All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

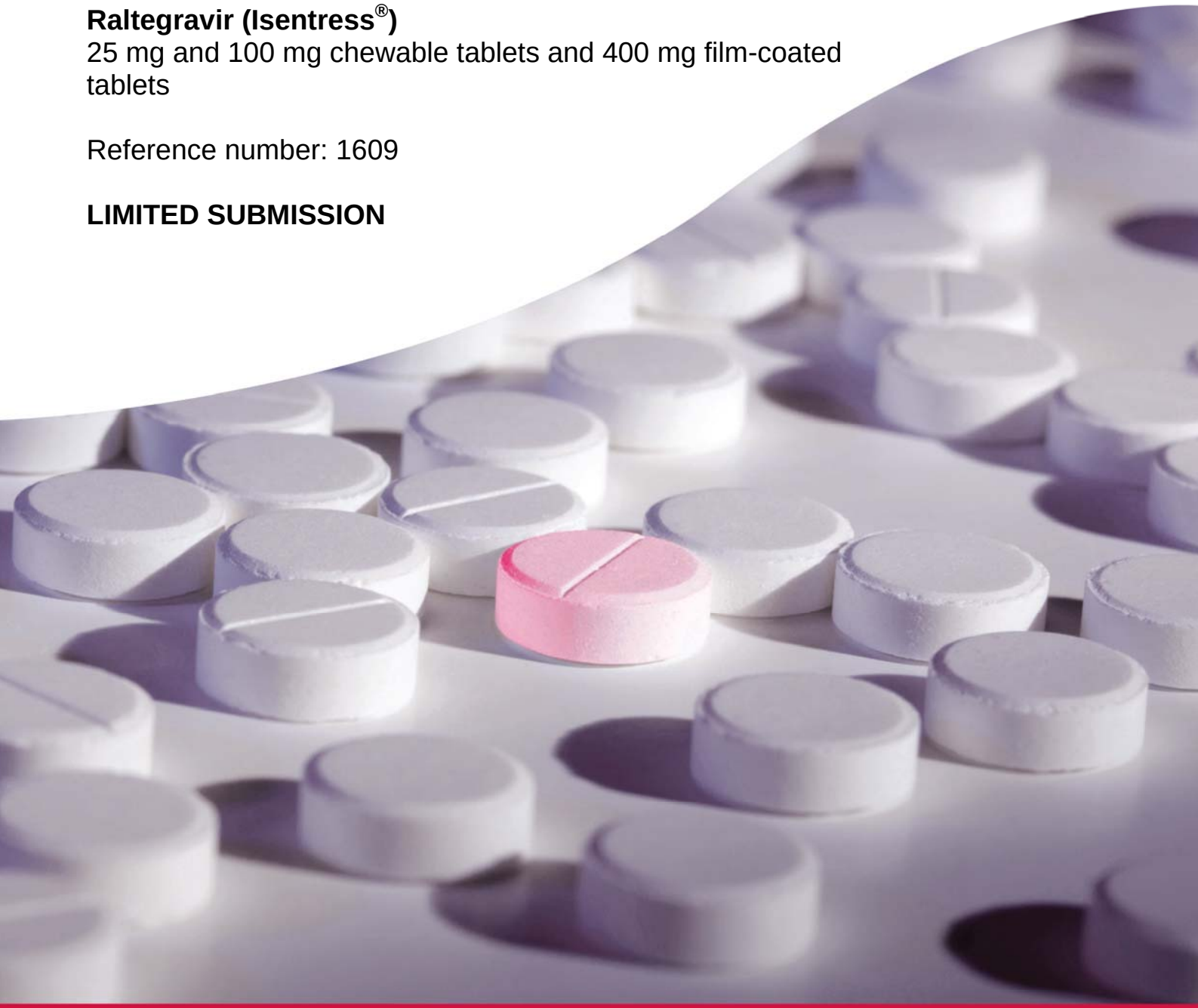
AWMSG SECRETARIAT ASSESSMENT REPORT

Raltegravir (Isentress®)

25 mg and 100 mg chewable tablets and 400 mg film-coated tablets

Reference number: 1609

LIMITED SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Raltegravir (Isentress®) 25 mg and 100 mg chewable tablets and 400 mg film-coated tablets

This assessment report is based on evidence from a limited submission by Merck Sharp & Dohme Ltd on 7 June 2013.

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Raltegravir (Isentress®) is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adolescents, and children from the age of 2 years[1]. Raltegravir (Isentress®) 25 mg and 100 mg chewable tablets are indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in children aged 2–11 years[1]. Raltegravir (Isentress®) 400 mg film-coated tablets are indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infection in adolescents and children from the age of 6 years and weighing ≥ 25 kg[2].
Dosing	In children aged 2–11 years, the recommended dose of raltegravir (Isentress®) 25 mg and 100 mg chewable tablets is weight-based, up to a maximum of 300 mg twice daily (refer to the Summary of Product Characteristics [SPC] for further information)[1]. In adolescents and children from the age of 6 years and weighing ≥ 25 kg, the recommended dose of raltegravir (Isentress®) 400 mg film-coated tablets is 400 mg twice daily[2]. These formulations are not bioequivalent and cannot be substituted for each other[1,2].
Marketing authorisation date	25 February 2013 (400 mg film-coated tablets were licensed for use in treatment-experienced adults December 2007; this was extended to include treatment-naïve adults September 2009)[1–3].
Comparators	The comparator included in the company submission was enfuvirtide (Fuzeon®)[4].
Limited submission details	The applicant company have submitted data for a subpopulation, i.e. for use in paediatric 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[4]. This is in line with the All Wales Medicines Strategy Group (AWMSG) restricted recommendation for the use of raltegravir 400 mg film-coated tablets in adults (Advice no. 1110) and the population recruited to the IMPAACT P1066 study (see Section 2.0)[5,6]. On this basis, raltegravir (Isentress®) met the following criteria for eligibility for a limited submission: • Significant new formulation with a pro-rata or lower cost per treatment. • A minor licence extension. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 IMPAACT P1066

The company submission included a phase I/II open-label, noncomparative, multicentre trial, IMPAACT P1066, which evaluated the pharmacokinetic (PK) profile, safety, tolerability and efficacy of raltegravir (Isentress®) in treatment-experienced, HIV-infected children and adolescents aged 2–18 years. Eligible patients had a viral load > 1,000 copies/ml and had failed on at least one antiretroviral therapy regimen. The initial dose-finding stage included intensive PK evaluation (see Section 2.1.1), and following dose selection, additional subjects were enrolled for the evaluation of long-term safety, tolerability and efficacy (see Sections 2.1.2 and 2.1.3)[4,6].

2.1.1 PK evaluation

For the chewable tablet formulation, a dose selection of approximately 6 mg/kg bodyweight for children aged 2–11 years was based upon subjects aged 2–5 years achieving similar raltegravir plasma exposure and trough concentration as seen in adults, as well as acceptable short-term safety[7]. For the film-coated tablet, a dose of 400 mg twice-daily was selected for adolescents and children aged 6–18 years and weighing ≥ 25 kg based on PK data and weight bands for children aged 6–11 years and adult data[8].

Based on a formulation comparison study in healthy adult volunteers, the chewable tablets have been shown to have higher oral bioavailability than the film-coated tablet[4].

2.1.2 Efficacy

Due to the single-arm nature of the study, IMPAACT P1066 was not powered to demonstrate efficacy; however, efficacy parameters including HIV RNA, $CD4^+$ cell counts and viral resistance were measured. Subjects received raltegravir as a 400 mg film-coated tablet if aged 6–18 years and weighing ≥ 25 kg, or as a chewable tablet (25 mg or 100 mg) if aged 2–11 years (subjects were enrolled sequentially into five age cohorts; children aged 6–11 received chewable tablets or film-coated tablets, depending on the cohort). Raltegravir was administered alongside an optimised background regimen. Of the 126 subjects enrolled, 96 received raltegravir at the dose selected in the PK evaluation (approximately 6 mg/kg chewable tablet twice-daily for children aged 2–11 years and 400 mg film-coated tablet twice-daily for adolescents and children aged 6–18 years and weighing ≥ 25 kg). At baseline, 8% of subjects had plasma HIV RNA > 100,000 copies/ml and 59% of subjects had a Centers for Disease Control and Prevention (CDC) HIV clinical classification of category B or C[4,6,9]. Most subjects had previously received at least one NNRTI (78%) or one PI (83%)[4,6,10].

At week 24, 71.6% of subjects met the primary endpoint of HIV RNA < 400 copies/ml or at least a 1 $\log_{10}$ HIV RNA drop from baseline. The secondary endpoint, HIV RNA < 50 copies/ml, was met by 53.7% of subjects. The mean $CD4^+$ count increase from baseline to week 24 was 119 cells/mm^3 (3.8%)[6]. Three subjects discontinued due to noncompliance[4].

2.1.3 Safety

At week 48, clinical adverse events (AEs) were reported by 82/96 (85.4%) patients; the most frequently reported were cough (42.7%), pyrexia (32.3%) and rhinorrhoea (27.1%). Fifteen patients experienced grade 3 or greater clinical AEs, of which one experienced treatment-related psychomotor hyperactivity, abnormal behaviour and insomnia. Serious clinical AEs were reported by 14 patients; one was deemed treatment-related (grade 2 allergic dermatitis). At week 48, one patient experienced treatment-related alanine aminotransferase elevation, which was deemed serious. There were no deaths or discontinuations due to the study drug[4,6,10].

There were no new safety findings in the paediatric population when compared to the adult population, with the frequency, type and severity of drug-related adverse reactions through week 48 being similar. Furthermore, no specific safety concerns were identified in the paediatric population[1,10].

2.2 Points to note

- A new formulation of raltegravir (25 mg and 100 mg chewable tablet) and a licence extension for the existing formulation (400 mg film-coated tablets; to include use in adolescents and children from the age of 6 years and weighing ≥ 25 kg) are under consideration in this appraisal. The chewable tablets are licensed in children aged 2–11 years, and have not been studied in HIV-infected adolescents or adults[1].
- The applicant company has submitted data for a subpopulation of the licensed indication under consideration, i.e. for use in paediatric patients who are resistant or intolerant to NNRTIs or PIs, or for whom these options are compromised due to drug–drug interactions[4]. This is in line with the AWMSG restricted recommendation for the use of raltegravir 400 mg film-coated tablets in adults and the population recruited to the IMPAACT P1066 study[5,6].
- The company submission does not include a clinical comparison to enfuvirtide, but refers to the AWMSG appraisal for adult patients, in which non-inferiority was shown to be met in two short-term studies that switched virologically stable patients with multidrug resistant HIV-1 from enfuvirtide to raltegravir (CHEER and EASIER). Further, safety was generally comparable for both treatments, although raltegravir was associated with higher incidence of abnormalities in lipid concentrations and liver function tests[4,5].
- Raltegravir chewable tablets are licensed in children from the age of 2 years; whereas, enfuvirtide is licensed for children aged ≥ 6 years[1,11].
- As both formulations of raltegravir are oral, this offers a more convenient method of administration than enfuvirtide, which is only available as a powder and solvent for solution for injection. After reconstitution, enfuvirtide should be used immediately or refrigerated and used within 24 hours[11].
- IMPAACT P1066 was conducted at sites in the United States, South Africa, Botswana, Brazil and Argentina. Of the 96 subjects, 59% were black and 34% were Caucasian[6]. It is unclear how well the study population matches that of children and adolescents in Wales with HIV.
- IMPAACT P1066 was designed to allow extrapolation of efficacy data obtained in adults to children. The numbers per enrolment cohort are 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). No new safety findings or concerns were identified[10].
- The PK profile was not affected to a clinically meaningful degree when the chewable tablet was administered with a high fat meal; therefore, it can be administered with or without food[1,2,4].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The budget impact evidence presented by the company includes a simple comparison of the annual costs associated with the use of raltegravir chewable tablets and enfuvirtide powder and solvent for solution for injection, based on a child aged between 6–11 years and weighing between 28 kg and < 40 kg. Patient numbers have been estimated by assuming an equal distribution of patients across age groups and by assuming the prevalence of HIV in Wales is the same as the UK (based on HIV patient numbers reported in the Health Protection Agency [HPA] 2011 report and Welsh population statistics reported by the Office of National Statistics [2010])[12,13]. The company estimates that approximately 10% of children and adolescents with HIV aged 2–17 years will be eligible for raltegravir, with eight patients in 2013 and one new incident case per year thereafter. The company estimates that the cost of treating one newly diagnosed patient per year will be £3,189 for raltegravir chewable tablets, compared to £13,168 for enfuvirtide (cost saving of £9,979). Therefore, in 2013, treating eight patients with raltegravir chewable tablets would cost £25,512, compared to £105,344 for enfuvirtide (cost saving of £79,832). Costs for the background regimen have not been included in the calculation as they are assumed to be equivalent for raltegravir and enfuvirtide[4].

3.2 AWTTC critique of the budget impact analysis

- The budget impact reported by the company takes into account the use of raltegravir chewable tablets in a child aged from 6–11 years and weighing between 28 kg and < 40 kg (i.e. a dose of 200 mg twice-daily). The budget impact of using the maximum dose of raltegravir chewable tablets (300 mg twice-daily) has not been provided.
- Uptake numbers appear to be reasonable based on 2011 HPA and Office of National Statistics data.
- The company stated that the 10% uptake figure has been estimated based on clinical expert opinion; however, this cannot be verified by AWTTC and is therefore subject to uncertainty.

3.3 Comparative unit costs

Table 1 provides comparative annual acquisition costs of raltegravir 25 mg and 100 mg chewable tablets, raltegravir 400 mg film-coated tablet and enfuvirtide 90 mg/ml powder and solvent for solution for injection.

Table 1 Example comparative annual acquisition costs for raltegravir and enfuvirtide

Medicine	Example regimen	Cost per patient per year*
Raltegravir (Isentress®) 25 mg and 100 mg chewable tablets	75–300 mg (dosed by weight) twice-daily for children aged 2–11 and weighing 12 to ≥ 40 kg	£1,195–£4,780
Raltegravir (Isentress®) 400 mg film-coated tablet	400 mg twice-daily for children aged 6–11 years weighing ≥ 25 kg and adolescents aged ≥ 12 years	£6,373
Enfuvirtide (Fuzeon®) 90 mg/ml powder and solvent for solution for injection†	27–90 mg (dosed by weight) twice-daily for children aged ≥ 6 years and adolescents	£13,159

*Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of June 2013[14].
† Enfuvirtide is supplied as a single-use vial.
This table does not imply therapeutic equivalence of medicines or the stated doses.
Refer to the SPCs for full dosing details[1,2,11].

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC 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.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 18 June 2013
Date range of evidence search: No date limits were applied to database searches.

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