Scottish Medicines Consortium

etravirine 100mg tablet (Intelence®) No. (530/09)
Tibotec

09 January 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

etravirine (Intelence®), in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is not recommended for use within NHS Scotland for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients.

In HIV-1 infected adults with resistance to currently available non-nucleoside reverse transcriptase inhibitors (NNRTIs) and at least three primary protease inhibitor (PI) mutations who were receiving an optimised background regimen that included boosted darunavir, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and optional enfuvirtide, etravirine produced significant improvements in virological, immunological and clinical outcomes when compared with placebo.

The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In combination with a boosted protease inhibitor and other antiretroviral medicinal products, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients.

This indication is based on week 24 analyses from two randomised, double-blind, placebo-controlled phase III studies in highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors, where etravirine was investigated in combination with an optimised background regimen (OBR) which included darunavir / ritonavir.

Dosing information

200mg orally twice daily following a meal. Etravirine must always be given in combination with other antiretroviral products.

Therapy should be initiated by a physician experienced in the management of HIV infection.

Product availability date

29 September 2008

Summary of evidence on comparative efficacy

Etravirine is a new non-nucleoside reverse transcriptase inhibitor (NNRTI) that is active against wild-type and NNRTI-resistant HIV. European regulatory approval was based on week 24 analysis of two identical 48-week, double-blind, phase III studies that recruited HIV-1 infected adults failing antiretroviral therapy with evidence of resistance to currently available NNRTIs and at least three primary protease inhibitor (PI) mutations. The current submission to SMC considers a pre-specified pooled analysis of both 24-week and 48-week data from these studies.

Patients were randomly assigned to receive either etravirine 200mg or placebo, each given twice daily with an optimised background regimen (OBR) that included darunavir 600mg boosted with low-dose ritonavir (100mg), both administered twice daily, investigator-selected nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), based on the patient's screening genotypic resistance and treatment history, and optional enfuvirtide.

The primary endpoint was the proportion of patients with a confirmed viral load of <50 copies/mL at week 24 according to the time to loss of virologic response (TLOVR) algorithm. The secondary immunological and virological efficacy outcomes were change in CD4 cell count from baseline, proportion of patients with viral load <400 copies/mL, mean change in $\log_{10}$ viral load and the proportion of patients with decrease in viral load of >1.0 $\log_{10}$ copies/mL. The Cochran-Mantel-Haenszel (CMH) test controlling for stratification factors (use of enfuvirtide in the underlying antiretroviral therapy, previous use of darunavir and baseline plasma viral load) was applied to test the difference between the treatment groups. The intention-to-treat (ITT) population was used as primary population for the entire analysis.

In the study conducted mainly in the Americas (North and South), significantly more patients treated with etravirine than placebo achieved a viral load of <50 copies/mL at week 24: 56% versus 39%, with similar significant results in the study conducted mainly in North America, Australia and Europe: 62% versus 44%, respectively. The pooled 24-week data showed that

61% of the 599 patients receiving etravirine plus OBR achieved an undetectable viral load (<50 copies/mL), versus 41% of the 604 patients in the placebo plus OBR group. The durability of this response was demonstrated to 48 weeks (61% versus 40%, respectively). Etravirine plus OBR also demonstrated significant improvements over placebo plus OBR when considering viral load <400 copies/mL. At 24 weeks this was achieved by 74% of patients in the etravirine plus OBR group versus 52% in the placebo plus OBR group, respectively. The corresponding figures at 48 weeks were 72% and 47% respectively. Similar benefits were demonstrated for the decrease in viral load of >1.0 $\log_{10}$ versus baseline; 79% at 24 weeks in the etravirine plus OBR group versus 58% in the placebo plus OBR group. The corresponding figures at 48 weeks were 74% and 51% respectively.

Patients treated with etravirine plus OBR had a significantly greater mean increase in CD4 cell count of 84 cells/mm^3 compared to an increase of 65 cells/mm^3 in patients treated with placebo plus OBR in the pooled 24 weeks analysis. This response was improved at 48 weeks, with 98 and 73 cells/mm^3 in the respective groups. The mean $\log_{10}$ viral load reduction from baseline was -2.37 in the etravirine plus OBR group at week 24 versus -1.69 in the placebo plus OBR group; the corresponding figures at week 48 were -2.25 and -1.49 respectively.

As a statistical interaction between etravirine and enfuvirtide use was demonstrated using the Breslow-Day test for the homogeneity of odds ratios, the primary analysis was performed for two separate categories reflecting enfuvirtide use (*de novo* use versus not *de novo* use that included re-use and no use). In patients, who were re-using or not using enfuvirtide (n=891) the etravirine plus OBR group was associated with a significantly higher virological response (viral load <50 copies/mL) compared with the placebo plus OBR group both at 24 weeks and at 48 weeks. In the group of patients using *de novo* enfuvirtide (n=312) the proportion of patients achieving viral load <50 copies/mL was higher in the etravirine plus OBR group compared with placebo plus OBR, and was statistically significant at week 48.

With regards to clinical outcomes, treatment with etravirine plus OBR resulted in a significantly greater reduction in hospitalisations, re-hospitalisations and total time (of the treatment group) spent hospitalised compared to placebo plus OBR by week 48. The proportion of patients experiencing any AIDS defining illness or death at 48 weeks was lower in the etravirine plus OBR group than in the placebo plus OBR group. Improvements in health-related quality of life were also seen in the etravirine plus OBR group when compared to the placebo plus OBR group although there were variations in the extent of improvement across the pre-defined parameters of the Functional Assessment of HIV infection Instrument (FAHI).

Analyses of the pooled data from the two pivotal clinical studies identified 17 etravirine resistance-associated mutations. A weighted etravirine mutation score was developed to provide guidance in the interpretation of etravirine susceptibility.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

No comparative safety data are available. The pooled data from the pivotal studies comparing etravirine plus OBR with placebo plus OBR demonstrated that etravirine was well tolerated and was not associated with any specific toxicity or tolerability issues with the exception of rash. In general, the nature and extent of adverse events observed in patients receiving etravirine plus OBR were similar to placebo plus OBR. Most adverse events were low in severity and infrequently led to discontinuations (7% versus 6% for patients in the etravirine plus OBR group and placebo plus OBR group, respectively). Twenty-three

patients died due to adverse events that started during the treatment period: 8 (1.3%) subjects in the etravirine plus OBR group and 15 (2.5%) subjects in the placebo plus OBR group.

Considering both the 24 week and 48 week analyses of data the most common adverse events (AEs) (in at least 10% of the etravirine-treated subjects) observed with etravirine plus OBR were diarrhoea, nausea and rash. The incidence of rash was higher in the etravirine plus OBR group than the placebo plus OBR group (17% versus 9% at 24 weeks and 19% versus 11% at 48 weeks). Overall, the etravirine rash was shown to have an early onset, most frequently appeared in the week following treatment initiation, had a short duration (median 15 days), was generally mild to moderate in severity (mostly maculopapular with no mucosal involvement) and infrequently resulted in study discontinuation. The incidence of rash was higher in female patients than in males but there were no clear differences in severity or treatment discontinuation according to gender. The incidence of rashes in the etravirine-treated subjects was higher in patients with a history of NNRTI-associated rash compared to patients without such history. Permanent discontinuations on etravirine were also more frequent in subjects with a history of NNRTI-associated rash compared to patients without such a history.

Summary of clinical effectiveness issues

The British HIV Association (BHIVA) guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy (2008) indicate that the virological and immunological efficacy outcomes used to assess treatment response in the pivotal studies (plasma HIV RNA levels and CD4 cell counts) are proven surrogate markers for HIV disease progression and are routinely used as markers of the biological activity of antiretroviral therapy. However, the guidelines note that CD4 count and viral load responses do not precisely reflect the expected clinical outcome and are not perfect surrogates of the clinical response. This point was addressed in the pivotal clinical studies for etravirine through an assessment of the rate and duration of hospitalisation, AIDS defining illnesses or death and health-related quality of life.

The main limitation of the pivotal etravirine clinical studies was the protease inhibitor component of the OBR that was fixed with darunavir/ritonavir. The European Medicines Agency (EMEA) European Public Assessment Report (EPAR) for etravirine notes that, based on available pharmacokinetic interaction data, darunavir/ritonavir has been shown to significantly decrease the etravirine exposure (by approximately 40%) and the C_{min} (by approximately 50%). Considering this point in combination with the noted high virological and immunological response seen in the placebo group (which has been attributed to the use of darunavir/ritonavir), the impressive clinical efficacy of etravirine demonstrated in the pivotal clinical studies could represent a conservative estimate of its true clinical potential.

Based on the advice of experts, the manufacturer suggests that darunavir is not often used in treatment-experienced patients in Scotland and hence the OBR used in the pivotal studies might not translate to Scottish clinical practice. However the EPAR states that, with the exception of the combined use of tipranavir/ritonavir, the extrapolation of the pivotal etravirine studies to the combined use of other boosted protease inhibitors appears reasonable. Nevertheless, to provide reassurance of the combined use of etravirine with boosted protease inhibitors other than darunavir/ritonavir, the EMEA has requested that a dedicated confirmatory study be conducted post-approval as part of the specific obligations of the conditional marketing authorisation.

When compared with currently available NNRTIs, etravirine appears to have a higher genetic barrier to resistance. The EPAR states that the available resistance data show that

the presence of the mutation K103N alone did not appear to affect the response in the etravirine group. However, the EMEA requested further analyses to substantiate whether K103N in combination with other NNRTI mutations influences the virologic response to etravirine. Moreover, it is important to take into account that etravirine's virologic response will be lost if three or more of the 13 identified resistance associated mutations are present at baseline. The EPAR concludes that, although improved as compared to that of existing NNRTIs, the genetic barrier of etravirine is limited. Its use will need to be adequately 'protected' by active components within the antiretroviral combination therapy.

Etravirine is an inducer of cytochrome P450 3A4 and has some clinically significant interactions with other antiretroviral drugs. With tipranavir/ritonavir, the area under the curve (AUC) for etravirine is decreased by 76%, while etravirine increases the AUC for amprenavir by 69% when given with fosamprenavir/ritonavir.

Summary of comparative health economic evidence

The manufacturer supplied a lifetime cost-utility Markov model with cycles of 3 months duration. This adapted a model developed for use in a previous SMC submission. The base case compared the cost effectiveness of etravirine plus OBR with OBR as observed within the two pivotal clinical studies.

Treatment duration was estimated from expert opinion and was a function of the degree of viral suppression. During treatment patients experienced an initial 6 months of rapid CD4 cell count increase, differentiated by degree of viral suppression and by treatment. Subsequent to this, patients with an undetectable viral load experienced 2.5 years of continued treatment, those with a suppressed viral load experienced an additional 6 months of continued treatment as did those whose viral loads were not suppressed. During this subsequent treatment patients experienced a further slow CD4 cell count increase, again differentiated by degree of viral suppression and by treatment. Thereafter patients moved on to a further regimen which was assumed to be mainly raltegravir.

The extent of viral suppression and associated CD4 cell count increases were drawn from the pooled results of the two pivotal clinical studies. HIV and non-HIV mortality rates were also taken from the two clinical studies for the first year of the model. Thereafter the HIV mortality rate was drawn from a reference within the literature, differentiated by CD4 cell count. The non-HIV mortality rate was drawn from a separate paper within the literature but not differentiated by CD4 cell count. Utility values were drawn from a standard reference within the literature, while non-anti-retroviral treatment costs were estimated from an analysis of a UK HIV-AIDS dataset. The effectiveness of subsequent treatment was drawn from raltegravir, maraviroc and tipranavir/ritonavir studies.

The central estimate was that the etravirine arm would cost an additional £13,638 and result in an additional 0.4 QALYs, thus yielding a cost-effectiveness ratio of £34,153 per QALY. A probabilistic analysis yielded a slightly worse central estimate of the cost-effectiveness ratio of £34,583 per QALY. Results were extremely sensitive to the assumed duration of continued treatment after the first six months, with the cost-effectiveness estimate worsening the longer patients with an undetectable viral load remained on the first regimen.

An additional pair of scenario analyses compared the active arm of the etravirine studies with the control arms of darunavir and maraviroc studies. These yielded cost-effectiveness estimates of £23,750 per QALY and £28,791 per QALY respectively. However in effect these estimated the joint cost-effectiveness of adding etravirine plus darunavir/ritonavir to OBR

due to the design of the pivotal etravirine studies. The manufacturer acknowledged that these analyses were not based on formal indirect comparisons.

Weaknesses of the analysis included:

- differentiating the CD4 cell count increases in patients with a viral load of less than 50 copies per ml by treatment arm when there did not seem to be strong evidence for this, further complicated by patients who achieved a lesser viral suppression typically experiencing a higher CD4 cell count increase;
- not considering the possibility of raltegravir as a first regimen comparator to be added to OBR rather than etravirine.

Supplementary analyses were provided to address the issue of the lack of comparison with raltegravir. Raltegravir, being more expensive and more effective than etravirine, had ICERs of £58,125 to £110,291 depending on the assumptions used. This led the manufacturer to conclude that etravirine was a cost-effective alternative to raltegravir. However, a full range of sensitivity analyses were not provided on these estimates and only limited information was provided on the indirect comparison.

Given these issues and the high cost per QALY estimate, the manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

BHIVA guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy, 2008, recommend that when there is sustained viral load rebound on initial therapy the choice of a new regimen should be guided by the results of current and previous resistance testing, treatment history and the ability of the patient to adhere to and tolerate individual drugs. Resistance testing is important to identify which drugs will possibly be of most benefit (i.e. active). The guidelines consider treatment options following virological failure with protease inhibitor mutations and NNRTI mutations.

Additional information: previous SMC advice

Following a full submission SMC published advice in June 2002: tenofovir disoproxil fumarate (Viread®) is recommended in combination with other antiretroviral agents in HIV infected patients over 18 years of age experiencing virological failure. Tenofovir produces a clinically relevant viral response in heavily pre-treated patients experiencing early virological failure. Tenofovir should be initiated under the general supervision of specialists experienced in the management of HIV/AIDS patients.

Following a full submission SMC published advice in August 2003: enfuvirtide (Fuzeon®) is recommended for restricted use within NHS Scotland. It is restricted to use by clinicians experienced in the management of HIV infected patients. It is licensed for use in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected patients who have received treatment with and failed on regimens containing at least one medicinal product form each of the following antiretroviral classes, protease inhibitors, non-nucleoside

reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors, or who have intolerance to previous antiretroviral regimens.

Following a full submission SMC published advice in September 2004: atazanavir (Reyataz®) is accepted for restricted use within NHS Scotland for the treatment of HIV-1 infected, antiretroviral treatment experienced adults, in combination with other antiretroviral medicinal products in those patients who do not require concomitant statin use. The combination of atazanavir and ritonavir was non-inferior to a standard boosted protease inhibitor (PI) regimen in patients with moderate previous exposure to PIs, however, it was inferior in patients with PI-resistant viruses. It was associated with lower incidences of diarrhoea and lipid adverse-effects and a higher incidence of hyperbilirubinaemia. The health economic case for use is acceptable when atazanavir is compared with a standard boosted protease inhibitor regime in patients receiving concomitant statins.

Following an abbreviated submission SMC published advice in May 2005: abacavir tablets 300mg (Ziagen®) are accepted for use in a once-daily dosing regimen in NHS Scotland for treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and adolescents over 12 years, in combination with other antiretroviral medicinal products.

Following an abbreviated submission SMC published advice in May 2005: tablets delivering a fixed dose combination of abacavir 600mg and lamivudine 300mg (Kivexa®) are accepted for use in NHS Scotland for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and adolescents over 12 years, in combination with other antiretroviral medicinal products. Both products are nucleoside reverse transcriptase inhibitors. In patients for whom this combination is appropriate, it offers a single tablet at a lower cost per dose compared with the individual components.

Following a full submission SMC published advice in July 2005: fosamprenavir (Telzir®) in combination with low dose ritonavir is accepted for use within NHS Scotland for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products. It should be prescribed by HIV specialists only.

Following a resubmission SMC published advice in February 2006: emtricitabine (Emtriva®) is accepted for use within NHS Scotland for the treatment of HIV-1 infected adults in combination with other antiretroviral agents. It should be prescribed only by HIV specialists. This indication is based on studies in treatment-naïve patients and treatment-experienced patients with stable virological control in whom, as part of antiretroviral therapy (ART) regimens, it has shown virological responses comparable with other ART. There is no experience of use in patients who are failing their current regimen or who have failed multiple regimens.

Following a resubmission SMC published advice in September 2006: tipranavir (Aptivus®) in combination with low dose ritonavir is accepted for restricted use within NHS Scotland for the treatment of HIV-1 infection in highly pre-treated adult patients with virus resistant to multiple protease inhibitors. At 48 weeks, tipranavir, in combination with low dose ritonavir, showed a significant improvement in the reduction of viral load compared with other protease inhibitor plus ritonavir regimens. Although the overall rate and type of adverse events were similar, tipranavir had a higher incidence of hepatotoxicity, hyperlipidaemia, bleeding events and rash. Tipranavir is more expensive than other protease inhibitors and it is restricted to patients with a tipranavir mutation score of less than 4.

Following an abbreviated submission SMC published advice in November 2006: lopinavir 200 mg, ritonavir 50 mg tablet (Kaletra®) is accepted for use in NHS Scotland for the treatment of HIV-1 infected adults and children above the age of 2 years, in combination with other antiretroviral agents. For patients for whom this drug combination is appropriate, it is

associated with a reduced pill burden compared to an existing solid oral dose formulation containing these drugs at no increased cost.

Following a full submission SMC published advice in June 2007: darunavir (Prezista®) is accepted for use within NHS Scotland, co-administered with ritonavir and in combination with other antiretroviral medicinal products, for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adult patients who have failed on more than one regimen containing a protease inhibitor (PI). At 24 and 48 weeks, darunavir, in combination with low dose ritonavir, showed a significant improvement in the reduction of viral load compared with other protease inhibitor plus ritonavir regimens.

In the absence of a submission from the holder of the marketing authorisation SMC published advice in December 2007: fosamprenavir (Telzir®) in combination with low dose ritonavir is not recommended for use within NHS Scotland for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adolescents and children of 6 years and above in combination with other antiretroviral medicinal products. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHS Scotland.

Following an abbreviated submission SMC published advice in April 2008: efavirenz 600mg, emtricitabine 200mg, tenofovir disoproxil 245mg as fumarate (Atripla®) is accepted for use in NHS Scotland for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in this fixed dose combination prior to initiation of their first antiretroviral treatment regimen. It may be used to simplify the regimen of patients for whom this combination is indicated (see above) and in whom all three agents are appropriate components at the doses provided by this fixed dose combination.

Following a full submission SMC published advice in May 2008: raltegravir (Isentress®) is accepted for restricted use within NHS Scotland in combination with other antiretroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV-1) infection in treatment experienced adult patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. It is restricted to triple class resistant HIV-1 infection. Addition of raltegravir to optimised background therapy in treatment experienced patients with documented resistance to at least one drug in each of the three HIV antiviral classes, significantly increased the number of patients achieving clinically significant reductions in viral load.

Following a resubmission SMC published advice in October 2008: maraviroc (Celsentri®) is not recommended for use within NHS Scotland in combination with other antiretroviral medicinal products for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable. When added to optimised background therapy, maraviroc was associated with a significant reduction in viral load compared with addition of placebo in heavily pre-treated patients. However, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Additional information: comparators

The pivotal clinical studies were placebo-controlled and did not include an active comparator to etravirine. The BHIVA guidelines (2008) recommend that when treatment-experienced patients with options experience sustained viral load rebound on initial therapy, the physician should construct a new HIV treatment that includes at least two (or preferably three) active agents. The use of an agent from a new drug class is likely to be more effective. There are therefore, no pre-specified treatment regimens and as such it is difficult to identify any specific comparator products. However, an advisory panel of Scottish experts convened by the submitting company advised that an OBR including a boosted protease inhibitor represents the most important comparison from a NHS Scotland perspective. Other products that may be used in treatment resistant patients include raltegravir, maraviroc and enfuvirtide.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Etravirine	**200mg twice daily**	**3,891**
Enfuvirtide	90mg subcutaneously twice daily	13,965*
Maraviroc	150mg to 600mg twice daily	6,705 to 13,410
Raltegravir	400mg twice daily	7,875
Tipranavir plus ritonavir	500mg tipravavir plus 200mg ritonavir twice daily	7,602
Darunavir plus ritonavir	600mg darunavir plus 100mg ritonavir twice daily	6,255
Atazanavir plus ritonavir	300mg atazanavir plus 100mg ritonavir once daily	4,251
Fosamprenavir plus ritonavir	700mg fosamprenavir plus 100mg ritinavir twice daily	4,165
Saquinavir plus ritonavir	1000mg saquinavir plus 100mg ritinavir twice daily	4,065
Lopinavir plus ritonavir	400mg lopinavir plus 100mg ritonavir twice daily	3,740

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 22 October 2008. *Cost from BNF 56, September 2008.

Additional information: budget impact

Based on an estimated eligible population of 172 in year 1 rising to 252 by year 5, coupled with a market share of 37% (64 patients) in year 1 rising to 58% (148 patients) by year 5, the manufacturer estimated a gross drug cost of £249k in year 1, rising to £576k by year 5. No drug cost offset was anticipated as etravirine is an add-on therapy.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 05 December 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

The undernoted references were supplied with the submission. Those shaded grey are additional to the references supplied with the submission.

Tibotec. Week 48 pooled DUET efficacy report, 18th May 2008

The European Medicines Agency (EMEA). European Public Assesment Report (EPAR) for etravirine (Intelence®), 04/09/08 EMEA H-C-900. www.emea.europa.eu

Trottier B, Johnson M, Katlama C et al. Pooled 48-Week Analysis of DUET-1 and DUET-2: durable efficacy and safety results of etravirine (ETR; TMC125) in treatment-experienced HIV-infected patients. Poster No-P167 at the 17th Annual Canadian Conference on HIV/AIDs Research, Canadian Association For HIV Research (CAHR), Montreal, Canada, April 24 to 27 2008

Madruga JV, Cahn P, Grinsztejn B et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. The Lancet 2007;370:29-38

Lazzarin A, Campbell T, Clotet B et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. The Lancet 2007;370:39-48