（9）有害事象発生報告書

年　月　日

有害事象が発生したら直ちに記入して、FAXで事務局03-3518-6014へお送り下さい。

主治医氏名	印	病院名・〒住所	
診療科名			
職　責			
患者氏名（イニシャル）　姓［　　］. 名［　　］.		男・女	
カルテ番号［　　］		生年月日	年　月　日

有害事象の内容		
発生日時	年　月　日　午前・午後　時	
経過と処置		
程度（主治医判断）	軽症　・　中等度　・　重篤	
薬剤との因果関係	1.関連有り　2. 関連が否定出来ない　3. 関連無し　4. 不明	
関連有ると思われる薬剤	薬剤名	理由

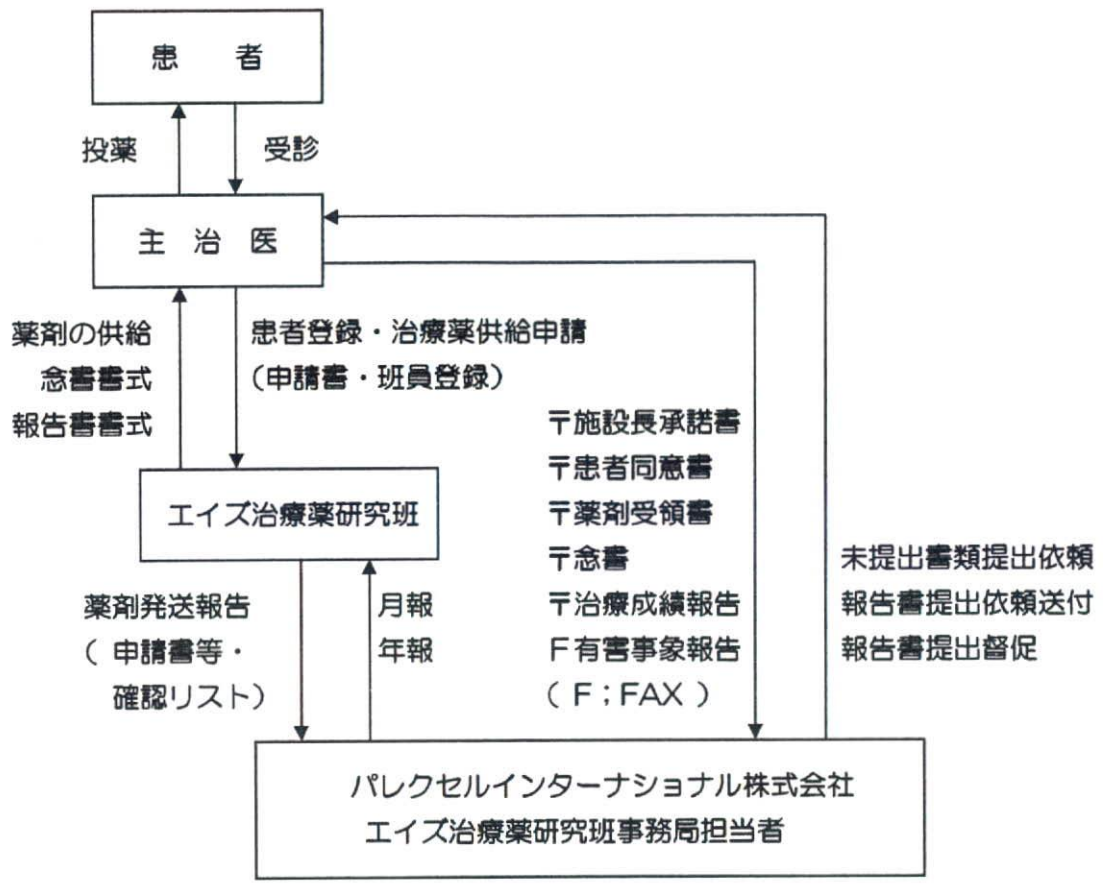
転帰報告書

転帰を判定したら直ちに記入し事務局へお送り下さい。

判定日時	年　月　日　午前・午後　時
転　帰	回復　・　軽快　・　死亡　・　後遺症
死因・後遺症	
薬剤との因果関係	1. 関連有り　2. 関連が否定出来ない　3. 関連無し　4. 不明

2007 年度エイズ治療薬研究班

臨床研究（薬剤供給）フローチャート



治療成績報告書の整理保存　（薬剤別；複数薬剤のときはコピー作成）
月報作成、　年報作成

注意点

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研究班薬剤の入手方法と治療成績の報告について

1．この研究班が取り扱う薬剤の供給を受けることを希望する医師は、必ずFAXサービスまたはインターネツトを通じて治療薬ごとに資料と文書の書式を取得し、当該患者がこの研究班からの薬剤供給の対象となることを確認して下さい。

2．当該患者が研究班供給薬剤の適応疾患に罹患していて、他の薬剤による治療が困難であるか、他に有効な治療薬がないことを確認した上で、必要事項を(1)患者登録確認書、治療薬供給申請書に記載して班長へFAXにて送付してください。初めて患者登録を行う場合は同時に(2)研究班班員登録書を班長へFAXし、(2):研究班班員登録書と(3)施設長承諾書の原本を事務局へ郵送してください。

3．班長は送付された書類の内容を確認の上、薬剤を担当医師へ宛てて発送します。

4．薬剤を受領後、直ちに(4)患者同意書と(5)薬剤受領書および「厚生労働省大臣宛ての念書」を書留郵便(プライバシー保護のため)にて事務局へ返送してください。

5．治療を開始したら(6)臨床研究使用成績調査票(1)と(7)臨床研究使用成績調査票(2)「臨床経過と臨床検査値の推移」について、開始時に記入できる範囲で記入しコピーを事務局へお送りください。

6．治療が継続される場合は、治療開始から少なくとも約1ヶ月毎に臨床検査などを行い、経過を観察し(7)臨床研究使用成績調査票(2)「臨床経過と臨床検査値の推移」の表に記載し、記載ごとにコピーを事務局までお送りください。治療が終了したら、全ての臨床研究使用成績調査票の記載可能に記載の上事務局へ郵送してください。なお、事務局は定期的集計のために臨床研究使用成績調査票の送付をお願いすることがあります。ご協力をお願いいたします.

7．その他の臨床検査を行った際は(7)臨床研究使用成績調査票(3)「その他の重要な臨床検査成績」に記載し、事務局へ郵送にてご報告下さい。

8．治擦経過中に有害事象が発生した場合には、薬剤に起因する副作用を疑わない事象であっても、直ちに(9)有害事象発生報告書を作成し、FAXにて事務局へ送付してください。

担当医師へのお願い

この研究班は、日本で未承認もしくは該当する適応症が未承認であるが、海外では目的とする疾患の治療のために既に承認されている薬剤を、主任研究者（班長）が医師個人輸入として輸入し、当該薬剤を必要とする患者の担当医師の要請に応じて治療研究のために無償で交付し、治療効果、安全性、副作用などを明確にするとともに、将来、国内での薬剤の入手難を緩和することを目的としています。
従って、研究班の円滑な運営と存続のために各種報告書の返送をお願いいたします。また、当該薬剤はわが国の薬事法上の承認を有しておらず、担当医師による患者への十分な説明よる同意を得た上で、担当医師の責任のもとに用いるものであることを承知してください。研究班では、研究班の薬剤を用いて賠償責任が生じた場合を想定して、担当医師が研究班薬剤の使用した際に生じた事故をカバーする班員に対する条項を加えた医師賠償責任保険に加入することをお勧めしています。

［別紙第２号様式］

念　　書

平成　　年　　月　　日

厚生労働大臣　殿

輸入業者（受取人）氏名（法人にあっては名称及び代表者の氏名）

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿印

同住所（法人にあっては主たる事務所の所在地）

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

今般、別紙輸入報告書により報告いたしました下記 医薬品は（　医師個人用　）として使用するもので、他に販売、授与するものではありません。

つきましては、本品の通関手続に関しよろしくお取り計らい願います。

上述のとおり、後日のため念書差入れます。

記

品　　名	数　　量

（この様式の大きさは日本工業規格Ａ４とすること）

念書の取扱についてのお願い

厚生労働省エイズ治療薬研究班
主任研究者(班長)　福武　勝幸

この念書は医師個人輸入の手続きにおいて厚生労働省へ必ず提出しなければならないものです。研究班の存続のために最も重要な書類ですので、遅滞なく班長へご返送いただきますようお願いいたします。

当研究班においては、厚生労働省の特別な配慮により薬剤を班長名であらかじめ輸入し通関しておりますが、本念書をご提出いただくことにより、各主治医か個人輸入したのと同等に扱うこととなり、薬事法に抵触することなく各医師へ薬剤をお届けする形で研究班が機能できる仕組みになっております。(この念書は当研究班専用のもので、一般の個人輸入の書式とは異なります。)

記載上の注意

日付欄には薬剤をお受け取りになった日付をご記入ください。輸入業者（受取人）氏名（法人にあっては名称及び代表者の氏名）の欄には、薬剤を研究班へ申請された医師の所属施設と氏名をご記入ください。また、同住所（法人にあっては主たる事務所の所在地）の欄には、医師の所属する施設の住所を御記載ください。お受け取りになった薬剤の品名と数量をご記載ください。

念書返送先

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INTELENCE® safely and effectively. See full prescribing information for INTELENCE®.

INTELENCE® (etravirine) [Tablets]

Initial U.S. Approval – 2008

----------RECENT MAJOR CHANGES----------

- Warnings and Precautions
  - Severe Skin and Hypersensitivity Reactions (5.1) 08/2009

----------INDICATIONS AND USAGE----------

INTELENCE® is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated:

- In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to an NNRTI and other antiretroviral agents. (1)

In patients who have experienced virologic failure on an NNRTI-containing regimen, do not use INTELENCE® in combination with only N[t]RTIs. (1)

The safety and efficacy of INTELENCE® have not been established in pediatric patients or treatment-naïve adult patients. (1)

----------DOSAGE AND ADMINISTRATION----------

200 mg (two 100 mg tablets) taken twice daily following a meal. (2)

----------DOSAGE FORMS AND STRENGTHS----------

100 mg tablets (3)

----------CONTRAINDICATIONS----------

None

----------WARNINGS AND PRECAUTIONS----------

Severe, potentially life threatening and fatal skin reactions have been reported. This includes cases of Stevens-Johnson syndrome, hypersensitivity reaction, toxic epidermal necrolysis and erythema multiforme. Immediately discontinue treatment if severe hypersensitivity, severe rash or rash with systemic symptoms or liver transaminase elevations develops and monitor clinical status, including liver transaminases closely. (5.1)

----------ADVERSE REACTIONS----------

The most common adverse drug reactions of moderate to severe intensity (≥ 2%) which occurred at a higher rate than placebo are rash and peripheral neuropathy. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Tibotec Therapeutics at 1-877-REACH-TT or 1-877-732-2488 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

INTELENCE® should not be co-administered with the following antiretrovirals:

- Tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir
- Protease inhibitors administered without ritonavir
- NNRTIs

Co-administration of INTELENCE® with drugs that inhibit or induce CYP3A, CYP2C9, and/or CYP2C19 may alter the therapeutic effect or adverse reaction profile of etravirine. (7)

Co-administration of INTELENCE® with drugs that are substrates of CYP3A, CYP2C9, and/or CYP2C19 or are transported by P-glycoprotein may alter the therapeutic effect or adverse reaction profile of the co-administered drug(s). (7)

Refer to the Full Prescribing Information for other drugs that should not be co-administered with INTELENCE® and for other drugs that may require a change in dose or regimen. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: *Pregnancy Category B*—Use during pregnancy only if the potential benefit justifies the potential risk. Antiviral Pregnancy Registry available. Register patients by calling 1-800-258-4263. (8.1)
- Nursing Mothers: Mothers should not breastfeed due to the potential for HIV transmission. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

[*Sections or subsections omitted from the full prescribing information are not listed]

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INTELENCE®*, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor (NNRTI) and other antiretroviral agents.

This indication is based on Week 48 analyses from 2 randomized, double-blind, placebo-controlled trials of INTELENCE®. Both studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, N[t]RTI, PI) treatment-experienced adults.

The following points should be considered when initiating therapy with INTELENCE®:

- Treatment history and, when available, resistance testing, should guide the use of INTELENCE®.
- The use of other active antiretroviral agents with INTELENCE® is associated with an increased likelihood of treatment response.
- In patients who have experienced virologic failure on an NNRTI-containing regimen, do not use INTELENCE® in combination with only N[t]RTIs [*see Clinical Studies (14)*].
- The risks and benefits of INTELENCE® have not been established in pediatric patients or in treatment-naïve adult patients.

2 DOSAGE AND ADMINISTRATION

The recommended oral dose of INTELENCE® tablets is 200 mg (two 100 mg tablets) taken twice daily following a meal [*see Clinical Pharmacology (12.3)*]. The type of food does not affect the exposure to etravirine. Patients who are unable to swallow INTELENCE® tablets whole may disperse the tablets in a glass of water. Once dispersed, patients should stir the dispersion well and drink it immediately. The glass should be rinsed with water several times and each rinse completely swallowed to ensure the entire dose is consumed.

3 DOSAGE FORMS AND STRENGTHS

100 mg white to off-white oval tablets debossed with "TMC125" on one side and "100" on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Severe Skin and Hypersensitivity Reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. In Phase 3 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 2.2% of HIV-1-infected subjects receiving INTELENCE® discontinued from Phase 3 trials due to rash [*see Adverse Reactions (6)*]. Rash occurred most commonly during the first 6 weeks of therapy.

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, angioedema). 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.

5.2 Fat Redistribution

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* Registered trademark of Tibotec Pharmaceuticals

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

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including INTELENCE®. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Severe skin and hypersensitivity reactions [*see Warnings and Precautions (5.1)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment is based on all data from 1203 subjects in the Phase 3 placebo-controlled trials, TMC125-C206 and TMC125-C216, conducted in antiretroviral treatment-experienced HIV-1-infected adult subjects, 599 of whom received INTELENCE® (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. Discontinuations due to adverse drug reactions (ADRs) were 5.2% in the INTELENCE® arm and 2.6% in the placebo arm.

The most frequently reported ADR at least Grade 2 in severity was rash (10.0%). Stevens-Johnson syndrome, drug hypersensitivity reaction and erythema multiforme were reported in < 0.1% of subjects during clinical development with INTELENCE® [*see Warnings and Precautions (5.1)*]. A total of 2.2% of HIV-1-infected subjects in Phase 3 trials receiving INTELENCE® discontinued due to rash. In general, in clinical trials, rash was mild to moderate, occurred primarily in the second week of therapy, and was infrequent after Week 4. Rash generally resolved within 1-2 weeks on continued therapy. The incidence of rash was higher in women compared to men in the INTELENCE® arm in the Phase 3 trials. 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.

Common Adverse Reactions

Clinical ADRs of moderate intensity or greater (≥ Grade 2) and reported in ≥ 2% of subjects treated with INTELENCE® and occurring at a higher rate compared to placebo (excess of 1%) are presented in Table 1. Laboratory abnormalities considered ADRs are included in Table 2.

Table 1: Treatment-Emergent Adverse Reactions* of at least Moderate Intensity† (Grades 2-4) in ≥ 2% of Adult Subjects in the INTELENCE® Treatment Groups and at a higher rate compared to placebo (excess of 1%)

System Organ Class, Preferred Term, %	Pooled TMC125-C206 and TMC125-C216 Trials	
	INTELENCE® + BR N=599	Placebo + BR N=604
Nervous System Disorders		
Peripheral neuropathy	4%	2%
Skin and Subcutaneous Tissue Disorders		
Rash	10%	3%

N=total number of subjects per treatment group, BR=background regimen

* Includes adverse reactions at least possibly, probably, or very likely related to the drug.

† Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).

Less Common Adverse Reactions

Treatment-emergent ADRs occurring in less than 2% of subjects (n=599) receiving INTELENCE® and of at least moderate intensity (≥ Grade 2) are listed below by body system:

Cardiac Disorders: myocardial infarction, angina pectoris, atrial fibrillation
Ear and Labyrinth Disorders: vertigo
Eye Disorders: blurred vision
Gastrointestinal Disorders: gastroesophageal reflux disease, flatulence, gastritis, abdominal distension, pancreatitis, constipation, dry mouth, hematemesis, retching, stomatitis
General Disorders and Administration Site Conditions: sluggishness
Hematologic Disorders: hemolytic anemia
Hepatobiliary Disorders: hepatic failure, hepatomegaly, cytolytic hepatitis, hepatic steatosis, hepatitis
Immune System Disorders: drug hypersensitivity, immune reconstitution syndrome
Metabolism and Nutrition Disorders: diabetes mellitus, anorexia, dyslipidemia
Nervous System Disorders: paraesthesia, somnolence, convulsion, hypoesthesia, amnesia, syncope, disturbance in attention, hypersomnia, tremor
Psychiatric Disorders: anxiety, sleep disorders, abnormal dreams, confusional state, disorientation, nervousness, nightmares
Renal and Urinary Disorders: acute renal failure
Reproductive System and Breast Disorders: gynecomastia
Respiratory, Thoracic and Mediastinal Disorders: exertional dyspnea, bronchospasm
Skin and Subcutaneous Tissue Disorders: night sweats, lipohypertrophy, prurigo, hyperhidrosis, dry skin, swelling face

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.

Laboratory Abnormalities in Treatment-Experienced Patients

Selected Grade 2 to Grade 4 laboratory abnormalities that represent a worsening from baseline observed in adult subjects treated with INTELENCE® are presented in Table 2.

Table 2: Selected Grade 2 to 4 Laboratory Abnormalities Observed in Treatment-Experienced Subjects

		Pooled TMC125-C206 and TMC125-C216 Trials	
Laboratory Parameter Preferred Term, %	**DAIDS Toxicity Range**	**INTELENCE® + BR N=599**	**Placebo + BR N=604**
GENERAL BIOCHEMISTRY			
Pancreatic amylase			
Grade 2	> 1.5-2 x ULN	7%	8%
Grade 3	> 2-5 x ULN	7%	8%
Grade 4	> 5 x ULN	2%	1%
Lipase			
Grade 2	> 1.5-3 x ULN	4%	6%
Grade 3	> 3-5 x ULN	2%	2%
Grade 4	> 5xULN	1%	< 1%
Creatinine			
Grade 2	> 1.4-1.8 x ULN	6%	5%
Grade 3	> 1.9-3.4 x ULN	2%	1%
Grade 4	> 3.4 x ULN	0%	< 1%
HEMATOLOGY			
Decreased hemoglobin			
Grade 2	90-99 g/L	2%	4%
Grade 3	70-89 g/L	< 1%	< 1%
Grade 4	< 70 g/L	< 1%	< 1%
White blood cell count			
Grade 2	1,500-1,999/mm^3	2%	3%
Grade 3	1,000-1,499/mm^3	1%	4%
Grade 4	< 1,000/mm^3	1%	< 1%
Neutrophils			
Grade 2	750-999/mm^3	5%	6%
Grade 3	500-749/mm^3	4%	4%
Grade 4	< 500/mm^3	2%	3%
Platelet count			
Grade 2	50,000-99,999/mm^3	3%	5%
Grade 3	25,000-49,999/mm^3	1%	1%
Grade 4	< 25,000/mm^3	< 1%	< 1%
LIPIDS AND GLUCOSE			
Total cholesterol			
Grade 2	> 6.20-7.77 mmol/L 240-300 mg/dL	20%	17%
Grade 3	> 7.77 mmol/L > 300 mg/dL	8%	5%
Low density lipoprotein			
Grade 2	4.13-4.9 mmol/L 160-190 mg/dL	13%	12%
Grade 3	> 4.9 mmol/L > 190 mg/dL	7%	7%
Triglycerides			
Grade 2	5.65-8.48 mmol/L 500 –750 mg/dL	9%	7%

Grade 3	8.49-13.56 mmol/L 751 - 1200 mg/dL	6%	4%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	4%	2%
Elevated glucose levels			
Grade 2	6.95-13.88 mmol/L 161-250 mg/dL	15%	13%
Grade 3	13.89-27.75 mmol/L 251 – 500 mg/dL	4%	2%
Grade 4	> 27.75 mmol/L > 500 mg/dL	0%	< 1%
HEPATIC PARAMETERS			
Alanine amino transferase			
Grade 2	2.6-5 x ULN	6%	5%
Grade 3	5.1-10 x ULN	3%	2%
Grade 4	> 10 x ULN	1%	< 1%
Aspartate amino transferase			
Grade 2	2.6-5 x ULN	6%	8%
Grade 3	5.1-10 x ULN	3%	2%
Grade 4	> 10 x ULN	< 1%	< 1%
ULN=Upper Limit of Normal, BR=background regimen			

Patients co-infected with hepatitis B and/or hepatitis C virus
In Phase 3 trials TMC125-C206 and TMC125-C216, 139 subjects (12.3%) with chronic hepatitis B and/or hepatitis C virus co-infection out of 1129 subjects were permitted to enroll. AST and ALT abnormalities occurred more frequently in hepatitis B and/or hepatitis C virus co-infected subjects for both treatment groups. Grade 2 or higher laboratory abnormalities that represent a worsening from baseline of AST, ALT or total bilirubin occurred in 27.8%, 25.0% and 7.1% respectively, of INTELENCE®-treated co-infected subjects as compared to 6.7%, 7.5% and 1.8% of non-co-infected INTELENCE®-treated subjects. In general, adverse events reported by INTELENCE®-treated subjects with hepatitis B and/or hepatitis C virus co-infection were similar to INTELENCE®-treated subjects without hepatitis B and/or hepatitis C virus co-infection.

6.2 Postmarketing Experience

The following events have been identified during postmarketing use of INTELENCE®. Because these events are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Fatal cases of toxic epidermal necrolysis have been reported. Severe hypersensitivity reactions including cases of hepatic failure have been reported [*see Warnings and Precautions (5.1)*].

7 DRUG INTERACTIONS

Etravirine is a substrate of CYP3A, CYP2C9, and CYP2C19. Therefore, co-administration of INTELENCE® with drugs that induce or inhibit CYP3A, CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse reaction profile of INTELENCE® (see Table 3). [*See also Clinical Pharmacology (12.3)*.]

Etravirine is an inducer of CYP3A and inhibitor of CYP2C9, CYP2C19 and P-glycoprotein. Therefore, co-administration of drugs that are substrates of CYP3A, CYP2C9 and CYP2C19 or are transported by P-glycoprotein with INTELENCE® may alter the therapeutic effect or adverse reaction profile of the co-administered drug(s) (see Table 3). *[See also Clinical Pharmacology (12.3)*.]

Table 3 shows the established and other potentially significant drug interactions based on which, alterations in dose or regimen of INTELENCE® and/or co-administered drug may be recommended. Drugs that are not recommended for co-administration with INTELENCE® are also included in Table 3.

Table 3: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction [*See Clinical Pharmacology (12.3)*]		
Concomitant Drug Class: Drug Name	**Effect on Concentration of Etravirine or Concomitant Drug**	**Clinical Comment**
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz* nevirapine*	↓ etravirine	Combining two NNRTIs has not been shown to be beneficial. Concomitant use of INTELENCE® with efavirenz or nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE®. INTELENCE® and other NNRTIs should not be co-administered.
delavirdine	↑ etravirine	Combining two NNRTIs has not been shown to be beneficial. INTELENCE® and delavirdine should not be co-administered.
HIV-Antiviral Agents: Protease Inhibitors (PIs)—Unboosted (i.e., without co-administration of low-dose ritonavir)		
atazanavir* fosamprenavir nelfinavir indinavir* (without ritonavir)	↓ atazanavir ↑ amprenavir ↑ nelfinavir ↓ indinavir	Concomitant use of INTELENCE® with PIs 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.
ritonavir*	↓ etravirine	Concomitant use of INTELENCE® with ritonavir 600 mg b.i.d. may cause a significant decrease in the plasma concentration of etravirine and loss of therapeutic effect of INTELENCE®. INTELENCE® and ritonavir 600 mg b.i.d. should not be co-administered.
HIV-Antiviral Agents: Protease Inhibitors (PIs)—Boosted (with co-administration of low-dose ritonavir)		
tipranavir/ritonavir*	↓ etravirine	Concomitant use of INTELENCE® with tipranavir/ritonavir may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE®. INTELENCE® and tipranavir/ritonavir should not be co-administered.
fosamprenavir/ritonavir*	↑ amprenavir	Due to a significant increase in the systemic exposure of amprenavir, the appropriate doses of the combination of INTELENCE® and fosamprenavir/ritonavir have not been established. INTELENCE® and fosamprenavir/ritonavir should not be co-administered.
atazanavir/ritonavir*†	↓ atazanavir ↑ etravirine	Concomitant use of INTELENCE® with atazanavir/ritonavir may cause a significant decrease in atazanavir C_{min} by about 38% and loss of therapeutic effect of atazanavir. In addition, the mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE® with atazanavir/ritonavir is anticipated to be about 100% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials after co-administration of INTELENCE® and darunavir/ritonavir (as part of the background regimen). INTELENCE® and atazanavir/ritonavir should not be co-administered.

darunavir/ritonavir*	↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced by about 37% when INTELENCE® was co-administered with darunavir/ritonavir. Because all subjects in the Phase 3 trials received darunavir/ritonavir as part of the background regimen and etravirine exposures from these trials were determined to be safe and effective, INTELENCE® and darunavir/ritonavir can be co-administered without any dose adjustments.
lopinavir/ritonavir*†	↑ etravirine	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 systemic exposure of etravirine observed in the Phase 3 trials after co-administration of INTELENCE® and darunavir/ritonavir (as part of the background regimen). The amount of safety data at these increased etravirine exposures is limited, therefore, INTELENCE® and lopinavir/ritonavir should be co-administered with caution.
saquinavir/ritonavir*	↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced by about 33% when INTELENCE® was co-administered with saquinavir/ritonavir. Because 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, INTELENCE® and saquinavir/ritonavir can be co-administered without any dose adjustments.
CCR5 Antagonists		
maraviroc*	↔ etravirine ↓ maraviroc	When INTELENCE® is co-administered with maraviroc in the absence of a potent CYP3A inhibitor (e.g., ritonavir boosted protease inhibitor), the recommended dose of maraviroc is 600 mg b.i.d. No dose adjustment of 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., ritonavir boosted protease inhibitor), the recommended dose of maraviroc is 150 mg b.i.d. No dose adjustment of INTELENCE® is needed.

Other Agents		
Antiarrhythmics: digoxin*	↔ etravirine ↑ digoxin	For patients who are initiating a combination of INTELENCE® and digoxin, the lowest dose of digoxin should initially be prescribed. For patients on a stable digoxin regimen and initiating INTELENCE®, no dose adjustment of either INTELENCE® or digoxin is needed. The serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.
amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↓ antiarrhythmics	Concentrations of these antiarrhythmics may be decreased when co-administered with INTELENCE®. INTELENCE® and antiarrhythmics should be co-administered with caution. Drug concentration monitoring is recommended, if available.
Anticoagulants: warfarin	↑ anticoagulants	Warfarin concentrations may be increased when co-administered with INTELENCE®. The international normalized ratio (INR) should be monitored when warfarin is combined with INTELENCE®.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ etravirine	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®.
Antifungals: fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole	↑ etravirine ↔ fluconazole ↓ itraconazole ↓ ketoconazole ↔ posaconazole ↑ voriconazole	Posaconazole is a potent inhibitor of CYP3A and fluconazole is a potent inhibitor of CYP2C9; both 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®. Voriconazole is a CYP2C19 substrate and CYP3A, CYP2C9 and CYP2C19 inhibitor. Concomitant use of voriconazole and INTELENCE® may increase plasma concentrations of both drugs. Dose adjustments for itraconazole, ketoconazole or voriconazole may be necessary depending on other co-administered drugs.
Antiinfectives: clarithromycin*	↑ etravirine ↓ clarithromycin ↑ 14-OH-clarithromycin	Clarithromycin exposure was decreased by INTELENCE®; 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. Alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC.
Antimycobacterials: rifampin, rifapentine	↓ etravirine	Rifampin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE® should not be used with rifampin or rifapentine as co-administration may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE®.
Antimycobacterials: rifabutin*	↓ etravirine	If INTELENCE® is NOT co-administered with a protease inhibitor/ritonavir, then rifabutin at a dose of 300 mg q.d. is

	↓ rifabutin ↓ 25-*O*-desacetylrifabutin	recommended. If INTELENCE® is co-administered with darunavir/ritonavir or saquinavir/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.
Herbal Products: St. John's wort (*Hypericum perforatum*)	↓ etravirine	Concomitant use of INTELENCE® with products containing St. John's wort may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE®. INTELENCE® and products containing St. John's wort should not be co-administered.
HMG-CoA Reductase Inhibitors: atorvastatin* fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	↔ etravirine ↓ atorvastatin ↑ 2-OH-atorvastatin ↔ etravirine ↑ fluvastatin, ↓ lovastatin, ↔ pravastatin, ↔ rosuvastatin, ↓ simvastatin	The combination of INTELENCE® and atorvastatin can be given without any dose adjustments, however, the dose of atorvastatin may need to be altered based on clinical response. No interaction between pravastatin, rosuvastatin and INTELENCE® is expected. Lovastatin and simvastatin are CYP3A substrates and co-administration with INTELENCE® may result in lower plasma concentrations of the HMG-CoA reductase inhibitor. Fluvastatin is metabolized by CYP2C9 and co-administration with INTELENCE® may result in higher plasma concentrations of the HMG-CoA reductase inhibitor. Dose adjustments for these HMG-CoA reductase inhibitors may be necessary.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↓ immunosuppressant	INTELENCE® and systemic immunosuppressants should be co-administered with caution because plasma concentrations of cyclosporine, sirolimus, or tacrolimus may be affected.
Narcotic Analgesics: methadone*	↔ etravirine ↔ methadone	INTELENCE® and methadone can 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*, vardenafil, tadalafil	↓ sildenafil ↓ N-desmethyl-sildenafil	INTELENCE® and sildenafil can be co-administered without dose adjustments, however, the dose of sildenafil may need to be altered based on clinical effect.

↑ = increase, ↓ = decrease, ↔ = no change

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

† The expected increase in the systemic exposure of etravirine when co-administered with either atazanavir/ritonavir (~100%) or lopinavir/ritonavir (~85%) is theoretical and is based on comparing exposures of etravirine from drug-drug interaction studies with exposures in the pivotal Phase 3 trials (in which darunavir/ritonavir was co-administered as part of the background regimen).

‡ The reference for etravirine exposure is the pharmacokinetic parameters of etravirine in the presence of

In addition to the drugs included in Table 3, the interaction between INTELENCE® and the following drugs were evaluated in clinical studies and no dose adjustment is needed for either drug [*see Clinical Pharmacology (12.3)*]: didanosine, enfuvirtide (ENF), ethinylestradiol/norethindrone, omeprazole, paroxetine, raltegravir, ranitidine, and tenofovir disoproxil fumarate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

No adequate and well-controlled studies of INTELENCE® use in pregnant women have been conducted. In addition, no pharmacokinetic studies have been conducted in pregnant patients. Animal reproduction studies in rats and rabbits at systemic exposures equivalent to those at the recommended human dose of 400 mg/day revealed no evidence of fetal harm. INTELENCE® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

8.3 Nursing mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. It is not known whether etravirine is secreted in human milk. Because of both the potential for HIV transmission and the potential for adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving INTELENCE®.**

8.4 Pediatric use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric use

Clinical studies of INTELENCE® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

No dose adjustment of INTELENCE® is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The pharmacokinetics of INTELENCE® have not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C).

8.7 Renal Impairment

Since the renal clearance of etravirine is negligible (< 1.2%), a decrease in total body clearance is not expected in patients with renal impairment. No 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 hemodialysis or peritoneal dialysis.

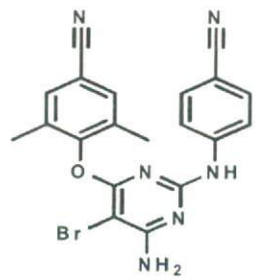
10 OVERDOSAGE

There is no specific antidote for overdose with INTELENCE®. Human experience of overdose with INTELENCE® is limited. The highest dose studied in healthy volunteers was 400 mg once daily. Treatment of overdose with INTELENCE® consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Because etravirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance.

11 DESCRIPTION

INTELENCE® (etravirine) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1).

The chemical name for etravirine is 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile. Its molecular formula is $C_{20}H_{15}BrN_6O$ and its molecular weight is 435.28. Etravirine has the following structural formula:



Etravirine is a white to slightly yellowish brown powder. Etravirine is practically insoluble in water over a wide pH range. It is very slightly soluble in propylene glycol and slightly soluble in ethanol. Etravirine is soluble in polyethylene glycol (PEG)400 and freely soluble in some organic solvents (e.g., N,N-dimethylformamide and tetrahydrofuran).

INTELENCE® is available as a white to off-white, oval tablet for oral administration containing 100 mg of etravirine. Each tablet contains the inactive ingredients hypromellose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and lactose monohydrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Etravirine is an antiviral drug [*see Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

Effects on Electrocardiogram

In a randomized, double-blind, active, and placebo-controlled crossover study, 41 healthy subjects 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 maximum mean (upper 1-sided 95% CI) baseline and placebo-adjusted QTcF were 0.6 ms (3.3 ms) for 200 mg b.i.d. and -1.0 ms (2.5 ms) for 400 mg q.d. dosing regimens.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

The pharmacokinetic properties of INTELENCE® were determined in healthy adult subjects and in treatment-experienced HIV-1-infected adult subjects. The systemic exposures (AUC) to etravirine were lower in HIV-1-infected subjects than in healthy subjects.

Table 4: Population Pharmacokinetic Estimates of Etravirine 200 mg b.i.d. in HIV-1-Infected Subjects (Integrated Data from Phase 3 Trials at Week 48)*	
Parameter	**Etravirine 200 mg b.i.d. N = 575**
AUC_{12h} (ng•h/mL)	
Geometric Mean ± Standard Deviation	4522 ± 4710
Median (Range)	4380 (458 - 59084)
C_{0h} (ng/mL)	
Geometric Mean ± Standard Deviation	297 ± 391
Median (Range)	298 (2 - 4852)

* All HIV-1-infected subjects enrolled in Phase 3 clinical trials received darunavir/ritonavir 600/100 mg b.i.d. as part of their background regimen. Therefore, the pharmacokinetic parameter estimates shown in Table 4 account for reductions in the pharmacokinetic parameters of etravirine due to co-administration of INTELENCE® with darunavir/ritonavir.

Note: The median protein binding adjusted EC50 for MT4 cells infected with HIV-1/IIIB in vitro = 4 ng/mL.

Absorption and Bioavailability

Following oral administration, etravirine was absorbed with a T_{max} of about 2.5 to 4 hours. The absolute oral bioavailability of INTELENCE® is unknown.

In healthy subjects, the absorption of etravirine is not affected by co-administration of oral ranitidine or omeprazole, drugs that increase gastric pH.

Effects of Food on Oral Absorption

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. Within the range of meals studied, the systemic exposures to etravirine were similar. The total caloric content of the various meals evaluated ranged from 345 kilocalories (17 grams fat) to 1160 kilocalories (70 grams fat). [*see Dosage and Administration (2)*].

Distribution

Etravirine is about 99.9% bound to plasma proteins, primarily to albumin (99.6%) and alpha 1-acid glycoprotein (97.66%-99.02%) *in vitro*. The distribution of etravirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Metabolism

In vitro experiments with human liver microsomes (HLMs) indicate that etravirine primarily undergoes 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.

Elimination

After single dose oral administration of 800 mg ^{14}C-etravirine, 93.7% and 1.2% of the administered dose of ^{14}C-etravirine was recovered in the 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. The mean (± standard deviation) terminal elimination half-life of etravirine was about 41 (± 20) hours.

Special Populations

Hepatic Impairment

Etravirine is primarily metabolized by the liver. The steady state pharmacokinetic parameters of etravirine were similar after multiple dose administration of INTELENCE® to subjects with normal hepatic function (n = 16), mild hepatic impairment (Child-Pugh Class A, n = 8), and moderate hepatic impairment (Child-Pugh Class B, n = 8). The effect of severe hepatic impairment on the pharmacokinetics of etravirine has not been evaluated.

Hepatitis B and/or Hepatitis C Virus Co-infection

Population pharmacokinetic analysis of the TMC125-C206 and TMC125-C216 trials showed reduced clearance for etravirine in HIV-1-infected subjects with hepatitis B and/or C virus co-infection. Based upon the safety profile of INTELENCE® [*see Adverse Reactions (6)*], no dose adjustment is necessary in patients co-infected with hepatitis B and/or C virus.

Renal Impairment

The pharmacokinetics of etravirine have not been studied in patients with renal impairment. The results from a mass balance study with ^{14}C-etravirine showed that <1.2% of the administered dose of etravirine is excreted in the urine as metabolites. No unchanged drug was detected in the urine. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

Gender

No significant pharmacokinetic differences have been observed between men and women. A limited number of women were included in clinical studies.

Race

Population pharmacokinetic analysis of etravirine in HIV-infected subjects did not show an effect of race on exposure to etravirine.

Geriatric Patients

Population pharmacokinetic analysis in HIV-infected subjects showed that etravirine pharmacokinetics are not considerably different within the age range (18 to 77 years) evaluated [*see Use in Specific Populations (8.5)*].

Pediatric Patients

The pharmacokinetics of etravirine in pediatric patients have not been evaluated. Dosing recommendations for pediatric patients cannot be made due to insufficient data.

Drug Interactions

[*See also Drug Interactions (7)*.]

Etravirine is a substrate of CYP3A, CYP2C9, and CYP2C19. Therefore, co-administration of INTELENCE® with drugs that induce or inhibit CYP3A, CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse reaction profile of INTELENCE®.

Etravirine is an inducer of CYP3A and inhibitor of CYP2C9, CYP2C19 and P-glycoprotein. Therefore, co-administration of drugs that are substrates of CYP3A, CYP2C9 and CYP2C19 or are transported by P-glycoprotein with INTELENCE® may alter the therapeutic effect or adverse reaction profile of the co-administered drug(s).

Drug interaction studies were performed with INTELENCE® and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of other drugs on the AUC, C_{max}, and C_{min} values of etravirine are summarized in Table 5 (effect of other drugs on INTELENCE®). The effect of co-administration of INTELENCE® on the AUC, C_{max}, and C_{min} values of other drugs are summarized in Table 6 (effect of INTELENCE® on other drugs). For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 5: Drug Interactions: Pharmacokinetic Parameters for Etravirine in the Presence of Co-administered Drugs

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	Exposure	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*	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)
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)
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 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						
Maraviroc	300 mg b.i.d.	14	↔	1.05 (0.95-1.17)	1.06 (0.99-1.14)	1.08 (0.98-1.19)
Maraviroc (when co-administered with darunavir/ ritonavir)†	150/600/100 mg b.i.d.	10	↔	1.08 (0.98–1.20)	1.00 (0.86–1.15)	0.81 (0.65–1.01)
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)
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)
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)