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Etravirine

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Contents

Abstract

▲ Etravirine is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) that demonstrates potent *in vitro* activity against wild-type strains of HIV type 1 (HIV-1), as well as against numerous strains resistant to available NNRTIs. Furthermore, the potential for resistance to etravirine developing appears to be lower than for first-generation NNRTIs.

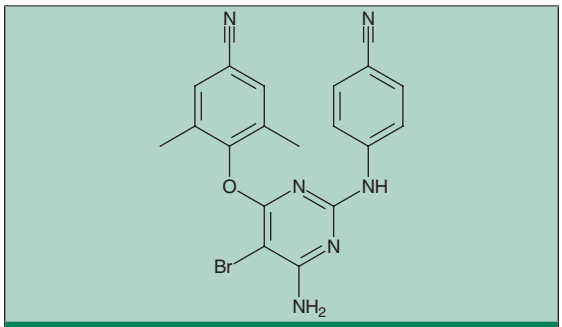
▲ In treatment-experienced patients infected with HIV-1 with NNRTI resistance, HIV-1 RNA levels of <50 copies/mL (primary endpoint) and <400 copies/mL were achieved by a significantly greater proportion of patients receiving etravirine 200 mg twice daily plus background therapy (BT) than placebo plus BT, according to the planned pooled and individual 24-week analyses of two large, well designed, continuing phase III trials (DUET-1 and DUET-2).

▲ In the pooled 24-week analysis, patients receiving etravirine plus BT achieved a significantly greater mean reduction in viral load from baseline and a significantly greater mean increase in CD4+ cell counts from baseline than patients receiving placebo plus BT.

▲ The pooled and individual findings of the DUET studies at 48 weeks indicate that the efficacy of etravirine is maintained with regard to these endpoints.

▲ In the DUET studies, etravirine was generally well tolerated in treatment-experienced patients infected with HIV-1, with a tolerability profile generally similar to that of placebo. Adverse events were mostly of mild or moderate severity.

Features and properties of etravirine (R165335; TMC125; Intelence™)	
Indication	
For the treatment of HIV-1 infection in treatment-experienced adults in combination with other antiretroviral agents, including a boosted protease inhibitor	
Mechanism of action	
Antiretroviral	Non-nucleoside reverse transcriptase inhibitor
Dosage and administration	
Dose	200 mg
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile of etravirine 200 mg twice daily in patients with HIV-1 infection after 8 days (in combination with other antiretroviral agents)	
Mean maximum plasma concentration (C_{max})	451.3 ng/mL
Area under the plasma concentration-time curve over 12 h	3713 ng • h/mL
Median time to C_{max}	4 h
Most frequent adverse event (24-week pooled data)	
Rash	



Etravirine (TMC125)

More than 33 million people worldwide were estimated to be living with HIV infection in 2007, with AIDS responsible for an estimated 2.1 million deaths, according to the most recent statistics from the Joint United Nations Programme on HIV/AIDS.[1]

The standard treatment currently recommended for HIV type-1 (HIV-1) infection is combination therapy with three or more antiretroviral drugs, often referred to as highly active antiretroviral therapy (HAART).[2-5] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are commonly used agents in HAART;[2-5] however, as with other antiretroviral agents, development of drug resistance is problematic.[6]

The currently available NNRTIs efavirenz, nevirapine and delavirdine have a low genetic barrier to resistance development, with single reverse transcriptase mutations capable of conferring marked reductions in drug susceptibility and cross-resistance to other agents in the class.[7-9] NNRTI resistance is widespread among treated patients with HIV-1 infection and is increasing in some patient populations,[10,11] limiting the use of currently available agents in this class to one line of therapy. Thus, new NNRTIs are needed that can provide a more effective barrier to the emergence of viral resistance and that are active against strains of HIV-1 resistant to currently available NNRTIs. One such next-generation NNRTI is the di-arylpyrimidine analogue etravirine (Intelence™)[1].

This article reviews the pharmacological properties of oral etravirine, and its efficacy and tolerability in treatment-experienced adult patients with HIV-1 infection. Medical literature on the use of etravirine in the treatment of HIV-1 infection was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

This section provides an overview of the pharmacodynamic properties of oral etravirine. Further results from some clinical trials[12,13] are discussed in section 3. Some data were obtained from the manufacturer's prescribing information.[14] The majority of data discussed in this section are fully published, although some data are only available as abstracts[15] or posters.[16-19]

Mechanism of Action

- Etravirine is a di-arylpyrimidine analogue that acts principally by directly binding to and inhibiting the activity of reverse transcriptase.[14,20,21] For example, the *in vitro* DNA polymerase and RNase H activity of wild-type HIV reverse transcriptase was inhibited by 50% at mean etravirine concentrations of 24.5 and 58.8 nmol/L.[21] Such inhibition was not affected to any great extent by mutations in the NNRTI-binding site such as K103N, Y181C or Y188L, or the double mutation K103N/Y181C; mutant versus wild-type 50% inhibitory concentration ratios were all <2.6.[21]
- Etravirine can adapt to changes (such as those caused by mutations) at the reverse transcriptase NNRTI-binding site by flexing, repositioning and reorienting itself within the binding pocket, according to crystallography and molecular modelling data.[22] The conformational and positional flexibility of etravirine may explain the potent *in vitro* antiviral activity of the drug against wild-type and some NNRTI-resistant strains of HIV-1.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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● In addition to blocking the reverse transcription of the HIV genome, etravirine may also have inhibitory effects elsewhere in the virus life cycle. The findings of an *in vitro* study[23] suggest that etravirine may enhance both the formation of inactive reverse transcriptase p66 subunit homodimers and the intracellular processing of gag and gag-pol polyproteins. Furthermore, production of viral particles from HIV-1-transfected cells treated with etravirine was 67% of that of untreated cells, a potential consequence of increased gag/gag-pol processing. Such effects were also generally seen with other potent NNRTIs such as efavirenz, but not with nevirapine or delavirdine.[23] However, the clinical significance of these findings are not known.

In Vitro Anti-HIV Activity

● *In vitro*, etravirine demonstrated antiviral activity against wild-type HIV-1 strains, with limited cytotoxicity.[20,22] For example, the median concentration at which 50% of viral replication was inhibited (EC_{50}) ranged from 1.4 to 4.8 nmol/L for etravirine against wild-type strains in infected cells (MT-4, monocytes or macrophages, or peripheral blood mononuclear cells) and was markedly lower than the 50% cytotoxic concentration of the drug (>100 μmol/L).[20] In contrast, etravirine was inactive against HIV-2.[20]

● Etravirine was active against a range of HIV-1 groups and subtypes *in vitro*.[20] Across a panel of 32 clinically derived recombinant viruses, the median EC_{50} for etravirine was 1.1–1.7 nmol/L for each group M subtype tested (subtypes B, C, D, F and H; fold change in EC_{50} [FC; i.e. vs wild-type virus] was 0.9–1.3 for all group M subtypes) and 0.9–1.8 nmol/L against circulating recombinant forms (CRF) of HIV-1 (CRF02_AG, CRF01_AE and CRF05_DF; FC 0.7–1.4). Etravirine was also moderately active against a group O virus (EC_{50} 13 nmol/L; FC 9.9).

● Etravirine also demonstrated antiviral activity against a large range of NNRTI-resistant strains of HIV-1 *in vitro*.[15,20,22] For example, against a panel of mutant viruses with single or double mutations associated with NNRTI resistance, etravirine had EC_{50} values of <5 nmol/L and an FC <4 for the majority of viruses tested (18 of 25 strains).[20] Only three viral strains, Y181I, F227C and L100I/K103N, had marked resistance to the drug *in vitro* (EC_{50} >10 nmol/L and an FC >10).[20]

● These data are generally supported by the findings of sensitivity analyses performed in clinical isolates.[14,20] For example, across a panel of 6171 NNRTI-resistant clinical isolates of HIV, 60% were susceptible to etravirine (FC ≤3).[14]

● Etravirine demonstrated a synergistic interaction with zidovudine, and additive interactions with other antiretroviral agents, including NNRTIs (efavirenz, nevirapine and delavirdine), nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs), in an *in vitro* combination assay in MT-4 cells infected with wild-type HIV-1_{LAI}.[20] No combinations displayed antagonism.

● Etravirine was effective in inhibiting adenosine triphosphate-mediated removal of zidovudine monophosphate from chain-terminated primers by both wild-type and mutant HIV-1 reverse transcriptase *in vitro*, which may, in part, explain the synergy observed between these agents.[24]

In Vitro Viral Resistance

● The potential for HIV to develop resistance to etravirine appears to be lower than for first-generation NNRTIs, according to data from *in vitro* selection experiments performed at high and low multiplicity of infection.[25] At least two mutations are usually required for the development of an etravirine-resistant phenotype, compared with only a single mutation conferring resistance to other currently available NNRTIs.[25]

Clinical Viral Resistance

● Certain mutations when present at baseline were associated with a lower virological response to etravirine in treatment-experienced patients infected with HIV-1.[16,26] For example, in a pooled analysis[16] of patients not using enfuvirtide *de novo*

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(n = 406 exclusive of patients who discontinued therapy for reasons other than unsuccessful virological response) in the DUET-1[13] and DUET-2[12] trials (see section 3 for study details), a total of 17 baseline mutations were found to confer resistance to etravirine in an assessment of virological response (HIV-1 RNA level <50 copies/mL). These mutations, termed etravirine resistance-associated mutations, included V90I, A98G, L100I, K101E/H/P, V106I, E138A, V179D/T, V179F (only present in combination with Y181C), Y181C/I/V, G190A/S and M230L.

- Notably, the baseline presence of K103N, a mutation commonly associated with NNRTI resistance, did not appear to affect the virological response to etravirine in the DUET studies; overall, 69% of such patients achieved a virological response with etravirine treatment (excluding patients who used enfuvirtide *de novo* or discontinued therapy for reasons other than unsuccessful response).[19]

- Using a genotypic-weighted scoring system, Y181I/V were shown to have the highest weight (i.e. greatest influence), yet were of low prevalence (≤1.5% in a panel of 4248 clinical isolates).[16] Virological response appeared to be a function of both the weight of baseline etravirine resistance-associated mutations and their number. Weighted mutation scores of 0–2 were associated with the highest virological response rate (74%), whereas scores of 2.5–3.5 and ≥4 corresponded to response rates of 52% and 38%.

- Phenotypic clinical cut-offs have been determined for etravirine in an analysis[17] of pooled data from the DUET studies[12,13] in treatment-experienced patients not receiving enfuvirtide *de novo* (n = 403 excluding patients who discontinued treatment for reasons other than unsuccessful virological response). Virological response rates after 24 weeks of treatment were highest in patients with a baseline etravirine FC ≤3 (71% of patients) and were intermediate in those with an FC 3–13 (50%). An upper clinical cut-off, above which treatment with etravirine would have no benefit, could not be determined as patients with a baseline FC >13 were too few and had a virological response rate of 37%.

- When both etravirine and darunavir resistance were considered in a subgroup analysis (n = 406)[18] of pooled DUET study[12,13] data, virological response rates of ≥65% were achieved after 24 weeks of treatment in treatment-experienced patients with HIV-1 infection without the use of enfuvirtide *de novo*, provided a total of three or less etravirine plus darunavir resistance-associated mutations were present or the etravirine FC was ≤3 in combination with a darunavir FC ≤40. The analysis excluded patients who discontinued treatment for reasons other than unsuccessful virological response.

- In treatment-experienced patients infected with HIV-1 who received etravirine in the DUET studies,[12,13] development of certain substitutions (e.g. V108I, V179F/I or Y181I), usually in combination with other NNRTI resistance-associated mutations, was commonly associated with an unsuccessful response to treatment.[14] The majority of these mutations, as well as L100I, E138G and H221Y, were among those commonly observed in other etravirine studies conducted in patients with HIV-1 infection (reported in the manufacturer's prescribing information).[14]

- Although etravirine can be used in treatment-experienced patients who have received other NNRTIs, efavirenz and/or nevirapine are not recommended in patients who have had an unsuccessful virological response with an etravirine-containing regimen because of potential cross resistance.[14]

Other Effects

Etravirine does not appear to be associated with QT-interval prolongation. In a randomized, double-blind, placebo- and active comparator-controlled, crossover study in 41 HIV-negative volunteers,[27] recipients of etravirine 200 mg twice daily (approved dosage) or 400 mg once daily had maximum mean differences in time-matched Fridericia-corrected QT-interval changes versus placebo of +0.1 msec and −0.2 msec after 1 day of treatment, and +0.6 msec and −1.0 msec after 8 days (i.e. at steady state). The corresponding values in recipients of once-daily moxifloxacin 400 mg were +10.1 and +10.3 msec.

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2. Pharmacokinetic Profile

The etravirine formulation used in phase II trials was redeveloped to enhance the oral bioavailability of the drug for use in phase III studies.[28] Data concerning the pharmacokinetic properties of the phase III oral formulation were obtained from studies in healthy or HIV-negative volunteers (n = 16–30)[29-34] and patients infected with HIV-1 (n = 12–574[35-37]), with discussion in this section focusing on the approved dosage of 200 mg twice daily. Supplementary data pertaining to alternative pre-phase III oral etravirine formulations from studies in healthy or HIV-negative volunteers (n = 16–32)[38-44] or patients with HIV infection (n = 8)[45] have also been included; the etravirine formulation was not specified in some studies conducted in healthy volunteers (n = 6–30)[46-49] or patients with HIV infection (n = 15).[50] Additional data from the EU manufacturer's prescribing information[14] and other sources[51] have been included. Some studies are fully published,[32,33,36] with other data available only as abstracts and/or posters.[28-31,34,37-50,52]

Absorption and Distribution

- After 1 and 8 days of etravirine 200 mg twice daily in treatment-experienced patients infected with HIV-1 also receiving other antiretroviral agents (n = 27), the mean maximum plasma concentration (C_{max}) of etravirine was 125.9 and 451.3 ng/mL, the mean area under the plasma concentration-time curve (AUC) over 12 hours (AUC_{12}) was 745 and 3713 ng • h/mL, and the median time to C_{max} was 4 hours (at both timepoints).[35]
- In patients with HIV-1 infection also receiving darunavir/ritonavir 600 mg/100 mg twice daily and other antiretroviral agents (n = 574), the mean plasma concentration at time zero (i.e. at the time of dose) and the mean AUC_{12} were 393 ng/mL and 5501 ng • h/mL after ≤24 weeks of twice-daily etravirine 200 mg, according to a population pharmacokinetic model.[37] The absolute oral bioavailability of etravirine is not yet known.[14]
- Administration of etravirine to healthy volunteers in a fasted state or after a high-fibre meal reduced etravirine exposure compared with administration after a standard meal.[30] Etravirine should therefore be taken following a meal.[14] In 24 HIV-negative volunteers who received a single 100-mg dose of etravirine, the least-squares mean ratios (relative to administration after a standard meal) for C_{max} and AUC at the last recorded timepoint were 56% (90% CI 41, 77) and 49% (90% CI 39, 61) in the fasted state and 62% (90% CI 47, 83) and 75% (90% CI 63, 90) after a high-fibre meal (all $p < 0.05$ vs a standard meal). Exposure to etravirine was not affected to any clinically relevant extent when administered after either a high-fat meal or a snack.[30]
- Etravirine is highly plasma protein bound (99.9%) *in vitro*.[14]

Metabolism and Elimination

- Metabolism of the drug occurs via cytochrome P450 (CYP) enzymes CYP3A4, CYP2C9 and CYP2C19, as well as via uridine diphosphate glucuronyltransferase (UDPGT).[14]
- Etravirine was metabolized predominantly via methyl hydroxylation in six HIV-negative male volunteers who received a single 800-mg dose of radiolabelled etravirine (pre-phase III formulation), with the resultant metabolites undergoing subsequent glucuronidation.[46] Unchanged drug was the most abundant component circulating in plasma after administration of the etravirine 800-mg dose, with methyl and di-methyl hydroxylated metabolites accounting for 10–15% and 30–50% of the plasma drug concentration.[46]
- Elimination of etravirine was mainly via the faeces (93.7%) with minimal excretion via the urine (1.2%) after administration of a single 800-mg radiolabelled dose of a pre-phase III etravirine formulation in healthy volunteers.[46] Up to 86.4% of the administered dose was excreted via faeces as unchanged drug; unchanged parent drug was not detected in the urine.[46] The majority of the radiolabelled dose was eliminated within 24–48 hours of administration.[46]

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- In a population pharmacokinetic model (n = 574),[37] the apparent oral clearance of etravirine was 43.7 L/h in patients infected with HIV-1 receiving etravirine 200 mg twice daily in addition to darunavir/ritonavir 600 mg/100 mg twice daily and other antiretroviral agents.
- The pharmacokinetic profile of etravirine generally does not appear to be affected by age,[14,37] sex,[14,37] race[14,37] or mild to moderate hepatic impairment (Child-Pugh class A or B).[14] There are currently no pharmacokinetic data for etravirine in patients with severe liver impairment (Child-Pugh class C), and consequently the drug is not recommended for use in this patient population.[14] Dosage adjustments are not required in patients with renal impairment or mild to moderate hepatic impairment, although it is advised that etravirine be used with caution in patients with moderate hepatic impairment.[14] The drug should also be used with caution in elderly patients because of limited data in this population.[14]
- Data from a population pharmacokinetic analysis indicate that hepatitis B and/or C virus co-infection and low bodyweight may increase etravirine exposure.[51] The manufacturer's prescribing information[14] reports a reduction in etravirine clearance in patients with HIV infection who are co-infected with hepatitis B and/or C, although viral hepatitis co-infection and bodyweight were not considered to alter the clearance of etravirine to any clinically relevant extent in a population pharmacokinetic model available as a poster[37] (quantitative data not reported[14,37,51]). Because of the currently limited data, caution is advised when using etravirine in patients with hepatitis B and/or C virus co-infection.[14]

Drug Interactions

- Etravirine is an inducer of CYP3A4 and UDPGT, and an inhibitor of CYP2C9 and CYP2C19.[14,47] Demonstrated and predicted pharmacokinetic drug interactions between etravirine and other agents commonly administered in patients infected with HIV-1 are summarized in table I.
- Etravirine did not demonstrate any clinically relevant pharmacokinetic interactions with tenofovir disoproxil fumarate,[29] didanosine,[38] the CYP3A4 substrates darunavir (administered in combination with ritonavir)[36] or saquinavir (when administered with lopinavir/ritonavir in a dual boosted PI regimen),[50] or the UDPGT substrate raltegravir[47] in patients with HIV-1 infection[36,50] or healthy volunteers.[29,38,47] Etravirine is not expected to interact with the HMG-CoA reductase inhibitor pravastatin or the antiviral agent ribavirin.[14] Coadministration with enfuvirtide appeared to have no clinically relevant affect on the apparent total clearance of etravirine according to a population pharmacokinetic study.[37]
- There were also no clinically relevant pharmacokinetic interactions observed between etravirine and ranitidine,[32] the CYP3A4 substrate methadone,[33] the CYP2C19/CYP3A4 substrate omeprazole[32] or the CYP2D6 substrate paroxetine[44] upon coadministration in HIV-negative volunteers. No dosage adjustments are required with concomitant administration of etravirine and methadone.[14]
- In addition, the pharmacokinetics of the oral contraceptive agents ethinylestradiol and norethisterone (both CYP3A4 substrates) were not affected to any clinically relevant extent when coadministered with etravirine in HIV-negative women.[34] Dosage adjustments are not recommended.[14]

3. Therapeutic Efficacy

The potential for oral etravirine to be used as an antiretroviral agent in the treatment of HIV-1 infection was established in several phase IIa[53,54] or IIb[26,55,56] trials conducted in HIV-1-infected patients who were naive to antiretroviral therapy,[53] had NNRTI resistance[26,54,55] (and PI resistance, where specified[26,55]) or were treatment experienced.[56] Nevertheless, in one exploratory phase II study conducted in PI-naive patients with NNRTI resistance,[57] treatment with etravirine (in combination with two NRTIs) was discontinued earlier than planned because of suboptimal virological suppression relative to an alternative regimen (PI plus two NRTIs). The observed suboptimal response to

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Table I. Potential pharmacokinetic drug interactions associated with etravirine (ETR). Data are from studies in HIV-negative[31,39,40,43,52] or healthy[41,42,48,49] volunteers, or patients with HIV type-1 infection.[45,50] Some data were sourced from the EU manufacturer's prescribing information[14]

Coadministered agent	Comments regarding coadministration with ETR	Recommendations regarding use in combination with ETR
Antiretroviral agents		
NNRTIs		
Efavirenz or nevirapine	May ↓ exposure to ETR to a clinically relevant extent[52]	NNRTIs not recommended[14]
PIs[a]		
Unboosted[b] indinavir, saquinavir, atazanavir	↓ Exposure to these PIs (specifically atazanavir C_{min}; $p < 0.05$)[39] to a clinically relevant extent[52]	Unboosted indinavir not recommended[14]
Unboosted[b] nelfinavir	↑ Plasma concentrations of nelfinavir[14c]	Unboosted nelfinavir not recommended[14]
Tipranavir/ritonavir	May ↓ exposure to ETR to a clinically relevant extent[41]	Not recommended[14]
Atazanavir/ritonavir	↓ Exposure to atazanavir and ↑ exposure to ETR[39]	No dosage adjustment recommended[14]
Fosamprenavir/ritonavir	Exposure to amprenavir ↑ when fosamprenavir/ritonavir and ETR were coadministered compared with fosamprenavir/ritonavir given alone[45]	Amprenavir/ritonavir and fosamprenavir/ritonavir dosage adjustments may be required[14]
Lopinavir/ritonavir	No clinically relevant interactions evident[49,50]	No dosage adjustments recommended[14]
High-dose ritonavir[d] (1200 mg/day)	May ↓ exposure to ETR to a clinically relevant extent[52]	There are no recommendations
Entry inhibitors		
Maraviroc[e]	Exposure to maraviroc ↓ when coadministered with ETR and ↑ when coadministered with ETR plus darunavir/ritonavir[48]	Maraviroc 150 mg bid is recommended when coadministered with a potent CYP3A inhibitor, such as a boosted PI; maraviroc 300 mg bid is recommended when coadministered with fosamprenavir/ritonavir[14]
Antibacterial drugs		
Clarithromycin[d,e]	↓ Exposure to clarithromycin and ↑ exposure to its active metabolite (which has reduced activity against *Mycobacterium avium*) relative to clarithromycin alone.[31] ↑ exposure to ETR	Although clarithromycin can be used in patients receiving ETR, alternatives (e.g. azithromycin) are recommended for the treatment of *M. avium* complex infection[14]
Antimycobacterial drugs		
Rifabutin	Exposure to ETR may be altered (AUC_{12} and C_{max} ↓ by 37%)[43]	Caution is advised[14]
Rifampicin (rifampin)[f] or rifapentine[f]	↓ ETR plasma concentrations[14c]	Not recommended[14]
HMG-CoA reductase inhibitors		
Fluvastatin,[a] lovastatin,[e] simvastatin,[e] rosuvastatin[a,e]	↓ Lovastatin, simvastatin or rosuvastatin plasma concentrations and ↑ fluvastatin or rosuvastatin plasma concentrations[14c]	Dosage adjustments of lovastatin, simvastatin, fluvastatin and rosuvastatin may be required[14]
Atorvastatin[e]	↓ Exposure to atorvastatin and ↑ exposure to its active metabolite[40]	Atorvastatin dosages may need to be adjusted depending on clinical response[14]
Other drugs		
Antiarrhythmic agents (e.g. amiodarone, flecainide and systemic lidocaine)	↓ Antiarrhythmic agent plasma concentrations[14c]	Caution is advised, although no dosage adjustments are required with digoxin.[14] Plasma concentration monitoring of antiarrhythmic agents is recommended[14]
Anticoagulants (e.g. warfarin)	↑ Warfarin plasma concentrations[14c]	Monitoring of the international normalized ratio is recommended[14]

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Table I. Contd

Coadministered agent	Comments regarding coadministration with ETR	Recommendations regarding use in combination with ETR
Anticonvulsants: carbamazepine, phenytoin, phenobarbital[f]	↓ ETR plasma concentrations[14]c	Not recommended[14]
Antifungal agents: itraconazole,[d,e] ketoconazole,[d,e] voriconazole,[a,d,g] posaconazole,[d] fluconazole[g]	↑ ETR plasma concentrations; ↑ voriconazole and ↓ itraconazole or ketoconazole plasma concentrations also predicted[14]c	Dosage adjustments not recommended[14]
Diazepam	↑ Diazepam plasma concentrations[14]c	Alternatives to diazepam recommended[14]
Herbal agent *Hypericum perforatum* (St John's Wort)[f]	↓ ETR plasma concentrations[14]c	Not recommended[14]
Immunosuppressants: ciclosporin, sirolimus and tacrolimus	↓ Plasma concentrations of the immunosuppressants[14]c	Caution is recommended[14]
Sildenafil[e]	May ↓ exposure to sildenafil and its active metabolite[42]	Sildenafil dosage may require adjustment based on clinical response[14]
Systemic dexamethasone[f]	↓ ETR plasma concentrations[14]c	Caution is advised; alternative agents are recommended, particularly for long-term treatment[14]

a Substrate of CYP (PIs), CYP2C9 (fluvastatin, rosuvastatin), CYP2C19 (voriconazole).

b Coadministered without low-dose ritonavir.

c Predicted pharmacokinetic drug interaction.

d Inhibitor of CYP3A4.

e Substrate of CYP3A4.

f Inducer of CYP (anticonvulsants, rifampicin, rifapentine), CYP3A4 (St John's Wort, dexamethasone) enzymes.

g Inhibitor of CYP2C9 (fluconazole), CYP2C (voriconazole).

AUC_{12} = area under the plasma concentration-time curve over 12 hours; **bid** = twice daily; **C_{max}** = maximum plasma concentration; **C_{min}** = minimum plasma concentration; **CYP** = cytochrome P450; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **PI** = protease inhibitor; ↑ indicates increase; ↓ indicates decrease.

etravirine relative to the PI regimen was suggested to be a result of the patients having a high degree of NNRTI and NRTI resistance, being naive to PI treatment and, in many cases, using previously used NRTIs. However, as these studies used an etravirine formulation different to the approved formulation[14] used in larger phase III trials, these earlier trials are not discussed further.

The clinical efficacy of oral etravirine used in combination with background therapy (BT; twice-daily darunavir 600 mg plus low-dose ritonavir 100 mg in conjunction with investigator-selected NRTIs [two or more where specified[12]], with or without enfuvirtide), has been evaluated in treatment-experienced patients infected with HIV-1 in two identically designed large (n >590), randomized, double-blind, placebo-controlled, multinational, phase III trials (DUET-1[13] and DUET-2[12]). These studies are ongoing, and the fully published results of predefined 24-week analyses are reviewed along with data from a planned pooled analysis at 24 weeks (n = 1203).[58,59] Longer-term data from the individual studies[60,61] and a pooled analysis[62] at 48 weeks are also discussed. Preliminary results from a pilot, noncomparative, open-label, multicentre, phase II trial evaluating the efficacy of etravirine used in combination with twice-daily raltegravir 400 mg and twice-daily darunavir 600 mg plus ritonavir 100 mg (in combination with BT [NRTIs and/or enfuvirtide], whenever possible) in treatment-experienced patients infected with HIV-1 resistant to multiple antiretroviral agents (n = 103) are also briefly discussed.[63,64] Some data are available as abstracts[59-61,63] and/or posters[58-62] or from other sources.[64,65]

DUET studies

In the DUET studies,[12,13] eligible patients were aged ≥18 years, infected with an HIV-1 strain with at least one mutation associated with NNRTI resistance and three or more primary PI mutations, had been treated for ≥8 weeks with a stable antiretroviral agent regimen and had a plasma HIV-1 RNA level

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of >5000 copies/mL at screening. Among exclusion criteria were an active AIDS-defining illness, chronic hepatitis B or C with AST or ALT levels >5 times the upper limit of normal and a <6-month life expectancy.[12,13]

Patients were randomized to receive etravirine 200 mg twice daily or placebo, in combination with BT.[12,13] In the randomization process, patients were stratified according to enfuvirtide use, previous darunavir use and viral load.

At baseline, patients in the two DUET studies had been infected with HIV for a median of 13.3–15.1 years, and 59–69% of patients in the individual treatment groups had a viral load <100 000 RNA copies/mL.[12,13] Those randomized to receive etravirine or placebo had a baseline median viral load of 4.8 or 4.9 $\log_{10}$ RNA copies/mL in DUET-1,[13] and 4.8 $\log_{10}$ RNA copies/mL (both treatment groups) in DUET-2[12] and the pooled analysis.[58] The median CD4+ cell counts at baseline in the respective treatment groups were 99 or 109 cells/μL (DUET-1[13] and the pooled analysis[58]) and 100 or 108 cells/μL (DUET-2).[12] At least three NNRTI-associated mutations were identified in 38% and 43% of etravirine and placebo recipients in DUET-1,[13] and 39% and 36% in DUET-2.[12] Fewer than 45% of patients in either trial had three or more mutations associated with darunavir resistance.[12,13] Enfuvirtide was used *de novo* in 24% of etravirine recipients and 26% of placebo recipients in DUET-1,[13] 27% of recipients in each of the treatment groups in DUET-2,[12] and in 26% and 27% of the respective recipients in the pooled analysis.[58]

The primary endpoint in both DUET studies was the proportion of patients achieving an HIV-1 RNA level of <50 copies/mL at week 24 of the trial.[12,13] Secondary endpoints included the proportion of patients achieving an HIV-1 RNA level of <400 copies/mL, and changes from baseline in HIV-1 RNA levels and CD4+ cell count. Limited data are also available for clinical endpoints including AIDS-defining illness or death.[12,13,59] Analyses were based on the modified intent-to-treat (ITT) population (i.e. those randomized who received at least one dose of study drug), which included 304[13] or 295[12] patients in the etravirine 200 mg twice-daily groups and 308[13] or 296[12] patients in the placebo groups.

In addition to these endpoints, the DUET studies[12,13] also evaluated health-related quality of life (HR-QOL) at 24 weeks using the Functional Assessment of HIV Infection (FAHI) questionnaire.[66] The prespecified primary analyses included the change from baseline in physical well-being and functional and global well-being subscale scores; the change from baseline in the three remaining FAHI subscale scores and total FAHI score were also reported.[66] HR-QOL assessments were based on the pooled modified ITT patient population (n = 1203) and used analysis of co-variance with last observation carried forward; data are available as a poster.[66]

Results at 24 Weeks

- Etravirine 200 mg twice daily plus BT demonstrated effective virological suppression in treatment-experienced patients infected with HIV-1 with resistance to other available NNRTIs, according to primary endpoint analyses of pooled[58] and individual[12,13] DUET study data. Significantly more etravirine plus BT than placebo plus BT recipients achieved an HIV-1 RNA level of <50 copies/mL after 24 weeks of treatment in the pooled analysis,[58] with similar findings reported in each of the individual DUET trials[12,13] (figure 1).
- According to the results of stratification, the proportion of patients achieving an RNA level of <50 copies/mL at 24 weeks with etravirine plus BT was significantly ($p < 0.0001$) greater than with placebo plus BT in patients who were not using or were re-using enfuvirtide both in the pooled DUET analysis (56% vs 34%)[58] and in the individual studies (55% vs 33% in DUET-1;[13] 58% vs 34% in DUET-2[12]). In contrast, there was no significant difference between etravirine and placebo treatment groups with regard to this endpoint in patients receiving enfuvirtide *de novo* (67% vs 62% of recipients [pooled analysis];[58] 59% vs 56% [DUET-1];[13] 73% vs 68% [DUET-2][12]), although in the pooled analysis,[58] the between-group difference was significant ($p < 0.05$) in favour of etravirine

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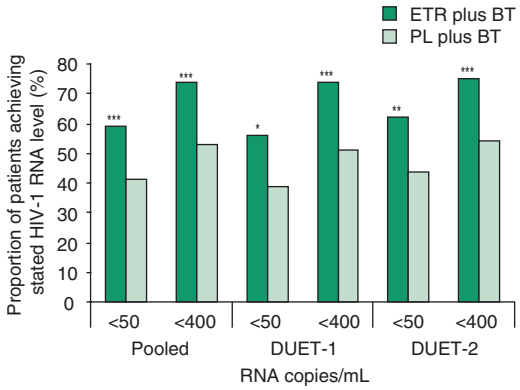

Fig. 1. Efficacy of etravirine (ETR) in treatment-experienced patients with HIV type 1 (HIV-1) infection. The proportion of patients achieving an HIV-1 RNA level of <50 copies/mL (primary endpoint) or <400 copies/mL in a planned 24-wk pooled analysis[58] of two ongoing randomized, double-blind, placebo (PL)-controlled, multinational studies, DUET-1[13] and DUET-2.[12] Patients were infected with an HIV-1 strain with at least one mutation associated with non-nucleoside reverse transcriptase inhibitor resistance and three or more primary protease inhibitor mutations. Patients received ETR 200 mg twice daily (n = 304[13] or 295[12]) or PL (n = 308[13] or 296[12]), in addition to background therapy (BT). Analyses were based on the modified intent-to-treat population. * $p = 0.005$, ** $p < 0.0005$, *** $p \leq 0.0001$ vs PL plus BT.

when adjusted for differences in darunavir resistance (73% vs 62%).

- Further stratification results of the pooled analysis[58] indicated that an RNA level of <50 copies/mL was achieved by a proportion of both etravirine plus BT and placebo plus BT recipients who had baseline viral loads of <30 000 (76% vs 62% of patients), ≥30 000 to <100 000 (61% vs 39%) or ≥100 000 (44% vs 26%) copies/mL.

- These findings are generally supported by data from the individual DUET trials. Among patients who had a viral load of <100 000 copies/mL at baseline, an RNA level of <50 copies/mL was achieved by 68% of etravirine plus BT recipients versus 47% of placebo plus BT recipients, where stated.[13] This endpoint was also achieved in some patients with very high baseline viral loads (≥100 000 RNA copies/mL) in both DUET-1 (38% of etravirine plus BT vs 27% of placebo plus BT recipients)[13] and DUET-2 (51% vs 24%).[12]

- Etravirine plus BT was also generally effective with regard to secondary endpoints. HIV-1 RNA levels were reduced to <400 copies/mL in a significantly greater proportion of etravirine plus BT than placebo plus BT recipients in the pooled DUET study analysis[58] and in each of the individual trials[12,13] (figure 1).

- Etravirine plus BT recipients also had a significantly ($p < 0.0001$) greater mean reduction from baseline in viral load than placebo plus BT recipients (−2.4 vs −1.7 $\log_{10}$ copies/mL [pooled analysis];[58] −2.41 vs −1.70 $\log_{10}$ copies/mL [DUET-1];[13] −2.34 vs −1.68 $\log_{10}$ copies/mL [DUET-2][12]).

- Furthermore, treatment with etravirine plus BT increased the mean CD4+ cell count from baseline to a significantly greater extent than placebo plus BT in DUET-1 (+89 vs +64 cells/μL; $p = 0.0002$),[13] but not in DUET-2 (+78 vs +66 cells/μL);[12] however, data from the pooled analysis indicated etravirine plus BT was superior to placebo plus BT in terms of this endpoint (+86 vs +67 cells/μL; $p < 0.0001$).[58]

- With regard to clinical endpoints, in a pooled analysis,[59] the overall incidence of any AIDS-defining illness or death did not differ significantly between etravirine plus BT and placebo plus BT recipients after 24 weeks' treatment (3.7% vs 6.8% of patients). However, such events occurred in significantly fewer etravirine plus BT than placebo plus BT recipients in the subgroup of patients who were not using or were reusing enfuvirtide (3.8% vs 8.3%; $p = 0.0051$). No significant between-group difference was evident in patients who were receiving enfuvirtide *de novo* with regard to this endpoint (3.3% of etravirine recipients vs 2.5% of placebo recipients).[59]

- In the individual studies, AIDS-defining illnesses (US Center for Disease Control [CDC] category C) were reported in significantly ($p < 0.05$) fewer etravirine plus BT than placebo plus BT recipients in both DUET-1 (2% vs 7%)[13] and DUET-2 (4% vs 5%).[12] However, the treatment groups did not significantly differ with regard to the incidence of CDC category C AIDS-defining illnesses or death (5%[12] and 3%[13] of etravirine recipients vs 7%[12,13] of placebo recipients).

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Results at 48 Weeks

- Preliminary longer-term data from the ongoing DUET studies indicate that the antiretroviral efficacy of etravirine was maintained at 48 weeks in treatment-experienced patients with HIV-1 infection.[60-62] The proportion of patients with an HIV-1 RNA level of <50 copies/mL at this timepoint remained significantly ($p < 0.0001$) greater with etravirine plus BT than with placebo plus BT in a pooled analysis of the DUET studies (61% vs 40%)[62] and in each of the individual trials (60% vs 39% [DUET-1];[60] 61% vs 41% [DUET-2][61]).

- Among patients reusing or not using enfuvirtide, there remained significantly ($p < 0.0001$) more etravirine plus BT than placebo plus BT recipients with an RNA level of <50 copies/mL at 48 weeks in each of the DUET studies (57% vs 33% in both trials).[60,61] However, the findings of the studies differed as to whether there was a significant between-group difference with regard to this endpoint among patients who received enfuvirtide *de novo* (68% vs 56% [DUET-1[60]]; 75% vs 61%; $p = 0.038$ [DUET-2[61]]). Notably, pooled data[62] from the two DUET trials indicated that a significantly ($p < 0.05$) greater percentage of etravirine plus BT than placebo plus BT recipients had an RNA level of <50 copies/mL at 48 weeks, irrespective of whether enfuvirtide was being used *de novo* (71% vs 58%) or was being reused or not used (57% vs 33%).

- After 48 weeks' therapy, there remained significantly ($p < 0.0001$) more etravirine plus BT than placebo plus BT recipients with an HIV-1 RNA level of <400 copies/mL both in the pooled DUET study analysis (72% vs 47%)[62] and in the individual trials (71% vs 47% [DUET-1];[60] 72% vs 48% [DUET-2][61]). Furthermore, mean reductions from baseline in viral load remained significantly ($p < 0.0001$) greater with etravirine plus BT than with placebo plus BT in each of these analyses (−2.3 vs −1.5 $\log_{10}$ copies/mL in the pooled analysis,[62] −2.4 vs −1.8 in DUET-1[65] and −2.2 vs −1.5 $\log_{10}$ copies/mL in DUET-2[61]). Etravirine plus BT recipients also had mean increases from baseline in CD4+ cell count that were significantly ($p < 0.05$) greater than those seen in placebo plus BT recipients at this timepoint (+98 vs +73 cells/μL [pooled analysis];[62] +103 vs +74 cells/μL [DUET-1];[60] +94 vs +72 cells/μL [DUET-2][61]).

Health-Related Quality of Life

- Etravirine plus BT improved HR-QOL in treatment-experienced patients infected with HIV-1 in the DUET studies.[66] After 24 weeks of therapy, etravirine plus BT recipients had significantly ($p < 0.05$) greater improvements from baseline than placebo plus BT recipients in both physical well-being (+2.2 vs +1.4) and functional and global well-being (+1.0 vs +0.3) scores (data estimated from a graph; primary HR-QOL endpoints). Improvement in each of the scores was significant ($p < 0.001$) versus baseline in patients treated with etravirine, whereas only the physical well-being score was significantly ($p < 0.001$) improved from baseline in those who received placebo.

- Etravirine plus BT also produced improvements from baseline in emotional well-being (+2.5 vs +1.6) and total FAHI (+5.5 vs +3.0) scores that were significantly ($p < 0.05$) greater than with placebo plus BT (data estimated from a graph), although improvements were significant ($p < 0.001$) versus baseline in each treatment group.[66] No significant improvement or deterioration in social well-being or cognitive functioning scores was observed in the recipients of either treatment.

Other Studies

- Preliminary data from a noncomparative phase II study suggest that etravirine used in combination with raltegravir and darunavir/ritonavir plus BT (NRTIs and/or enfuvirtide) may be effective in the treatment of treatment-experienced patients infected with HIV-1 with resistance to multiple antiretroviral therapies.[63] An HIV-1 RNA level of <50 copies/mL was achieved by 90% of patients after 24 weeks of treatment (primary endpoint); 55% and 88% of patients had achieved such a viral load after 4 and 12 weeks. The majority of patients (95%) had achieved an HIV-1 RNA level <400 copies/mL at week 24.

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4. Tolerability

The tolerability of oral etravirine 200 mg twice daily was examined in treatment-experienced patients infected with HIV-1 participating in the two well designed, placebo-controlled, phase III studies, DUET-1[13,60] and DUET-2[12,61] (see section 3 for study details, including details of BT regimens). Discussion in this section focuses on a planned pooled analysis (n = 1203)[67] of the 24-week tolerability data from the two DUET studies[12,13] and data from a 48-week pooled analysis (n = 1203) of DUET-1[60] and DUET-2.[61] Data from other pooled analyses[68-70] of these trials are also included. Some data are available only as abstracts and/or posters,[60,61,67-70] or from other sources.[71]

- Etravirine was generally well tolerated in treatment-experienced patients with HIV-1 infection, with a tolerability profile generally similar to that of placebo.[67] Treatment-emergent adverse events were reported in 92.5% of both etravirine and placebo recipients after 24 weeks of therapy in a pooled analysis[67] of the DUET-1[13] and DUET-2[12] trials. The majority of treatment-emergent adverse events were reported as being of mild to moderate severity.[12,13]
- After 24 weeks of treatment, serious treatment-emergent adverse events considered related to study drug had been reported in 2.3% of etravirine recipients compared with 2.5% of placebo recipients.[67] Grade 3 or 4 treatment-emergent adverse events were reported in 24.7% and 27.2% of the respective recipients.[67]
- Rash was the most common treatment-emergent adverse event in etravirine recipients and was the only adverse event that occurred in significantly more etravirine than placebo recipients (17.0% vs 9.4% of patients; p = 0.0001).[67] In general, rashes occurred soon after initiating treatment (median onset on day 11[13] or 14[12] of treatment), although they were generally mild or moderate in severity,[67] of limited duration (median 12[13] or 16[12] days) and were considered unrelated to CD4+ cell count.[67] Although rash occurred in a significantly higher proportion of female than male etravirine recipients in DUET-1 (34% vs 18%; p = 0.0192), there was no appreciable between-sex difference in terms of severity.[13]
- There was no significant difference between etravirine and placebo recipients with regard to the incidence of nervous system (14.9% vs 18.5% of patients), psychiatric (12.9% vs 15.1%) or hepatic (5.3% vs 5.1%) treatment-emergent adverse events after 24 weeks' therapy.[67] Neuropsychiatric adverse events were generally mild or moderate in severity.[12,13]
- In another pooled analysis of the DUET studies (n = 1130),[68] the tolerability profile of etravirine (excluding rash) was generally similar to that of placebo after 24 weeks' therapy regardless of whether patients were (n = 140) or were not (n = 990) co-infected with hepatitis B and/or C. Hepatic treatment-emergent adverse events occurred in 11% and 6% of etravirine and placebo recipients who were co-infected compared with 5% of patients in each treatment group who were not co-infected.[71] A proportion of patients co-infected with hepatitis B and/or C had hyperbilirubinaemia or elevations in levels of AST, ALT or alkaline phosphatase of grade 3 or 4 in severity (0–7% of etravirine recipients vs 1–6% of placebo recipients) as did patients who had no such co-infection (0.2–2% vs 0.4–1.2%).[68]
- Discontinuation of treatment because of adverse events had occurred in 5.8% of etravirine recipients compared with 4.5% of placebo recipients in the DUET trials after 24 weeks of therapy.[67] Rash was the reason for discontinuation in 2.2% of etravirine recipients; no placebo recipients discontinued because of this event.[67]
- The proportion of patients who died because of treatment-emergent adverse events at 24 weeks was not significantly different between etravirine and placebo recipients in DUET-1 (4 of 304 patients [1%] vs 8 of 308 patients [3%]),[13] although was significantly (p = 0.0217) lower with etravirine in DUET-2 (4 of 295 etravirine recipients [1%] vs 7 of 296 placebo recipients [2%]).[12] No deaths in either study were considered related to the study drug.
- Etravirine continued to be well tolerated for up to 48 weeks in the DUET studies,[60,61] with treatment-

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emergent adverse events, mostly mild to moderate in severity, documented in 96% of both etravirine and placebo recipients in a pooled analysis of the studies.[60,61]

- Consistent with 24-week data, rash remained the most commonly reported treatment-emergent adverse event in etravirine recipients in the pooled 48-week data analysis (19% vs 11% of placebo recipients).[60,61] The overall occurrence of rash was significantly greater with etravirine than with placebo in DUET-1 (22% vs 11% of patients; p = 0.0003),[60] although the between-group difference did not reach statistical significance in DUET-2 (17% vs 11%; p = 0.0577).[61] Notably, rash generally occurred most frequently within the first 2 weeks of treatment, with fewer than 1.0%[60] or 1.5%[61] of all patients reporting new cases of rash after the first 6 weeks of therapy. The majority of documented rashes were mild or moderate in severity; no grade 4 rashes were reported. Moreover, in a detailed analysis of rash (n = 1203),[70] the incidence of etravirine-associated rash did not significantly differ between patients who had previously had an NNRTI-related rash (n = 46) and patients who had not (n = 553) [21.7% vs 19.0% of patients].

- The tolerability profile of etravirine remained similar to that of placebo with regard to the incidence of nervous system adverse events of interest (17% vs 20% of patients) and psychiatric adverse events (17% vs 20%) in a pooled 48-week data analysis of the DUET studies.[69] There was also no significant difference between etravirine and placebo recipients in the incidence of any neuropsychiatric adverse events of interest (30% vs 34%), irrespective of whether patients had a history of psychiatric symptoms (40% vs 40%) or not (22% vs 30%) [some p-values were not reported].

- Discontinuation of therapy because of adverse events occurred in 7% of etravirine versus 6% of placebo recipients throughout 48 weeks of treatment in the pooled analysis,[60,61] with 2% and 2.4% of etravirine recipients in DUET -1[60] and DUET-2[61] discontinuing because of rash.

- In general, there were no clinically relevant changes in ECG or laboratory measurements (including liver enzymes and lipids) in either etravirine or placebo recipients during 24[67] or 48[60,61] weeks of treatment.

5. Dosage and Administration

The recommended dosage of oral etravirine in treatment-experienced adult patients with HIV-1 infection is 200 mg twice daily taken after a meal, in combination with other antiretroviral agents, including a boosted PI.[14] Etravirine is not recommended for use in combination with only NRTIs in patients who have experienced an unsuccessful virological response with an NRTI- and NNRTI-containing regimen.[14]

There are several pharmacokinetic interactions between etravirine and other drugs that inhibit, induce and/or are substrates of CYP enzymes (see section 2). Consequently, coadministration of etravirine with such agents may not be recommended or dosage adjustments may be required. In pregnancy, etravirine therapy should only be considered if the potential maternal benefits justify the possible fetal risks.[14] Local prescribing information should be consulted for detailed information regarding drug interactions, dosage adjustments, contraindications, warnings and other precautions.

6. Etravirine: Current Status

In the EU,[14] etravirine has received conditional approval, in combination with a boosted PI and other antiretroviral drugs, for the treatment of HIV-1 infection in treatment-experienced adult patients. The drug is also approved in the US,[72] 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 are infected with HIV-1 strains resistant to an NNRTI and other antiretroviral agents. Etravirine is also approved in Canada[73] and several other countries worldwide for similar indications. There are currently no data pertaining to the efficacy or tolerability of etravirine in paediatric or treatment-naive patients.

In combination with other antiretroviral agents (including darunavir/ritonavir, NRTIs and optional

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enfuvirtide), etravirine was effective in suppressing HIV-1 RNA levels relative to placebo after 24 weeks of therapy in treatment-experienced adult patients with HIV-1 infection with resistance to previous NNRTIs, according to the results of two well designed, ongoing, phase III studies, DUET-1 and DUET-2. The antiretroviral efficacy of etravirine was maintained at 48 weeks. Etravirine was generally well tolerated, with a tolerability profile generally similar to placebo.

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