Scottish Medicines Consortium

fosamprenavir 700mg tablets and oral suspension 50mg/ml (Telzir®) No. (188/05)

GlaxoSmithKline UK

10 June 2005

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

ADVICE: following a full submission

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.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Fosamprenavir 700mg tablets and oral suspension 50mg/ml (Telzir®)

Licensed indication under review

In combination with low dose ritonavir, fosamprenavir is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products. In moderately antiretroviral experienced patients, fosamprenavir in combination with low dose ritonavir has not been shown to be as effective as lopinavir / ritonavir. In heavily pretreated patients the use of fosamprenavir in combination with low dose ritonavir has not been sufficiently studied. In protease inhibitor (PI) experienced patients the choice of fosamprenavir should be based on individual viral resistance testing and treatment history.

Dosing information under review

700mg twice daily

UK launch date

September 2004

Comparator Medications

Other protease inhibitors: nelfinavir, lopinavir/ritonavir, atazanavir, amprenavir, indinavir, saquinavir and ritonavir

Cost per treatment period and relevant comparators

Basic NHS costs based on Mims March 2005 prices.

Drug	Daily Dose	Cost per Day	Cost per Year
Fosamprenavir + ritonavir	**700mg +100mg twice daily**	**£10.28**	**£3755**
Atazanavir + ritonavir	300mg +100mg daily	£11.64	£4251
Lopinavir/ritonavir	400mg/100mg twice daily	£10.25	£3740
Amprenavir +ritonavir	600mg + 100mg twice daily	£9.22	£3366
Nelfinavir	1250mg twice daily or 750mg three times daily	£9.11 £8.19	£3323 £2991
Saquinavir + ritonavir	1g + 100mg twice daily	£7.64	£2788
Indinavir	800mg three times daily	£6.03	£2202

Summary of evidence on comparative efficacy

Fosamprenavir is the phosphate ester pro-drug of amprenavir, and has no inherent antiretroviral (ART) activity of its own. It is hydrolysed in the intestinal epithelium to amprenavir, a non-peptide competitive inhibitor of HIV protease, which binds to the active site of HIV protease and prevents the processing of viral polyprotein precursors. Low dose ritonavir is used in combination as it inhibits cytochrome P450 3A4 isoenzyme increasing drug exposure and prolonging serum half-life.

There are two pivotal, 48 week studies of boosted fosamprenavir in combination with ritonavir; the SOLO study in ART naïve patients followed by an ongoing extension study and the CONTEXT study in protease inhibitor experienced patients. The open-label SOLO study randomised 660 patients, to either fosamprenavir 1400mg plus ritonavir 200mg daily (licensed dose: 700mg fosamprenavir plus 100mg ritonavir, both twice daily) (n=327) both in combination with lamivudine 150mg twice daily and abacavir 300mg twice daily. The primary endpoint, the proportion of patients with plasma HIV-1 RNA <400 copies/ml at 48 weeks, was reached by 69% (221/322) of fosamprenavir patients and 68% (221/327) of nelfinavir patients. The secondary endpoint of patients with <50 copies/ml at 48 weeks was reached by 55% and 53% of fosamprenavir and nelfinavir patients, respectively. The increase in median CD4+ cell count was similar in both groups and was > 350 cells/mm^3 at week 48. More patients taking nelfinavir experienced virological failure, 17% vs 7%, 95% CI for difference 10 (5%, 15%). The open follow-on study is assessing the long-term antiviral effect of a fosamprenavir-containing regimen. Background regimens of the patients enrolled in the follow-on, were at the discretion of the investigator. Sustained virological suppression and immunological improvement was demonstrated at 120 weeks by plasma HIV-1 RNA levels of <400 and <50 copies/ml achieved by 75% (159/211) and 66% (139/211) of patients, respectively; a median CD4+ cell count of 451 cells/mm^3 (range 90-1595), and median change from baseline of +205 cells/mm^3 at week 48 and +292 cell/mm^3 at week 120.

The open-label, CONTEXT study randomised 320 patients who had documented virological failure on a prior protease inhibitor regimen to fosamprenavir plus ritonavir 1400mg and 200mg daily (n=105) or 700mg and 100mg twice daily (n=107) or lopinavir/ritonavir 400mg/100mg twice daily (n=103). Most patients had moderate antiretroviral experience and all had background nucleoside reverse transcriptase inhibitor treatment. The aim of the study was to assess the non-inferiority of the two fosamprenavir, boosted arms to lopinavir/ritonavir measured using the average area under the curve minus baseline (AAUCMB) of plasma HIV-1 RNA (log_{10} copies/ml) at week 24 and week 48. Non-inferiority was demonstrated if the upper limit of the 97.5% confidence interval of the difference in mean AAUCMB was below 0.5 log_{10} copies/ml. At 48 weeks the results did not support non-inferiority of fosamprenavir plus ritonavir compared to lopinavir/ritonavir, which was consistently, numerically superior to both fosamprenavir boosted arms. This was especially noticeable in the difficult-to-treat population who had a high viral load at baseline (>100,000 copies). Secondary endpoints included the proportion of patients with HIV-1 RNA levels <400 and <50 copies/ml and the change from baseline in CD4+ cell count over 24 and 48 weeks. Plasma HIV-1 RNA levels showed a trend towards improved efficacy in the twice daily compared to the once daily fosamprenavir arm. At week 48 the median CD4+ cell counts were 370 and 379 cells/mm^3 for fosamprenavir plus ritonavir once and twice daily and 342 cells/mm^3 for lopinavir/ritonavir, giving increases from baseline of +61 cells/mm^3, +81 cells/mm^3 and +91 cells/mm^3, respectively. At 48 weeks, 23% of patients had prematurely discontinued treatment; 26% in the fosamprenavir boosted arms due mainly to virological failure (11% vs 1% in the lopinavir/ritonavir arm) and 17% in the lopinavir/ritonavir arm due mainly to adverse effects.

Resistance

In the SOLO study, in ART-naïve patients with virological failure, there was no evidence of selection by fosamprenavir plus ritonavir of any primary or secondary protease mutations, however, these occurred in 50% of patients in the nelfinavir arm. Resistance to the nucleoside reverse transcriptase inhibitor was observed in both the fosamprenavir plus ritonavir and nelfinavir groups', although it was significantly more frequent in nelfinavir treated patients (69% and 13%, respectively ($p<0.001$)). In the protease inhibitor experienced patients additional primary and/or secondary protease mutations were acquired by 44% of fosamprenavir plus ritonavir daily, 58% of fosamprenavir plus ritonavir twice daily and 25% of lopinavir/ritonavir patients.

Summary of evidence on comparative safety

Safety data were available for 534 patients and showed that fosamprenavir had a predictable and manageable safety profile. Treatment was generally well tolerated with no new safety concerns compared with amprenavir. In the SOLO trial the incidence of diarrhoea was significantly higher in the nelfinavir compared with the fosamprenavir group ($p=0.008$), although four patients in the fosamprenavir group compared with one patient in the nelfinavir group discontinued treatment due to diarrhoea. In the CONTEXT trial there were no statistically significant differences between the fosamprenavir plus ritonavir and lopinavir/ritonavir groups for any specific drug-related grade 2-4 adverse event.

In the SOLO study, the increases in the lipids profile were comparable between groups. There was no clinically relevant change in the total cholesterol /HDL ratio. The median increase in triglyceride levels was greater in the fosamprenavir plus ritonavir compared to the nelfinavir group. Previous experience suggested that this effect on triglycerides may be caused by ritonavir and nelfinavir. In the CONTEXT study, there were only limited changes in serum lipids in all treatment groups. Lipodystrophy has been associated with protease inhibitor use but the incidence was low in patients treated with fosamprenavir plus ritonavir and nelfinavir plus ritonavir being reported in four patients (1%) and six patients (2%) in the respective groups in the SOLO study with no further reports in the follow-on study.

Summary of clinical effectiveness issues

Long term therapeutic success in HIV-1 infected patients is dependent on immunological and virological characteristics at treatment initiation, level of adherence, tolerability of the regimen, and emergence of drug resistant virus in treatment failure. Fosamprenavir plus ritonavir showed comparable efficacy to nelfinavir in treatment naïve patients (although the dose used in this trial differed from the licensed dose) but was not comparable to lopinavir/ritonavir in patients with previous protease inhibitor exposure. The primary outcome measure of average area under curve minus baseline of plasma HIV-1 RNA used in the CONTEXT trial is a recognised method of analysis in both the British HIV Association (BHIVA) guidelines and the European Medicines Evaluation Agency guideline on the clinical development of medicinal products for the treatment of HIV, and may have advantages in patients with very high viral load in whom it may be difficult for the virus to be controlled to undetectable levels (<50 copies/ml). Sub-optimal adherence has been identified as a key cause of treatment failure. This hydrophilic formulation of fosamprenavir reduces the pill burden of amprenavir and when co-administered with ritonavir reduces the pill burden further. The company suggests that the simpler pill regimen with no food restrictions will be an important factor in adherence for long-term multi-drug therapy. In the SOLO trial, perfect adherence was reported in 81-84% of fosamprenavir patients compared with 72-78% of nelfinavir patients. However percentages in the CONTEXT trial were much lower with perfect

adherence reported in only 41% of patients in both fosamprenavir groups and 48% in the lopinavir/ritonavir group. Treatment emergent resistance in patients with virological failure is also an important consideration and the relatively low potential of fosamprenavir plus ritonavir to select for mutations in treatment naïve patients should not preclude treatment with subsequent protease inhibitors. However, in ART-naïve patients, protease inhibitor based regimens are less likely to be used given the increased safety concerns compared with nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors.

Summary of comparative health economic evidence

The manufacturer submitted an economic evaluation that reported separate results for treatment-naïve and treatment-experienced patients. For each patient group fosamprenavir/ritonavir (RTV) was compared to the alternative regimen used in the clinical trials and to another regimen (based on an indirect comparison of the evidence). The economic evaluation was a cost-consequence analysis, so the NHS costs were quantified, but health consequences were measured using a range of different measures.

The cost results were as follows:

Patients	**Regimen**	**NHS cost over 48 weeks**
Treatment-naïve	Fosamprenavir/RTV	£9,556
	Lopinavir (LPV)/RTV	£9,165
	Nelfinavir (NFV)	£9,165
Treatment-experienced	Fosamprenavir/RTV	£10,538
	LPV/RTV	£10,754
	Atazanavir (ATZ)/RTV	£10,617

For treatment-naïve patients the manufacturer argues that the extra cost of the fosamprenavir-based regimen is justified by the lower pill burden and likely increased patient adherence to treatment schedules. For treatment-experienced patients they conclude that the three regimens have similar costs and outcomes.

The economics study design suffered from several weaknesses. However, the benefit of once daily administration may be useful in some patients who fulfil the very restricted licensed indication.

Patient and Public involvement

Patient Interest Group Submission – HIV Scotland.

Budget Impact

While each drug regimen can be quite expensive in itself, the manufacturer proposes swapping a fosamprenavir-based regimen for existing medicines. As a result, the net budget impact is limited, rising from £18k in 2005 (based on 25 patients) to £87k in 2009 (based on 120 patients). The budget impact seems plausible.

Existing or proposed guidelines and protocols

BHIVA committee guidelines 2003 state that a measurement of a regimen's success is achieving a viral load of <50 HIV-1 RNA copies/ml within 3-6 months of starting therapy and maintaining this out to 48 weeks. They also recommend that a boosted protease inhibitor should be the standard of care if a protease inhibitor is chosen as part of an initial regimen. A boosted protease inhibitor is a combination (co-formulated or co-administered) of low dose ritonavir and another protease inhibitor. An update to these guidelines was published in April 2005 and recommended that treatment simplification should not be at the price of reduced clinical efficacy and that adherence support should be part of routine clinical care.

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 13 May 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

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