Resubmission

maraviroc, 150 mg and 300 mg tablets (Celsentri®) No. (458/08)
Pfizer Ltd

05 September 2008

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 resubmission

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.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In combination with other antiretroviral medicinal products, for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable.

Dosing information

150 mg, 300 mg or 600 mg twice daily depending on interactions with co-administered antiretroviral therapy and other medicinal products.

Product availability date

19th November 2007

Summary of evidence on comparative efficacy

Human immunodeficiency virus (HIV) requires binding to both the CD4-receptor and a co-receptor to enter a cell. The two relevant co-receptors are CCR5 and CXCR4. HIV can be tropic (inclined to interact) with either or both co-receptors. Maraviroc blocks the CCR5 co-receptors to prevent CCR5-tropic HIV from entering the cell.

Antiretroviral (ARV) efficacy has been demonstrated in two identical randomised, double-blind placebo-controlled studies. A total of 426 patients were treated with maraviroc 300 mg twice daily (bd) dose equivalent and 209 patients were treated with placebo. A third group received maraviroc 300 mg once daily, but this dose has not been licensed.

For inclusion, treatment experienced patients with CCR5-tropic HIV-1 only were required either to have been treated for ≥6 months with at least one drug from three of four ARV classes (≥2 for protease inhibitors) or to have documented multi-class resistance. They were also required to have a viral load (plasma HIV-1 RNA) ≥5,000 copies/ml.

Maraviroc or placebo was given in combination with optimised background therapy (OBT) determined by a clinical investigator on an individual-patient basis which (after two weeks) could be changed only for reasons of toxicity. An interim analysis was conducted at 24 weeks and a final analysis at 48 weeks.

The primary end point was the change in viral load (log_{10} HIV-1 RNA) from baseline to end point. Secondary end-points included response rates for viral load, with response defined at end point as <400 copies/ml at endpoint or <50 copies/ml, change from baseline in CD4 cell counts, and tropism comparing baseline and time of failure.

Analysis was performed on the full analysis set including all patients randomised who received at least one dose of study drug. For the primary end point, an analysis of covariance model was used with baseline viral load (< or > 100,000 copies/ml), use of enfuvirtide and treatment group as main effects. This gave a least squares mean difference between maraviroc dose group and placebo, and superiority of maraviroc over placebo was concluded if the 2-sided 97.5% confidence interval for this difference excluded zero. The final value was imputed as baseline (no change) for patients who discontinued for reasons other than for treatment failure, and as last observation carried forward for patients with missing values or treatment failure.

In both studies, and in a combined analysis, significant superiority of maraviroc over placebo was demonstrated at 24 and 48 weeks for the primary end-point (Table 1). Maraviroc was

also superior to placebo for viral load response rates and for increase in CD4 cell counts in the combined analysis. For viral response defined as <50 copies/ml, the response rate combining data from both studies was significantly higher for maraviroc compared with placebo at 24 weeks (45% versus 23%) and at 48 weeks (46% versus 17%).

Table 1: Viral load (HIV-RNA log_{10} copies/ml) at week 24 and 48 in two pivotal randomised placebo-controlled trials

HIV-RNA log_{10} copies/ml	24-week				48-week			
	Trial 1		Trial 2		Trial 1		Trial 2	
	Mar (N=235)	Pl (N=118)	Mar (N=191)	Pl (N=91)	Mar (N=235)	Pl (N=118)	Mar (N=191)	Pl (N=91)
Baseline	4.9	4.8	4.8	4.9	4.9	4.8	4.8	4.9
LSM change	-2.0	-1.0	-2.0	-0.90	-1.8	-0.80	-1.9	-0.76
Difference	-0.94		-1.1		-1.0		-1.1	
97.5% CI	(-1.3 to -0.58)		(-1.5 to -0.67)		(-1.4 to -0.66)		(-1.5 to -0.70)	

Mar=maraviroc Pl=placebo N=number of patients LSM=least squares mean CI=confidence intervals

In patients with treatment failure, the percentage with a change from CCR5 tropism at baseline to CXCR4 or dual tropism at the time of failure was 62% (29/47) with maraviroc bd in the first trial and 43% (12/28) in the second. The corresponding results for placebo were 5.4% (3/56) and 6.7% (3/45). About two thirds of patients showed CXCR4 virus at rebound but most reverted to CCR5 virus at follow up visit.

Summary of evidence on comparative safety

The incidence of adverse events with the addition of maraviroc to OBT was similar to that for the addition of placebo. The most common events in both groups were diarrhoea, nausea, fatigue and headache.

Summary of clinical effectiveness issues

Maraviroc is only appropriate for use when CCR5-tropic HIV-1 is exclusively present and should not be used when CXCR4-tropic HIV is present, thus excluding patients with dual tropism.

Although the indication is not further restricted, the pivotal trials recruited a heavily pre-treated population with a long history of HIV-1 infection and there is a lack of data for less experienced patients. However, the company has proposed that the target population in clinical practice is the same as in pivotal trials.

Tropism is not detectable in virally suppressed patients, therefore in the trials most data on tropism post-baseline come from a relatively small sub-group of patients who failed treatment. The majority of failing patients (two thirds) showed CXCR4 virus at rebound and it was shown to be primarily of pre-existing origin, rather than mutated CCR5 virus. After stopping maraviroc treatment, there was reversion to CCR5 tropism in 30/31 patients with a follow-up of more than 4 weeks.

The European Medicines Agency (EMEA) noted that no major safety concerns were found in the clinical trial programme and that the incidence and character of adverse events reported were similar between treatment groups in placebo-controlled studies. However it also noted

concerns about lack of data on the effect of maraviroc in patients with hepatic deficiency, ischaemic heart disease, congestive heart failure and prior intracranial vascular events. In addition, it considered that patient exposure was insufficient to address concerns about potential effects of maraviroc on immune function and malignancy. A safety registry is to be established.

Summary of comparative health economic evidence

The manufacturer presented three modelling exercises: two cost utility Markov models based around revisions of the Markov model of the original submission to SMC; and, a revision of the ARAMIS (Anti-retroviral Analysis of Monte-Carlo Individual Simulation) cost utility microsimulation model. The ARAMIS model has been developed by i3 Innovus in collaboration with Pfizer.

The Markov models compared maraviroc as additional to OBT with OBT alone over a 26-year time horizon. Patients continued with maraviroc treatment until failure, after which OBT transition probabilities applied. Treatment success was defined as a viral load of <400 copies/ml. The monthly probability of treatment failure among those who were initially treatment successes was differentiated between the maraviroc and the OBT arms, with treatment failures experiencing a common monthly CD4 cell count decline. Treatment success experienced CD4 cell count increases observed within the clinical trials up to 48 weeks, after which their CD4 cell count was assumed to remain static.

The drug costs for OBT as observed within the clinical trials and the costs of AIDS defining events were excluded from the analyses on the basis that there may have been some double counting within the previous model. Other than the costs of maraviroc and enfuvirtide, the modelling relied entirely upon the results of a dated paper within the literature for the cost inputs. It would have been preferable to have retained the OBT drug costs and costs of AIDS defining events, while adjusting the costs derived from the paper to account for any possible double counting. Utility values were drawn from a paper within the literature. It appears that the two excel models differed mainly in the mortality rates assumed, though this was not documented within the submission.

The original ARAMIS model structure and input parameter values were not documented within the submission. The main change to the ARAMIS model appears to have been to also remove OBT drug costs and the costs of AIDS defining events, and with some further assumptions, use the utility values from the markov model. The assumption that virological suppression would end after ten years may also have been dropped.

Three cost effectiveness ratios were presented in the resubmission;

- The first Markov model resulted in an anticipated additional 1.55 years survival, 1.51 quality adjusted life years, £28,922 lifetime cost and a cost effectiveness estimate of £19,204 per quality adjusted life year.

- The second Markov model resulted in an anticipated additional 1.01 years survival, 0.99 quality adjusted life years, £25,096 lifetime cost and a cost effectiveness estimate of £25,259 per quality adjusted life year.

- The revised ARAMIS model resulted in an anticipated additional 1.04 years survival, 1.06 quality adjusted life years, £29,982 lifetime cost and a cost effectiveness estimate of £27,402 per quality adjusted life year.

Sensitivity analyses suggested that if the observed drug costs of OBT and the costs of AIDS defining events had not been excluded, cost effectiveness ratios would have been unfavourable.

Weaknesses of the submission were;

- Uncertainty with regard to the true level of OBT costs and effects, with resulting sensitivity in the cost effectiveness ratios.
- The reliance upon a dated paper within the literature for all costs other than the drug costs of maraviroc and enfuvirtide.
- Mortality data in the models came from older studies and may not reflect what might be expected in the Scottish population.
- General lack of clarity over which of the cost-effectiveness ratios provided by the company is likely to represent the most appropriate figure.

Given these issues, the manufacturer has not presented a sufficiently robust economic case for acceptance by the SMC.

Summary of patient and public involvement

Patient Interest Group Submission: HIV Scotland

Additional information: guidelines and protocols

The British HIV Association (BHIVA), guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006) state that for treatment-experienced patients with therapy options, the physician should construct a new HIV treatment that includes at least two (or preferably three) active agents guided by HIV resistance testing and by the patient's previous antiretroviral drug history. However this strategy may not be a realistic option when managing some highly treatment-experienced patients. The use of an agent from a new class is likely to be more effective.

Additional information: previous SMC advice

Following a full submission, SMC published advice in April 2008: maraviroc (Celsentri®) as 150 mg and 300mg tablets 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. The licence holder has indicated their intention to resubmit.

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 patients with 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.

Additional information: comparators

No other members of this class are currently licensed, and maraviroc is added to background therapy therefore there are no relevant direct comparators. However raltegravir, a new drug belonging to another new class of antiviral agents, strand transfer inhibitor of HIV integrase, is also added to background therapy in treatment-experienced patients.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Maraviroc	**150mg to 300mg twice daily***	**6687**
Raltegravir	400mg twice daily	7855

** A dose of 600mg twice daily is indicated for patients receiving efavirenz in the absence of a protease inhibitor or other potent CYP3A4 inhibitor. This would cost £13,373 per year.*
Costs from eVADIS on 24 June 2008.

Additional information: budget impact

The manufacturer anticipated that 50 patients in year 1 rising to 84 patients by year 5 would have triple class experience and a viral load of more than 1000 copies/ml, and so be eligible for tropism testing. With 56% of these screening positive for CCR5 and a market share of 50% in year 1 rising to 100% by year 5 the manufacturer estimated a gross drug cost of £73k in year 1, rising to £914k by year 5.

An additional £2k in year 1 rising to £15k in year 5 would be incurred from the costs of tropism testing.

Opinion from SMC experts suggests that the number of patients likely to receive maraviroc may be less than the manufacturer suggests.

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 14 August 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.

The undernoted reference was supplied with the submission.

European Medicines Agency (EMEA) European Public Assessment Report Maraviroc (Celsentri®). 18/09/2007, EMEA H-C-811.
www.emea.europa.eu/humandocs/Humans/EPAR/celsentri/celsentri.htm