Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

rilpivirine 25mg, emtricitabine 200mg, tenofovir disoproxil (as fumarate) 245mg tablet (Eviplera®) SMC No. (951/14)

Gilead Sciences Ltd.

07 March 2014

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission:

rilpivirine, emtricitabine, tenofovir disoproxil fumarate tablet (Eviplera®) is accepted for use within NHS Scotland.

Indication under review: treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine, and with viral load ≤100,000 HIV-1 RNA copies/mL. As with other antiretroviral medicinal products, genotypic resistance testing and/or historical resistance data should guide the use of Eviplera®.

Rilpivirine, emtricitabine, tenofovir (Eviplera®) maintained virological suppression in patients switched from other antiretroviral regimens. There is no evidence of efficacy in patients switching from other antiretroviral regimens due to virological failure.

SMC issued advice in February 2012 regarding the use of Eviplera® in antiretroviral treatment-naive adult patients. The current advice extends use to antiretroviral treatment-experienced patients.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine, and with viral load ≤100,000 HIV-1 RNA copies/mL. As with other antiretroviral medicinal products, genotypic resistance testing and/or historical resistance data should guide the use of Eviplera®.

Dosing Information

One tablet once daily. It must be taken with food and should be swallowed whole. Therapy should be initiated by a physician experienced in the management of HIV infection.

Product availability date

29 November 2013

Summary of evidence on comparative efficacy

This is a new indication for a single tablet formulation of the non-nucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine, with two nucleoside reverse transcriptase inhibitors (NRTI), emtricitabine and tenofovir (Eviplera®). The previous indication was for treatment of human immunodeficiency virus type 1 (HIV-1) in antiretroviral treatment (ART)-naïve adult patients with viral load ≤100,000 HIV-1 RNA copies/mL. As with other antiretroviral medicinal products, genotypic resistance testing should guide the use of Eviplera®. The new indication removes the restriction for use in "ART-naïve" adults, thereby extending use to ART-experienced patients and specifies an additional criterion that the patient's HIV-1 virus is: "without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine."[1,2] The submitting company has requested that SMC considers this formulation when positioned for use in switches of ART due to tolerability, simplification or patient request.

A phase III open-label study (SPIRIT) recruited 476 adults with HIV-1 infection virologically suppressed (viral load <50copies/mL) on a boosted protease inhibitor (PI) plus two NRTI for at least 6 months and who had received no more than one prior regimen, had no previous exposure to NNRTI and no known resistance to study drugs. They were randomised in a 2:1 ratio to switch to a single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) once daily or continue their current regimen for 24 weeks then switch to this formulation for a further 24 weeks. The primary outcome was percentage of patients with viral load <50copies/mL at week 24. This was achieved by 94% (297/317) of patients in the single tablet formulation of rilpivirine, emtricitabine and tenofovir group (Eviplera®) and 90% (143/159) of patients in the boosted-PI group, with a between treatment difference of 3.8% (95% confidence interval (CI): -1.6% to 9.1%), which was within the pre-specified 12% non-inferiority margin. At 48 weeks 89% (283/317) and 92% (140/152) of patients had viral load <50 copies/mL in the respective groups. At 24 weeks three and eight patients in the respective groups had virological failure.[2-5]

An open-label phase II study recruited 49 adults with HIV-1 infection who were virologically suppressed with a single tablet formulation of efavirenz, emtricitabine and tenofovir (Atripla®),

their first ART, and who wanted to switch from this for tolerability issues associated with efavirenz. Also prior to starting ART they had no known resistance to any of the study drugs. All patients received open-label single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) once daily. The primary outcome was the proportion of patients with viral load <50 copies/mL at week 12. This was achieved by all 49 patients at weeks 12 and 24 and by 94% (46/49) patients at week 48. The mean rilpivirine trough concentrations at weeks 1, 2, 4, 6, 8, 12, 24, 36 and 48 were 31.6, 52.3, 65.5, 67.8, 76.0, 89.0, 74.1, 85.5 and 77.6ng/mL, respectively. At week 1 mean rilpivirine trough concentration appears indicative of the inductive effect of efavirenz on rilpivirine metabolism. Around weeks 4 to 6 rilpivirine trough concentrations were in the normal range.[2,6-8]

Summary of evidence on comparative safety

Data from these studies are in keeping with current understanding of the adverse event profile of the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) and do not appear to substantially alter this. Comparative data from the SPIRIT study indicate that the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) compared with existing boosted-PI based ART was associated with higher rates of adverse events 80% versus 57%, adverse events related to study drug, 25% versus 2.5%, and discontinuations due to adverse events, 2.2% versus 0%, respectively.[2-5] In two retrospective observational studies of practice within HIV centres in the UK rates of discontinuation from the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) among patients who had switched to this from another ART were higher than those observed in the phase III studies (i.e. about 15% to 22% at 6 months), with the majority of discontinuations due to adverse events (44% to 46%).[9,10]

Summary of clinical effectiveness issues

This new indication allows patients receiving ART to switch to the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®). The submitting company has requested that SMC considers this formulation when positioned for use in switches of ART due to tolerability, simplification or patient request. In patients virologically suppressed on a boosted-PI regimen this formulation demonstrated non-inferiority compared to continuation of existing boosted-PI therapy and in a non-comparative pilot study similar results were observed in patients switching from an efavirenz-based regimen.[2-8]

These studies were open-label and this limits the quality of data they provide on subjective outcomes and reporting of adverse events. Also, the comparative study recruited patients who were stabilised on an existing ART regimen and therefore likely to be tolerating this well. This may bias rates of adverse events reported by patients continuing this regimen compared to those switched to the new regimen. These factors may account to some extent for the higher rates of adverse events, including those related to study drug, and discontinuations due to adverse events associated with the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) compared to continuation of boosted-PI regimen.

In the comparative SPIRIT study patient-reported adherence to treatment was high and similar in the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) and boosted-PI regimen groups.

There is no evidence from the comparative study that the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) is associated with advantages in terms of adherence or adverse effects compared with an alternative treatment and no studies have been designed and powered to investigate this.

There are no studies in patients who have switched to the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) due to virological failure of their current ART. The submitting company has not requested SMC to consider use in this context.

The phase III studies (C209 and C215) supporting the initial indication for the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) (in ART-naïve patients) indicated that in patients with viral load >100,000copies/mL virological failure rates and development of resistance were greater with rilpivirine compared to efavirenz.[11] During the EU regulatory review of the new licence (in switch from existing ART) additional analyses of virological failure were conducted to address concerns about efficacy of the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) in patients who had viral load >100,000copies/mL prior to initiation of their first ART. The European regulatory authority concluded that there were no issues regarding baseline viral load or CD4 count.[2]

Rilpivirine is sensitive to small pharmacokinetic disturbances, e.g. due to lack of sufficient food concomitant with drug intake or drug interactions, such as that with proton pump inhibitors. In the phase II study described previously mean serum rilpivirine concentration in the first weeks may have been affected by an inductive effect of efavirenz from the preceding ART.[2] When the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) is used in a switch of ART it may be appropriate to take account of the elimination half-life of drugs in the preceding ART and any potential effects on the new regimen, for example due to induction or inhibition of metabolism.

SMC clinical experts consider this to be an alternative to other ART regimens, such as those based on boosted-PIs.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis (CMA) assessing the use of a single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) for the treatment of adults infected with HIV-1 without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine and with viral load ≤100,000copies/mL. The main comparators were several multi-tablet regimens of ritonavir-boosted PI associated with a NRTI backbone. The secondary comparator was an alternative single tablet formulation that included the NNRTI, efavirenz, plus a NRTI backbone, emtricitabine and tenofovir (Atripla®). Other comparators were the multi-tablet regimens of the constituents of Atripla® and Eviplera®.

For completeness, the submitting company also included costing comparisons of a single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) with: an integrase inhibitor, raltegravir-based regimen, with a single tablet formulation of elvitegravir, cobicistat, emtricitabine and tenofovir (Stribild®) and with two other multiple-tablet NNRTI regimens: rilpivirine and efavirenz combined with NRTI backbones. However, the submitting company requested the SMC does not treat them as primary comparators as they had not provided any

clinical evidence to support the comparable efficacy assumption. A one year time horizon was used and the analysis was carried out from an NHS Scotland perspective.

The clinical evidence to support the analysis of the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) versus boosted-PI regimens was drawn from the phase III open-label study (SPIRIT). The Eviplera® versus Atripla® economic case was supported by the phase II open-label study. The SPIRIT study demonstrated non-inferiority of the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) compared with boosted PI-based regimens and the phase II study demonstrated maintenance of virological suppression.

In terms of costs, the submitting company presented the annual cost per patient of the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) versus all aforementioned comparators. Costs included were medicine costs only.

In the first year, the base case results showed annual per patient savings associated with the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) versus boosted-PI regimens that ranged from £1,037 to £1,493 for the sub-group of boosted-PI regimens that have an emtricitabine plus tenofovir backbone. This backbone is likely to be the most widely used in Scotland. Savings ranged from £230 to £686 for the sub-group of boosted-PI regimens that have an abacavir plus lamivudine backbone, believed to be the second most used in Scotland. Regarding the comparison with the single tablet formulation of efavirenz, emtricitabine and tenofovir (Atripla®) alone, savings were found to be £99 per patient per year.

Despite being noted as not for consideration as primary comparators, the results for the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) versus the single tablet formulation of elvitegravir, cobicistat, emtricitabine and tenofovir (Stribild®) and NNRTI regimens were also presented. Results for the comparisons with multiple tablet rilpivirine- and efavirenz-based regimens showed that the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) was cost neutral when the NRTI backbone is emtricitabine plus tenofovir and with incremental costs of £807 when the NRTI backbone is abacavir plus lamividine. A patient access scheme (PAS) is in place in NHS Scotland for Stribild® and was incorporated into the analysis as the relevant price of Stribild®. The comparison with the single tablet formulation of elvitegravir, cobicistat, emtricitabine and tenofovir (Stribild®) resulted in an incremental saving of £5,064 without the Stribild® PAS and a small incremental cost with the PAS. The comparison with the integrase inhibitor raltegravir resulted in incremental savings associated with Eviplera® of £3,939 when raltegravir was combined with emtricitabine plus tenofovir and of £3,132 when combined with abacavir plus lamivudine.

No sensitivity analyses were performed.

The main uncertainty surrounding the analysis concerns the company's choice of comparators, especially as the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) is shown to be more expensive than some of the comparators. Although IMS data supports the company's view that boosted-PI are the most appropriate comparator for this patient group, it was deemed useful to see a weighted average of the comparator costs based on their market share. The submitting company subsequently provided an analysis of Eviplera® versus a weighted average of the comparators according to their market share. This analysis showed annual savings of £1,044.

The cost analysis included drug costs only but there might be some concerns regarding the failure to include of costs of switching which may be relevant for patients switching from some of the multi-tablet regimens.

In summary, the economic case for the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) has been demonstrated.

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

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The British HIV Association guidelines for the treatment of HIV-positive adults with ART 2012 make the following recommendation in relation to switching antiretrovirals in combination ART in virological suppression. In patients on suppressive ART regimens, consideration should be given to differences in side effect profile, drug-drug interaction and drug resistance patterns before switching any antiretroviral component. In patients with previous nucleos(t)ide reverse transcriptase inhibitor resistance mutations it is recommended against switching a ritonavir boosted PI to either a NNRTI or an integrase inhibitor as the third agent.[12]

Additional information: comparators

Relevant comparators would be all other ART regimens. SMC clinical experts indicate that the single tablet formulation of rilpivirine, emtricitabine and tenofovir (Eviplera®) may replace other ART regimens, such as those based on boosted-Pis.

Cost of relevant comparators

Drug Regimen	Dose	Cost per year (£)
Rilpivirine 25mg, emtricitabine 200mg, tenofovir disoproxil 245mg (Eviplera®)	**One tablet daily**	**7,508**
Rilpivirine 25mg (Edurant®) Emtricitabine 200mg (Emtriva®) Tenofovir disoproxil 245mg (Viread®)	25mg daily 200mg daily 245mg daily	7,332
Efavirenz (Sustiva®) Emtricitabine 200mg (Emtriva®) Tenofovir disoproxil 245mg (Viread®)	600mg daily 200mg daily 245mg daily	7,332
Rilpivirine (Edurant®) Emtricitabine 200mg, tenofovir disoproxil 245mg (Truvada®)	25mg daily One tablet daily	7,508

Efavirenz (Sustiva®) Emtricitabine 200mg, tenofovir disoproxil 245mg (Truvada®)	600mg daily One tablet daily	7,508
Efavirenz 600mg, emtricitabine 200mg, tenofovir disoproxil 245mg (Atripla®)	One tablet daily	7,607
Lopinavir 200mg, ritonavir 50mg (Kaletra®) Emtricitabine 200mg, tenofovir disoproxil 245mg (Truvada®)	Two tablets twice daily One tablet daily	8,541
Darunavir (Prezista®) Ritonavir (Norvir®) Emtricitabine Emtriva®) Tenofovir disoproxil (Viread®)	800mg daily 100mg daily 200mg daily 245mg daily	8,751
Atazanavir (Reyataz®) Ritonavir (Norvir®) Emtricitabine (Emtriva®) Tenofovir disoproxil (Viread®)	300mg daily 100mg daily 200mg daily 245mg daily	8,819
Darunavir (Prezista®) Ritonavir (Norvir®) Emtricitabine 200mg, tenofovir disoproxil 245mg (Truvada®)	800mg daily 100mg daily One tablet daily	8,927
Atazanavir (Reyataz®) Ritonavir (Norvir®) Emtricitabine 200mg, tenofovir disoproxil 245mg (Truvada®)	300mg daily 100mg daily One tablet daily	8,995

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 17 December 2013.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 213 in year 1 and 497 in year 5 to which estimates of treatment uptake were applied.

The gross impact on the medicines budget was estimated to be £1.6m in year 1 and £3.7m over 5 years. As other drugs were assumed to be displaced the net medicines budget impact is expected to be a saving of £175k in year 1 and a saving of £408k over 5 years.

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

References

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

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3. Gilead Sciences. 48 week clinical study report for GS-US-264-0106.
4. Clinicaltrials.gov. NCT01252940
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6. Gilead Sciences. Clinical study report for GS-US-264-0111
7. Mills AM, Cohen C, Dejesus E, et al. Efficacy and safety 48 weeks after switching from efavirenz to rilpivirine using emtricitabine/tenofovir disoproxil fumarate-based single-tablet regimens. HIV Clin Trials. 2013; 14(5): 216-23.
8. Clincaltrials.gov. NCT01286740
9. Saxon C. Safety and efficacy of the single tablet regimen rilpivirine-tenofovir, emtricitabine (Eviplera) in clinical practice: Experience from the UK & Ireland. European AIDS Clincial Society. 2013.
10. Hedley L. Switching to rilpivirine from a non-nucleoside reverse transcriptase inhibitor based ART: Experience in clinical practice. European AIDS Clincial Society. 2013.
11. European Medicines Agency. CHMP assessment report for Eviplera: EMEA/H/C/002312, 22 September 2011.
12. British HIV Association. British HIV Association guidelines for the treatment of HIV-positive adults with antiretroviral therapy 2012. HIV medicine 2012; 13 (suppl 2): 1-85.

This assessment is based on data submitted by the applicant company up to and including 14 February 2014.

**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/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.