a randomized, exploratory, active-controlled, open-label, Phase IIb trial. Eligible adult subjects were treatment-experienced, PI-naïve HIV-1-infected patients with genotypic evidence of NNRTI resistance at screening or from prior genotypic analysis. The virologic response was evaluated in 116 subjects who were randomized to Intelence (n=59) or an investigator-selected PI (n=57), each given with 2 investigator-selected N(t)RTIs. Compared to the control PI-treated subjects, Intelence-treated subjects had lower antiviral responses associated with reduced susceptibility to the N(t)RTIs and to Intelence.

Treatment-Experienced Pediatric Patients

(6 years to <18 years of age)

PIANO (TMC-125-C213) is a single-arm, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of Intelence in 101 antiretroviral treatment-experienced HIV-1 infected pediatric subjects 6 years to < 18 years of age and weighing at least 16 kg (35.2 lbs). The study enrolled subjects on a stable but virologically failing antiretroviral treatment regimen, with a confirmed HIV-1 RNA plasma viral load ≥500 copies/mL. Sensitivity of the virus to Intelence at screening was required.

The median baseline plasma HIV-1 RNA was 3.9 $\log_{10}$ copies/mL, and the median baseline CD4 cell count was 385 $\times$ 10^6 cells/L.

The virologic response rate was evaluated in pediatric subjects receiving Intelence in combination with other antiretroviral agents (see 4 DOSAGE AND ADMINISTRATION for dosage recommendations per body weight). Virologic response was defined as the percentage of subjects with plasma viral load <50 HIV-1 copies/mL at week 24 or Week 48 calculated according to the TLOVR imputation algorithm.

At Week 24, 51.5% of all pediatric subjects had an undetectable viral load <50 HIV-1 RNA copies/mL. The proportion of pediatric subjects with <400 HIV-1 RNA copies/mL was 65.3%. The mean change in plasma HIV-1 RNA from baseline to Week 24 was -1.51 $\log_{10}$ copies/mL, and the mean CD4 cell count increase from baseline was 112 $\times$ 10^6 cells/L.

At Week 48, 53.5% of all pediatric patients had a confirmed undetectable viral load <50 HIV-1 RNA copies/mL. The proportion of pediatric patients with <400 HIV-1 RNA copies/mL was 63.4%. The mean change in plasma HIV-1 RNA from baseline to Week 48 was -1.53 $\log_{10}$ copies/mL, and the mean CD4 cell count increase from baseline was 156 $\times$ 10^6 cells/L.

14.2 Comparative Bioavailability Studies

Pivotal Comparative Bioavailability Study

In a Phase I, open-label, randomized, 4-period crossover bioavailability trial, the relative oral bioavailability of etravirine administered as either two Intelence (etravirine) 100 mg non-coated tablets (Treatment A; F060), two etravirine 100 mg coated tablets (Treatment B; F069), one etravirine 200 mg non-coated tablet (Treatment C; F068), or one etravirine 200 mg coated tablet (Treatment D; F070) under fed conditions (21 g fat; 533 kcal) was assessed in 24 healthy male and female adult subjects

A summary of the results based on the comparison between the current marketed Intelence (etravirine)100 mg non-coated tablets (F060; Treatment A [n=24] and the proposed for marketed etravirine 200 mg non-coated tablets (F068); Treatment C [n=23]) is presented in Table 15.

Table 15: Summary Table of the Comparative Bioavailability Data Under Fed Conditions

Etravirine (TMC125) 1 x 200 mg tablet (F068) and 2 x 100 mg tablets(F060) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter[1]	Test[2]	Reference[3]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (ng.h/mL)	3741 4247 (50.81)	3697 4037 (42.95)	98.26	90.61 – 106.6
C_{max} (ng/mL)	389 425(46.62)	369 392 (37.59)	103.3	94.42 – 113.0
T_{max}[4] (h)	4.0 (2.0 – 6.0)	5.0 (2.0- 6.0)		

1. Due to the design of the study AUCI and T1/2 parameters could not be accurately estimated
2. Etravirine 200 mg non-coated tablets (F068) (Janssen Inc.)
3. Intelence (etravirine) 100 mg non-coated tablets (F060) (Janssen Inc.)
4. Expressed as the median (range) only

15 MICROBIOLOGY

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 EC_{50} values ranging from 0.9 to 5.5 nM (i.e., 0.4 to 2.4 ng/mL).

Etravirine demonstrated antiviral activity in cell culture against a broad panel of HIV-1 group M isolates (subtype A, B, C, D, E, F, G) with EC_{50} values ranging from 0.29 to 1.65 nM and EC_{50} values ranging from 11.5 to 21.7 nM against group O primary isolates. These EC_{50} values are well below the 50% cellular toxicity concentration range of 15 to >100 µM.

The EC_{50} 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; the fusion inhibitor enfuvirtide; the integrase inhibitor raltegravir and the CCR5 antagonist maraviroc. Etravirine shows additive to synergistic antiviral activity in combination with the NRTIs emtricitabine, lamivudine, and zidovudine.

Resistance *In Vitro*

Etravirine showed antiviral activity against 55 of 65 HIV-1 strains with single amino acid substitutions at RT positions associated with NNRTI resistance, including the K103N. The amino acid substitutions which led to the highest resistance to etravirine in cell culture are Y181I (13-fold change in EC_{50} value) and Y181V (17-fold change in EC_{50} 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 vitro selection of etravirine-resistant strains originating from wild type HIV-1 of different origins and subtypes as well as NNRTI-resistant HIV-1 was performed at high and low virus inoculum. At high virus inoculum, emergence of resistant strains from wild type HIV-1 was delayed or prevented at concentrations of 40 nM or 200 nM. Regardless of the experimental design and the original HIV-1 strain, development of resistance against etravirine typically required multiple mutations in the RT of which the following were observed most frequently: L100I, E138K, E138G, V179I, Y181C, and M230I.

Resistance in treatment-experienced subjects

In the Phase III trials DUET-1 and DUET-2, mutations that developed most commonly in subjects with virologic failure to the Intelence-containing regimen were V179F, V179I and Y181C 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 subjects, the following mutations emerged most commonly: L100I, E138G, V179F, V179I, Y181C and H221Y.

Cross-Resistance *In Vitro*

The single amino acid substitutions associated with an etravirine reduction in susceptibility >3-fold were K101A, K101P, K101Q, E138G, E138Q, Y181C, Y181I, Y181T, Y181V, and M230L, and of these, the greatest reductions were Y181I (13-fold change in EC_{50} values) and Y181V (17-fold change in EC_{50} value). Mutant strains containing a single NNRTI resistance associated substitution (K101P, K101Q, E138Q, or M230L) had cross-resistance between etravirine and efavirenz. The majority (39 of 61; 64%) of the NNRTI mutant viruses with 2 or 3 amino acid substitutions associated with NNRTI resistance had decreased susceptibility to etravirine (fold-change >3). The highest levels of resistance to etravirine were observed for HIV-1 harbouring a combination of substitutions V179F + Y181C (181 fold-change), V179 + Y181I (123 fold-change), or V179F + Y181C + F227C (888 fold-change). Etravirine retains an EC_{50} value

<10 nM against 83% of 6171 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.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

In DUET-1 and DUET-2, the presence at baseline of three or more of the following mutations: V90I, A98G, L100I, K101E, K101P, V106I, V179D, V179F, Y181C, Y181I, Y181V, G190A, and G190S (Intelence-RAMs) was associated with a decreased virologic response to Intelence (see Table 16). These individual mutations mainly occurred in the presence of other NNRTI RAMs. V179F was never present without Y181C.

K103N, which was the most prevalent NNRTI mutation in DUET-1 and DUET-2 at baseline, was not identified as a mutation associated with resistance to Intelence. The presence of this mutation did not affect the response in the Intelence arm.

Table 16: Proportion of Subjects with <50 HIV-1 RNA copies/mL at Week 48 by Baseline Number of TMC125 Resistance Associated Mutations (RAMs) in the non-Viral Failure excluded Population of the Pooled DUET Studies

Number of TMC125 RAMs[1]	Etravirine Arms N=540		Placebo Arms N=541	
	Re-Used/Not Used Enfuvirtide	De Novo Enfuvirtide	Re-Used/Not Used Enfuvirtide	De Novo Enfuvirtide
All ranges	63.3% (254/401)	78.4% (109/139)	37.1% (147/396)	64.1% (93/145)
0	74.1% (117/158)	91.3% (42/46)	42.7% (61/143	73.6% (39/53)
1	61.3% (73/119)	80.4% (41/51)	38.6% (59/153)	64.7% (33/51)
2	64.1% (41/64)	66.7% (18/27)	26.2% (16/61)	52.6% (10/19)
≥3	38.3% (23/60)	53.3% (8/15)	28.2% (11/39)	50.0% (11/22)

1. TMC125 RAMs = V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.

Response rates assessed by baseline etravirine phenotype are shown in Table 17. These baseline phenotype groups are based on the select subject populations in DUET-1 and DUET-2 and are not meant to represent definitive clinical susceptibility breakpoints for Intelence. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to etravirine in treatment-experienced patients.

Table 17: Proportion of Subjects with <50 HIV-1 RNA copies/mL at Week 48 by Baseline Phenotype and Enfuvirtide Use in the Pooled DUET studies[1]

Etravirine Fold Change	Etravirine Arms N=539		Placebo Arms N=534	
	Re-Used/Not Used Enfuvirtide	De Novo Enfuvirtide	Re-Used/Not Used Enfuvirtide	De Novo Enfuvirtide
All ranges	63% (253/400)	78% (109/139)	37% (145/391)	64% (92/143)

0 – ≤3	70% (188/267)	85% (78/88)	43% (112/262)	64% (61/95)
>3 – ≤13	53% (39/74)	68% (25/37)	29% (22/77)	69% (18/26)
>13	44% (26/59)	64% (9/14)	21% (11/52)	59% (13/22)

1. non-VF Excluded Population

In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the treatment history and to resistance testing results where available.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

In mice and rats, there were no relevant effects following oral or subcutaneous administration of etravirine at doses up to 1000 and 320 mg/kg, respectively. Similarly, in dogs there was no effect of etravirine treatment following oral administration at doses up to 160 mg/kg.

Chronic Toxicity

Chronic repeat dose toxicity studies were conducted in mice (3 month duration), rats (6 month duration) and dogs (12 month duration). In mice the key target organs identified were the liver and the coagulation system. Haemorrhagic cardiomyopathy was only observed in male mice and was considered to be secondary to severe coagulopathy mediated via the vitamin K pathway. This is considered not relevant to humans. In the rat, the key target organs identified were the liver, the thyroid, and the coagulation system. Exposure in mice was equivalent to human exposure while in rats it was below the clinical exposure at the recommended dose (200 mg b.i.d.).

In the dog, changes in the liver and gall bladder were seen at exposures approximately 8-fold higher than human exposure observed at the recommended dose (200 mg b.i.d.).

Carcinogenicity: Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. A statistically significant increase in the incidences of hepatocellular adenomas and carcinomas was observed in treated female mice. Administration of etravirine did not cause a statistically significant increase in the incidence of tumors in female or male rats. The relevance of the findings in mice to humans is not known. At the highest tested doses, the systemic exposures (based on AUC) to etravirine were lower than those in humans at the clinical therapeutic dose (200 mg b.i.d.) with animal versus human AUC ratios being 0.6 (mice) and between 0.2 and 0.7 (rats).

Genotoxicity: In a range of mutagenicity studies, etravirine tested negative in the *in vitro* Ames reverse mutation assay, *in vitro* chromosomal aberration assay in human lymphocytes, and *in vitro* clastogenicity mouse lymphoma assay, in the absence and presence of a metabolic activation system. Etravirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

Reproductive and Developmental Toxicology: In a study conducted in rats, there were no effects on mating or fertility with etravirine treatment up to 500 mg/kg/day and exposure levels equivalent to those in humans at the clinically recommended dose.

There was no teratogenicity with etravirine in rats (1000 mg/kg) and rabbits (375 mg/kg) at exposures equivalent to those observed in humans at the recommended clinical dose. In a pre- and postnatal development assessment in rats, etravirine had no effect on offspring development during lactation or post-weaning when the mother was dosed up to 500 mg/kg and at exposures equivalent to those observed at the recommended clinical dose.

Local Tolerance: Etravirine was classified as "nonsensitizing" based on an *in vivo* guinea pig skin sensitization study and was also found to be unlikely to cause skin sensitization in a mouse local lymph node assay. Etravirine was also classified as "nonirritant" based on an *in vivo* rabbit skin irritation study. In an *in vitro* eye irritation assay, etravirine was considered as a "mild" eye irritant. No effects were observed in an *in vitro* phototoxicity study.

Immunotoxicity: Immunotoxicity has been evaluated in rats. Etravirine was administered at a dose of 600 mg/kg/day for 4 weeks and effects on lymphoid organs (lymph nodes, spleen and thymus) were evaluated. There were no relevant effects of treatment with etravirine, and the immune response, as measured by IgM production, was not affected by treatment.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr**INTELENCE**®
etravirine tablets

Read this carefully before you start taking **Intelence** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Intelence**.

What is Intelence used for?

- Intelence is an oral tablet used for the treatment of HIV (Human Immunodeficiency Virus) infection in adults, children and adolescents (6 years to less than 18 years of age). HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). Intelence is a type of anti-HIV drug called a non-nucleoside reverse transcriptase inhibitor (NNRTI), otherwise known as a "non-nuke".

  Intelence does not reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Never use or share dirty needles.

  Ask your healthcare professional if you have any questions on how to prevent passing HIV to other people.

How does Intelence work?

Intelence blocks HIV reverse transcriptase, an enzyme which the virus needs to multiply. When used with other anti-HIV medicines, Intelence reduces the amount of HIV in your blood (called "viral load") and increases your CD4 (T) cell count. HIV infection destroys CD4 (T) cells, which are important to the immune system. The immune system helps fight infection. Reducing the amount of HIV and increasing the CD4 (T) cell count can improve your immune system and, thus, reduce the risk of death or infections that can happen when your immune system is weak (opportunistic infections).

Intelence must be taken in combination with other anti-HIV medicines.

Intelence does **not** cure HIV infection or AIDS. At present, there is no cure for HIV infection. People taking Intelence may still develop infections or other conditions associated with HIV infection. Because of this, it is very important for you to remain under the care of a healthcare professional. Although Intelence is not a cure for HIV or AIDS, Intelence can help reduce your risks of getting illnesses associated with HIV infection (AIDS and opportunistic infection) and eventually dying from these conditions.

What are the ingredients in Intelence?

Medicinal ingredient:
etravirine

Non-medicinal ingredients:

Intelence 25 mg tablets:
colloidal anhydrous silica, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

Intelence 100 mg tablets:
colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

Intelence 200 mg tablets:
colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, and silicified microcrystalline cellulose.

Intelence comes in the following dosage forms:

25 mg tablets
100 mg tablets
200 mg tablets

Do not use Intelence if:

- you are taking combinations that contain ombitasvir/paritaprevir/ritonavir (TECHNIVIE) and if you are taking drugs containing dasabuvir (HOLKIRA PAK) (see "**INTERACTIONS WITH THIS MEDICATION**").
- you are allergic to etravirine or any of the other ingredients in Intelence (see "**What the nonmedicinal ingredients are**").

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Intelence. Talk about any health conditions or problems you may have, including if you:

- have had or currently have liver problems, including hepatitis B and/or C.
- are pregnant or planning to become pregnant. It is not known if Intelence can harm your unborn baby. You and your healthcare professional will need to decide if taking Intelence is right for you. If you take Intelence while you are pregnant, talk to your healthcare professional about how you can be included in the Antiretroviral Pregnancy Registry.
- are breast-feeding or planning to breast-feed. Do not breast-feed if you are taking Intelence. You should not breast-feed if you have HIV because of the chance of passing HIV to your baby. Talk with your healthcare professional about the best way to feed your baby.
- have hereditary problems of lactose intolerance. You should not take this medicine if you have hereditary problems of lactose intolerance.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Intelence:

Tell your healthcare professional about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements, including St. John's Wort (*Hypericum perforatum*). Intelence and many other medicines can interact. Sometimes serious side effects will happen if Intelence is taken with certain other medicines.

Tell your healthcare professional if you take other anti-HIV medicines, particularly atazanavir, darunavir, didanosine, fosamprenavir, maraviroc, nelfinavir, ritonavir, cobicistat, indinavir, saquinavir, tipranavir, nevirapine, efavirenz, rilpivirine, dolutegravir and delavirdine or any combinations of these medications. Intelence can be combined with some other anti-HIV medicines while other combinations are not recommended.

Do not take the following medications while taking Intelence:

- anticonvulsants (to treat epilepsy and prevent seizures) such as carbamazepine (TEGRETOL), phenobarbital and phenytoin (DILANTIN) while on an Intelence treatment regimen.
- rifampin (RIFADIN, RIFATER) (to treat bacterial infections) while on an Intelence treatment regimen.
- elbasvir/grazoprevir (ZEPATIER), or simeprevir (GALEXOS®) (to treat hepatitis C).

Avoid grapefruit or grapefruit juice as this may increase the blood levels of Intelence.

Tell your healthcare professional if you are taking any of the following medicines:

Type of Drug	Examples of Generic Names (Brand Names)	Type of Drug	Examples of Generic Names (Brand Names)
Antiarrhythmics (to treat abnormal heart rhythms)	bepridil disopyramide digoxin (LANOXIN) flecainide lidocaine mexiletine propafenone quinidine amiodarone (CORDARONE)	**Corticosteroids** (to treat inflammation or asthma)	dexamethasone (DECADRON) fluticasone propionate (ADVAIR DISKUS, CUTIVATE, FLONASE, FLOVENT DISKUS)
Anticoagulants (to prevent the clotting of red blood cells)	warfarin (COUMADIN)	**Hepatitis C Virus (HCV) Protease Inhibitor** (to treat hepatitis C)	daclastavir (DAKLINZA)
Anti-infectives (to treat bacterial infections)	clarithromycin (BIAXIN)	**HMG-CoA Reductase Inhibitors** (to lower cholesterol)	atorvastatin (LIPITOR) lovastatin (MEVACOR) pravastatin (PRAVACHOL) simvastatin (ZOCOR)
Antifungals (to treat fungal infections)	Fluconazole (DIFLUCAN) ketoconazole (NIZORAL®) itraconazole (SPORANOX®) voriconazole (VFEND) posaconazole (POSANOL)	**Immunosuppressants** (to prevent organ transplant rejection)	cyclosporine (SANDIMMUNE, NEORAL) tacrolimus (PROGRAF) sirolimus (RAPAMUNE)
Antimalarials	artemether/lumefantrine (COARTEM/RIAMET*)	**Platelet Aggregation Inhibitors** (to prevent blood clots)	clopidogrel (PLAVIX)

Type of Drug	Examples of Generic Names (Brand Names)	Type of Drug	Examples of Generic Names (Brand Names)
	*COARTEM and RIAMET are not marketed in Canada		
Antimycobacterials (to treat bacterial infections)	rifabutin (MYCOBUTIN)	**PDE-5 Inhibitors** (to treat erectile dysfunction)	sildenafil (VIAGRA) vardenafil (LEVITRA) tadalafil (CIALIS)
Benzodiazepines (to treat anxiety)	diazepam (VALIUM, DIASTAT)		

Tell your healthcare professional if you are taking any medicines that you obtained without a prescription.

This is **not** a complete list of medicines that you should tell your healthcare professional that you are taking. Know and keep track of all the medicines you take and have a list of them with you. Show this list to all of your healthcare professionals any time you get a new medicine. Your healthcare professional can tell you if you can take these other medicines with Intelence. Do not start any new medicines while you are taking Intelence without first talking with your healthcare professional. You can ask your healthcare professional for a list of medicines that can interact with Intelence.

How to take Intelence:

Always use Intelence exactly as your healthcare professional has told you. You must check with your healthcare professional if you are not sure

You should always take Intelence following a meal. You should not take Intelence on an empty stomach. Taking Intelence on an empty stomach may lessen the effect of Intelence. Follow your healthcare professional's advice on the type of meal you should be taking with Intelence.

Swallow the tablets whole with a liquid such as water. Do not use warm (> 40°C) or carbonated beverages when taking Intelence tablet(s). Do not chew the tablets.

If you are unable to swallow the Intelence tablets whole, you may do the following:

- place the tablets 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 of water or alternatively orange juice or milk (do 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 you take the entire dose.

If you mix INTELENCE tablet(s) with water, take this first, before other liquid anti-HIV medicines that you need to take at the same time.

Contact your healthcare professional if you are not able to swallow the entire dose when mixed with water.

If your child needs to take INTELENCE tablet(s) mixed with water, it is very important that the entire dose is taken so that the right amount of medicine enters into the body. If the full dose is not taken, the risk of the virus developing resistance is higher. Contact your healthcare professional if your child is not able to swallow the entire dose when mixed with water, as they may consider giving another medicine to treat your child.

Do not use warm (> 40°C) or carbonated beverages when taking INTELENCE tablet(s).

Usual dose:

Take Intelence tablets every day exactly as prescribed by your healthcare professional. The usual adult dose is 200 mg (one 200 mg tablet or two 100 mg tablets) of Intelence, twice daily *every day*. It may be easier to remember to take Intelence if you take them at the same time every day. If you have questions about when to take Intelence, your healthcare professional can help you decide which schedule works for you.

Continue taking Intelence unless your healthcare professional tells you to stop. Take the exact amount of Intelence that your healthcare professional tells you to take, right from the very start. To help make sure you will benefit from Intelence, you must not skip doses or interrupt therapy. If you do not take Intelence as prescribed, the benefits of Intelence may be reduced or even lost.

Instructions for proper use for children and adolescents (6 years to less than 18 years of age) and weighing at least 16 kg.

The healthcare professional will work out the right dose based on the weight of the child. The healthcare professional will inform you exactly how much Intelence the child should take.

Do not stop administering Intelence without talking to the child's healthcare professional. The other HIV medicines used in combination with Intelence should be taken by the child as recommended by the child's healthcare professional.

Overdose:

If you think you, or a person you are caring for, have taken too much Intelence, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you miss a dose of Intelence by more than 6 hours, wait and then take the next dose of Intelence at the regularly scheduled time. If you miss a dose of Intelence by less than 6 hours, take your missed dose of Intelence immediately, following a meal. Then take your next dose of Intelence at the regularly scheduled time.

If a dose of Intelence is skipped, do not double the next dose. Do not take more or less than your prescribed dose of Intelence at any one time.
Do not stop using Intelence without talking to your healthcare professional first.

What are possible side effects from using Intelence?

These are not all the possible side effects you may have when taking Intelence. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects include the following:

- Skin rash: The rash is usually mild to moderate.
- Diarrhea, nausea, abdominal pain, vomiting, heartburn, gas, and inflammation of the stomach
- Fatigue, tingling or pain in hands or feet, numbness, headache, sleeplessness, and anxiety
- Night sweats
- Changes in some values of your blood cells or chemistry; These can be seen in the results from blood tests. Your healthcare professional will explain these to you. Examples are low red blood cell count, low blood platelet count, high or abnormal blood fat levels, high cholesterol levels, and high sugar levels.

Other side effects of Intelence which can be serious, include muscle pain, tenderness or weakness.

As with other anti-HIV medicines, Intelence may cause side effects, including:

- Changes in body shape or body fat. These changes can happen in patients taking anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck, breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Graves' disease (which affects the thyroid gland), autoimmune hepatitis (which affects the liver), Guillain-Barré syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, abdominal pain, yellowing of the skin and eyes, or fatigue or any new symptoms contact your healthcare professional straight away.

Be alert to the following serious side effects which are possible for those taking Intelence.

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Uncommon				
	Serious skin rash with blistering, peeling skin (particularly around the mouth or eyes), mouth ulcers, fever, swelling of face or lips, tongue or parts of the body, shortness of breath			✓
	Liver problems such as hepatitis (liver inflammation) and symptoms such as abdominal pain, persistent vomiting, feeling unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine.		✓	
	Diabetes and symptoms such as excessive thirst, excessive urination, excessive eating, unexplained weight loss, poor wound healing, infections		✓	
	Kidney failure and symptoms such as nausea, loss of appetite and weakness, pass little or no urine, breathlessness		✓	
	High blood pressure and symptoms such as headache, dizziness, blurred vision, nausea	✓		
	Heart attack or symptoms associated with a heart attack		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store Intelence tablets at room temperature between 15–30°C. Keep Intelence in the bottle given to you by your healthcare professional. Keep the bottle tightly closed in order to protect from moisture.

The bottle of 25 mg tablets contains 2 little pouches (desiccants) and the bottles of 100 mg and 200 mg contain 3 little pouches of drying agent (desiccants) to keep the tablets dry. Keep the pouches in the bottle. Do not eat the pouches. Ask your healthcare professional if you have any questions about storing your tablets.

This medication is prescribed for your particular condition. Do not use it for any other condition or give it to anybody else. Keep Intelence and all of your medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, contact your local poison control centre or emergency room immediately.

Keep out of the reach and sight of children.

If you want more information about Intelence:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.janssen.com/canada, or by contacting the manufacturer at: 1-800-567-3331 or 1-800-387-8781

This leaflet was prepared by Janssen Inc.
Toronto, Ontario M3C 1L9

Last revised: October 14, 2022