



AWMSG Secretariat Assessment Report – Limited submission

Raltegravir (Isentress[®]) 100 mg granules for oral suspension

Company: Merck Sharp & Dohme Ltd

Licensed indication under consideration:

In combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents, children, toddlers and infants from the age of four weeks.

The company has focussed their submission on the treatment of patients aged four weeks to less than two years of age; AWMSG advice for raltegravir (as chewable tablets) is available from two years of age.

Marketing authorisation date: 22 August 2014.

Comparator(s):

- No comparators were included in the company submission. There are limited licensed treatment options available for this population. Clinical experts contacted by the All Wales Therapeutics and Toxicology Centre (AWTTC) confirmed that raltegravir is likely to be used only in those patients who have drug resistance or in patients who are intolerant of other treatment options.

Limited submission details:

The limited submission criteria were met as it is considered a minor licence extension with anticipated minimal budgetary impact within NHS Wales.

Clinical effectiveness:

- Raltegravir (Isentress[®]) has previously been approved for use by AWMSG in a restricted population for adults, adolescents and children over two years in combination with other anti-retroviral medicinal products. The company has requested that the appraised licence extension for the new granules for suspension formulation is considered under the same restriction i.e. for use in patients who are resistant or intolerant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) or for whom these options are compromised due to drug-drug interactions.
- Evidence of clinical effectiveness was provided from the IMPAACT P1066 study; a Phase I/II open-label, non-comparative, multi-centre trial designed to evaluate the pharmacokinetic profile, safety, tolerability and efficacy of raltegravir in HIV-infected children. All children recruited into the study were treatment-experienced, either for prevention of mother to child transmission and/or as combination therapy for treatment.
- The study was designed to allow extrapolation of efficacy data obtained in adults to children. Evidence for the granules for oral suspension was derived from a small number of patients (n = 26) with a median age of 28 weeks (range 4–100 weeks).

Thirty-five percent of patients were female, 8% were Caucasian and no UK centres recruited into the study. It is therefore unclear how well the study population matches that of children in Wales with HIV infection.

- The proportion of patients less than two years of age (for whom data were available) who achieved a greater than 1 log₁₀ HIV RNA drop from baseline in HIV RNA or HIV RNA <400 copies/ml at week 48 was 85.0%, and 52.6% achieved HIV RNA < 50 copies/ml. Pharmacokinetic parameters were similar to those observed in the overall study.
- The number of children, aged less than two years, in the study was too small to draw definite conclusions, but the overall virological and immunological response rates were considered satisfactory by the Committee for Medicinal Products for Human Use (CHMP). In addition CHMP broadly supported the conclusion that the pharmacokinetic profiles observed in this age range should result in similar anti-viral efficacy to that observed in the adult population who received the 400 mg tablet formulation.
- The frequency, type and severity of drug-related adverse reactions were comparable to those observed in older children and adults. A Grade 3 serious drug-related allergic rash was reported in one patient that resulted in treatment discontinuation.
- Although the company has focussed their submission on the treatment of patients from four weeks to less than two years, the licensed indication states that patients can remain on granules for suspension as long as their weight is below 20 kg. No evidence for use in patients from two years of age was included in the company submission.
- Isentress[®] granules for oral suspension contain fructose, sorbitol and sucrose and is therefore not recommended in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency.

Budget impact:

- There are likely to be low number of patients who would be eligible for therapy with raltegravir for the indication under consideration. Fifteen patients aged between 0 and 15 years received treatment for HIV in Wales in 2013. The company has assumed an equal distribution of patients across this age group to give a prevalent population of two patients under the age of two. Based on an extrapolation of new diagnosis of HIV in the UK to the Welsh population, an incidence of a maximum of one patient per year is assumed.
- As the 100 mg sachets are intended for single use the cost per patient per year for those less than two years of age treated with raltegravir granules for oral suspension is £2,594. The company estimates a budget impact of £7,782 in year one reducing to £2,594 in subsequent years.
- The budget impact estimate does not consider use in patients from the age of two years. The company expect the majority of patients would switch from granules for oral suspension to chewable tablets when permitted. It is uncertain to what extent prescribing in those over two years of age and less than 20 kg will occur in clinical practice which may lead to an underestimate in expenditure. The annual cost per patient could increase by £1,516 per year if the oral suspension is used in place of chewable tablets in children over two years.
- The company highlights that approximately 24% of patients with HIV are undiagnosed and so there may be an underestimate of the true numbers. In addition there is uncertainty regarding the assumption of equal distribution of patients across the 0 to 15 year age range.

- Collectively, there are limitations in the budget impact estimates provided by the company. However, any associated uncertainty is unlikely to have a significant impact on the expenditure for patients eligible for treatment.

Additional information:

- AWTTTC is of the opinion that, if recommended, raltegravir (Isentress[®]) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.
- The company do not anticipate that raltegravir (Isentress[®]) will be supplied by a home healthcare provider.

Evidence search:

Date of evidence search: 2 July 2015

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

Further information:

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

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

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Raltegravir (Isentress[®]) 100 mg granules for oral suspension. Reference number: 2366. October 2015