Scottish Medicines Consortium

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

07 March 2008

The Scottish Medicines Consortium 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

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.

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 2 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 each ARV class (≥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 with CXCR4 virus at rebound 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 in those patients, 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 a cost utility Markov model with a monthly cycle comparing maraviroc plus standard care to standard care over a 26-year time horizon. Patients were assumed to be treated with maraviroc up to treatment failure or one year, whichever was the shorter. Treatment successes in terms of viral load were as defined within the clinical trials. Patients experiencing a treatment success experienced improvements in their CD4 cell count, while those deemed to be treatment failures experienced declines in their CD4 cell count. The CD4 cell count was related to patients' quality of life, the likelihood of patients experiencing a category C Aids Defining Event and the likelihood of them dying.

The rates of treatment successes in the maraviroc and standard care arms were drawn from the clinical trials. The monthly percentage decline in the number of patients remaining a treatment success over the 24-week to 48-week period was applied to the subsequent 25-year period. The monthly rates of CD4 cell count increases among treatment successes were also taken from the clinical trials, and were differentiated by treatment. The rates of CD4 cell count decline among treatment failures were drawn from the literature, it being assumed that treatment failures would revert to the pre-trial viral load and associated CD4 cell count decline. Quality of life values and non-drug treatment costs for HIV were drawn from the literature.

The central estimate of cost effectiveness was £24,705 per QALY. The manufacturer also presented a probabilistic sensitivity analysis which estimated the probability of maraviroc being cost effective at £30,000 per QALY was 97%, of being cost effective at £25,000 per QALY was 62%, but of being cost effective at £20,000 per QALY was 0%.

There were a number of uncertainties and possible weaknesses within the analysis, the main ones being:

- assuming only one year of treatment with maraviroc among treatment successes for the base case; a sensitivity analysis that assumed that treatment successes would remain on maraviroc treatment produced a cost-effectiveness estimate of around £30,000 per QALY;
- possibly being overoptimistic in assuming that, provided patients remained treatment successes, they would continue to experience a constant monthly increase in their CD4 cell count as a sensitivity analysis assuming a steady CD4 cell count further worsened the cost effectiveness estimate by 8%;
- some uncertainty as to what has been included in the non-drug costs of HIV treatment with the possibility of there having been some double counting of routine drug costs within this;
- use of a different modelling structure based on the established CEPAC model would have resulted in a higher ICER.

Given these issues, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The British HIV Association (BHIVA), guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006) state that key considerations in the choice of HIV therapy for treatment-experienced patients include treatment history, co-morbid conditions, tolerability, adherence, drug-drug interactions and resistance testing.

Additional information: comparators

No other members of this class are currently licensed, and maraviroc is added to background therapy therefore there are no relevant comparators.

Cost of relevant comparators

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

* 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 January 8th.

Additional information: budget impact

Based upon a patient population of 5 in the first year rising to 49 by year 5, the manufacturer estimated a gross drug cost of £26k in year 1 rising to £505k by year 5. The increase between years one and five was largely due to an assumed increase in the percentage of patients being screened for CCR5 tropism.

It should be noted that in contrast to the economics of the submission, the budget impact section assumed an average duration of treatment of 24 weeks among the 24% of patients failing on maraviroc but of three years among the remaining 76% treatment successes.

The manufacturer states that within the budget impact analysis there were no cost offsets predicted within the budget impact analysis.

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 11 February 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