AWMSG Secretariat Assessment Report – Limited submission

Efavirenz (Sustiva®) 50mg, 100mg, 200mg hard capsules and 600mg film-coated tablets

Company: Bristol-Myers Squibb Pharmaceuticals Ltd

Licensed indication under consideration:

Efavirenz (Sustiva®) in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected children 3 months of age to 3 years and weighing at least 3.5kg.

Sustiva® has not been adequately studied in patients with advanced HIV disease, namely patients with CD4 counts < 50 cells/mm^3, or after failure of protease inhibitor (PI) containing regimens. Although cross-resistance of efavirenz with PIs has not been documented, there are at present insufficient data on the efficacy of subsequent use of PI based combination therapy after failure of regimens containing Sustiva®.

Refer to the Summary of Product Characteristics (SPC) for the full licensed indication.

Marketing authorisation date: 8 April 2015

Comparator(s)

Nevirapine

Limited submission details

- Minor licence extension
- Anticipated minimal budgetary impact in NHS Wales

Clinical effectiveness

- The company submission includes three dose-finding studies which were considered as part of the evidence for market authorisation with regards to the licence extension to include children aged 3 months to 3 years.

- These studies (PACTG382, PACTG1021 and AI266922) were not originally designed to assess the efficacy of efavirenz administered as the sprinkled capsule method in the target population which is now the only proposed method of administration available to infants and younger children to whom the hard capsules cannot be administered. The European Medicines Agency therefore also considered a fourth study (AI266059) which demonstrated the bioequivalence of dosing with intact capsules or capsule sprinkles with different food vehicles in adults.

- The total population across the dose-finding studies comprise a broad age range (2.4 months to 21 years of age) and weight range (3.3 kg to 117 kg). Both efavirenz oral solution as well as sprinkled and intact capsules were administered in different dosing regimens and in combination with other anti-retrovirals. Only a sub-cohort of study AI266922 (24 patients) are therefore directly relevant to the licensed population under consideration.

- The Committee for Medicinal Products for Human Use (CHMP) however considered that an extrapolation of efficacy data obtained in adults to children was acceptable; in line with the CHMP guideline on the clinical development of medicinal products for the treatment of HIV and based on the identification of suitable dose regimens and the expectation that pharmacokinetic/pharmacodynamic relationships are the same in children as in adults.

- The currently preferred non-nucleoside reverse transcriptase inhibitor [NNRTI] in paediatric patients < 3 years of age is nevirapine. In view of the lack of head-to-head evidence, the company therefore also highlighted three meta-analyses providing comparative effectiveness of efavirenz and nevirapine in combination with two nucleoside reverse transcriptase inhibitors (NRTI). Results were broadly supportive of equivalence but should be treated with caution due to the inherent limitations associated indirect analyses. It should also be noted that these patients were adults and children > 3 years of age, and were all treatment naive.

- Although the number of relevant children in the safety dataset was small, there was no new or unexpected safety signal or characteristic detected providing CHMP with sufficient reassurance to conclude that the specific safety profile does not differ from the one already well known for efavirenz.

Budget impact

- Based on 2012 data from the Collaborative HIV Paediatric Study (CHIPS), the company estimate 30 newly reported cases of children receiving HIV-related care per year in Wales, with 1% eligible for treatment with efavirenz for the indication under consideration.

- The company have assumed all cases are in newborns or children under the age of 3 years old. The cost to NHS Wales for the treatment of paediatric patients is therefore based on 0.3 additional patients per year.

- Calculations have been based on one patient receiving the maximum recommended daily dose for children under the age of 3 years and weighing ≥ 40kgs. The company therefore estimate a maximum total budget impact for this licensed extension to be £2,437 per annum.

- Following the dosing schedule and costs provided by the company for the comparator nevirapine, the annual per-patient incremental cost of prescribing efavirenz instead of nevirapine would be between £408.33 and £1,661.38.

Additional information

AWTTC is of the opinion that, if recommended, efavirenz (Sustiva®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

Evidence search

Date of evidence search: 8 July 2015
Date of range of evidence search: No date limits were applied to database searches.

AWMSG review

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Efavirenz (Sustiva®) 50mg, 100mg, 200mg hard capsules and 600mg film-coated tablets. Reference number: 2666. November 2015.