



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Raltegravir

Proprietary Product Name: Isentress

Sponsor: Merck Sharp and Dohme (Australia)
Pty Ltd

June 2013

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List of abbreviations used in this AusPAR

Abbreviation	Meaning
AIDS	Acquired Immunodeficiency Syndrome
ANOVA	Analysis of Variance
AUC	Area Under the Concentration-time Curve
AUC _{0-12h} /AUC _{12h}	Area Under the Concentration-time Curve from time zero to 12 h postdose
AUC _{0-∞} :	area under the plasma concentration time curve from time zero to infinity
B-hCG	Human chorionic gonadotrophin
BLQ	Below limit of quantification
BMI	Body Mass Index
C _{12h}	Concentration 12 h postdose
CL/F -	oral clearance
CLt	apparent clearance
CLiwt	intercept term between weight and CLt
CLswt	slope term between weight and CLt
C _{max}	Peak plasma concentration
CRO	Contract research organisation
CSR	Clinical study report
DNA	Deoxyribonucleic acid
EC	ethylcellulose
ECG	Electrocardiogram
GMR	Geometric mean ratio
HAART	Highly active anti-retroviral therapy
HIV	Human immunodeficiency virus
IC50	50% inhibitory concentration
i.e.	that is

Abbreviation	Meaning
IRB	Institutional review board
LLOQ	Lower level of quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRL	Merck Research Laboratory
MSE	Mean square error
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OG	Oral granules for suspension
PI	Protease inhibitor
Q/F	apparent distributional clearance
SD	Standard deviation
$t_{1/2I}$	Initial phase Half-life
$t_{1/2T}$	Terminal phase Half-life
T_{max}	Time of peak plasma concentration
Vc	apparent volume of distribution of the central compartment
Viwt	intercept term between weight and Vc
Vswt	slope term between weight and Vx

I. Introduction to Product Submission

Submission details

<i>Type of Submission:</i>	New dosage form
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	31 January 2013
<i>Active ingredient:</i>	Raltegravir
<i>Product Name:</i>	Isentress
<i>Sponsor's Name and Address:</i>	Merck Sharp and Dohme (Australia) Pty Ltd 66 Waterloo Rd, North Ryde NSW 2113
<i>Dose form:</i>	Chewable tablets
<i>Strengths:</i>	25 mg and 100 mg
<i>Container:</i>	High-density polyethylene (HDPE) bottle
<i>Pack size:</i>	60 tablets
<i>Approved Therapeutic use:</i>	<p>The new approved full indications for this therapeutic good is now:</p> <p><i>Isentress, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents and children from the age of 2 years.</i></p> <p><i>This indication is based on analyses of plasma HIV-1 RNA levels in controlled studies of Isentress (see Clinical Trials).</i></p> <p><i>The indication in paediatric patients is based on the evaluation of safety, tolerability, pharmacokinetic parameters and efficacy of Isentress through at least 24 weeks in a multicentre, open label, non-comparative study in HIV-1 infected, treatment-experienced children and adolescents 2 to 18 years of age.</i></p> <p><i>The use of other active antiretroviral agents in combination with Isentress is associated with a greater likelihood of treatment response (see Clinical Trials.)</i></p> <p><i>There are no study results demonstrating the effect of Isentress on clinical progression of HIV-1 infection.</i></p>
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	<p>6 years of age and older (if at least 25 kg in weight): one 400 mg tablet twice daily.</p> <p>2 to 11 years of age: Chewable tablets: weight based to maximum dose 300 mg, twice daily as recommended in Table 15 (in PI).</p>

ARTG Numbers: 193383 and 193388

Product background

This AusPAR describes the application by the sponsor to extend the indication of raltegravir to include treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in children and adolescents from 2 to 18 years of age and to register the new formulation, chewable tablets (25 mg and 100 mg), for use in the paediatric population. In view of the small numbers of affected Australian children, the application has been granted orphan status.

Raltegravir belongs to the class of HIV integrase inhibitors which prevent covalent insertion of the HIV genome into the host cell genome during the early phase of infection preventing viral propagation.

The paediatric development program for raltegravir began with Phase I pharmacokinetic and safety studies of paediatric formulation candidates evaluated in healthy adult volunteers. The data from the pivotal study were used to select two formulations, the chewable tablets and the oral granules for suspension, which were further evaluated, along with the adult formulation, in the pivotal clinical Phase I/II study P1066, in HIV-infected-paediatric patients.

Isentress (raltegravir) 400 mg tablet, in combination with other antiretroviral agents, was approved by for the treatment of HIV-1 infection in adult HIV patients. The registered dose for adults is 400 mg twice daily (bd).

The proposed dose for 12 years of age and older was one 400 mg bd. For children 6-11 years of age, two options were proposed: One 400 mg tablet bd (if at least 25 kg in weight) or using the chewable tablets (weight based to maximum dose 300 mg) bd as specified in Table 15 in the proposed PI; for children 2-5 years of age, it is proposed to use the chewable tablets (weight based to maximum dose 300 mg) bd as specified in Table 15 of the PI (shown as Table 1 below).

Table 1 (Table 15 in PI): Recommended dose for Isentress chewable tablets in paediatric patients 2 through 11 years of age

Body Weight (kg)	Dose	Number of Chewable Tablets per dose
7 to < 10	50 mg twice daily	0.5 x 100 mg*
10 to < 14	75 mg twice daily	3 x 25 mg
14 to < 20	100 mg twice daily	1 x 100 mg
20 to < 28	150 mg twice daily	1.5 x 100 mg*
28 to < 40	200 mg twice daily	2 x 100 mg
At least 40	300 mg twice daily	3 x 100 mg

* The 100 mg chewable tablet can be divided into equal halves.

Note: the dosage recommendation of 6 mg/kg was derived from a clinical study where it was found to result in key pharmacokinetic values that closely approximate those in adults.

Regulatory status

Isentress 400 mg tablets were registered in Australia for adult use for the treatment of HIV-1 in January 2008.

As of 26 September 2012, raltegravir potassium (Isentress) has been registered and approved in 105 countries for the treatment of HIV-1 infection in treatment experienced adult patients. Isentress has also been approved in 72 countries for the use in treatment naïve adult patients. Isentress has been approved in the USA (21 December 2011) for use in children (see Table 2 below).

Table 2. Approved indication in the USA

Country	Submission Date	Approval Date	Approved Indication
USA	30-June-2011	21-Dec-2011	<p>Adults ISENTRESS is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection. This indication is based on analyses of plasma HIV-1 RNA levels in three double-sided controlled studies of ISENTRESS. Two of these studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults through 96 weeks and one was conducted in treatment-naïve adults through 156 weeks. The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response [see <i>Clinical Studies (14)</i>]</p> <p>Pediatrics¹ ISENTRESS is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in children and adolescents 2 years of age and older and weighing at least 10 kg [see <i>Use in Specific Populations (8.4)</i>] This indication is based on the evaluation of safety, tolerability, pharmacokinetic parameters and efficacy of ISENTRESS through at least 24-weeks in a multi-center, open-label, noncomparative study in HIV-1 infected children and adolescents 2 to 18 years of age [see <i>Clinical Studies (14.3)</i>]. The safety and efficacy of ISENTRESS have not been established in children less than two years of age.</p>

¹Text in **bold** represents the amended indication.]

European Union (EU): On 18 October 2012, the CHMP adopted a positive opinion recommending a variation to the terms of the marketing authorisation for ISENTRESS. The extension adopted by the Committee for Medicinal Products for Human Use (CHMP) is to add two new strengths and a new pharmaceutical form (25 mg and 100 mg chewable tablets) to the existing product range. The CHMP also adopted a change to the indication, as follows (text in bold represents the amended indication):

*“Isentress is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infections in **adults, adolescents, and children from the age of 2 years.** (see sections 4.2, 4.4, 5.1 and 5.2).”*

Canada: An application was submitted on 29 September 2011 and is still under evaluation.

Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

The drug substance used in the manufacture of the chewable tablets is identical to that approved for use in the manufacture of the registered tablets.

Drug product

The 25 mg chewable tablets are pale yellow, round, unscored tablets. The 100 mg chewable tablets are pale orange, oval, scored tablets, intended to be divisible for provision of a 50 mg dose. The two strengths are not direct scales. Identical drug-containing granules are used in the two strengths but they are mixed with different proportions of extra-granular excipients. The granules are coated to inhibit dissolution in

the mouth but allow rapid dissolution in the stomach. This is necessary to mask the bitter taste of the drug substance.

The chewable tablets are subject to a slightly different dissolution limit to that of the approved conventional tablets.

Adequate stability data have been provided to support the proposed shelf life of 2 years below 30°C for the chewable tablets.

Biopharmaceutics

Bioavailability of the 100 mg chewable tablet

One bioavailability study (Study P068) was submitted. It showed that the 100 mg chewable tablets have considerably higher bioavailability at equal dose than the registered 400 mg conventional tablets. The peak plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC) values of the chewable tablets are 3.22 and 1.78 times greater, respectively, than those of the conventional tablets. This is not surprising, as the conventional tablets were registered knowing that their bioavailability was sub-optimal. The PI includes a warning that because the formulations are not bioequivalent, the chewable tablets should not be substituted for the 400 mg tablet.

The study also showed that despite the increased bioavailability of the chewable tablets, they still have sub-optimal oral bioavailability. The bioavailability of the chewable tablets relative to an oral granule formulation was below 70% for both C_{max} and AUC.

Food delays the absorption of the chewable tablets, reducing C_{max} by 62%, but has no significant effect on AUC.

Bioavailability of the 25 mg chewable tablet

A justification was provided for not conducting a bioavailability study on the 25 mg chewable tablet. There are several reasons why the justification might not be accepted:

- i. Raltegravir is poorly soluble over the physiological pH range; it is classified as BCS Class II (low solubility, high permeability)¹.
- ii. The formulations of the 25 mg and 100 mg chewable tablets are not direct scales.
- iii. In water and in pH 1.2, 5.5 and 6.8 buffers, the 25 mg chewable tablets dissolve much more rapidly than the 100 mg chewable tablets.

On the other hand, although the formulations are not direct scales, they do contain identical coated granules which are designed to inhibit drug release in the mouth. Chewing the tablets would be expected to release those granules rapidly and the granules would then be expected to behave similarly despite the presence of different levels of extra-granular excipients.

Provided the tablets are chewed, therefore, the two strengths would be expected to be bioequivalent at equal dose. The sponsor has agreed to amend the product labels and PI to stipulate that the tablets must be chewed, not swallowed whole.

¹ The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Quality summary and conclusions and advisory committee considerations

This submission was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on prescription Medicines (ACPM) at its 147th meeting on 24 September 2012. The PSC agreed that the 25 mg and 100 mg chewable tablets would be expected to be bioequivalent at equal dose provided they are chewed, not swallowed whole.

The PSC agreed that there should be no objections to registration on chemistry and quality control grounds but recommended that the PI be amended to include the pKa and solubility data of the drug substance.

The PSC made a number of comments about the submitted population pharmacokinetic data. Those comments have been referred to the Clinical Delegate for consideration. The PSC also considered that the dosing recommendations in the PI were overly complicated and led to inconsistencies, as they took into account both age and body weight when body weight alone would appear to be more appropriate.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The paediatric development program for raltegravir began with Phase I pharmacokinetic and safety studies of paediatric formulation candidates evaluated in healthy adult volunteers, the pivotal study being Protocol 068. The data from this study were used to select two formulations, the chewable tablets and the oral granules for suspension, which were further evaluated, along with the adult formulation, in the pivotal clinical Phase I/II study P1066, in HIV-infected-paediatric patients.

Good clinical practice and ethics

The applicant stated that all trials were conducted following contemporary Good Clinical Practice guidelines and considerations for the ethical treatment of human subjects.

The application by Merck Sharp and Dohme (Australia) to register raltegravir chewable tablets for use in HIV-1 infected children included two pivotal studies, Protocols 068 and P1066. The same formulation of chewable tablet was used in each of these studies and differed from the formulation planned for registration only in colour (25 mg) and shape (100 mg).

Study P068

Summary of Study P068

Study P068 evaluated relative bioavailability of the raltegravir paediatric chewable tablet, raltegravir oral granules for suspension (not relevant to this evaluation) and the registered raltegravir adult 400 mg tablet. The effect of a high fat meal on the

pharmacokinetic profile of the paediatric chewable tablet formulation was also assessed. Twelve healthy adults, three women and nine men each received four treatments randomised in a balanced, crossover design in Periods 1 to 4. Treatments A to C were administered in fasted conditions.

- Treatment A: single oral dose of 400 mg raltegravir adult formulation tablet (1 x 400 mg tablet).
- Treatment B: single oral dose of 400 mg raltegravir paediatric chewable tablet (4 x 100 mg tablets).
- Treatment C: single oral dose of 400 mg raltegravir oral granules in liquid suspension.
- Treatment D: single oral dose of 400 mg paediatric chewable tablet (4 x 100 mg) following a standard high fat meal.

Key findings relevant to this application were as follows.

The results for AUC and C_{max} were well outside the accepted bioequivalence 90% confidence limits of 80% - 125%. The lower limit of the 90% confidence interval (CI) for C_{min} was below acceptance level.

The geometric means of AUC from time 0 to infinity ($AUC_{0-\infty}$) were 19.2 $\mu\text{M}\cdot\text{h}$ for the adult tablet and 34.2 $\mu\text{M}\cdot\text{h}$ for the chewable formulation. The geometric mean ratio (GMR) (90% CI) was 1.78 (1.47, 2.15).

The geometric means of C_{max} were 5.0 μM for the adult tablet and 16.1 μM for the chewable tablet. The GMR (90% CI) was 2.73 (2.37, 4.38).

The geometric means for C_{12h} of 400 mg adult formulation and 400 mg chewable formulation were 149 nM and 134 nM respectively. The GMR (90% CI) was 0.90 (0.7, 1.18).

The chewable tablet was absorbed more rapidly than the adult formulation tablet as evidenced by the difference in time of C_{max} (T_{max}) estimations: 4 hours versus 0.5 hours for the adult and chewable tablets respectively.

Compared to the fasted state, administration of the chewable tablet with a high-fat meal led to an increase in C_{12h} . The GMR (90% CI) for fed/fasted was 2.88 (2.21, 3.75), a decrease in C_{max} with GMR (90% CI) equalling 0.38 (0.28, 0.52), a delay in T_{max} (median 0.5 hour in the fasted state and 1.0 hour in the fed state), and an $AUC_{0-\infty}$ with GMR (90% CI) of 0.94 (0.78, 1.14).

There was considerable variability in individual results. The differing means and the large standard deviations suggested skewed data with widespread distribution which was visible in the figures. These findings are consistent with those of previous studies.

With regard to safety, one participant experienced somnolence following ingestion of both oral granules and chewable tablets; the event was considered study drug related. However, in general the various formulations were well tolerated.

Discussion of Study P068

A strong association had not been found between raltegravir pharmacokinetic summary measures and efficacy parameters and thus a target pharmacokinetic parameter known to strongly influence outcome had not yet been identified. For other classes of antiretroviral agents, there is a reasonable association of efficacy with doses that achieve C_{trough} values that exceed the IC_{95} in the HIV spread assay.

The applicant contends that the higher $AUC_{0-\infty}$ and C_{max} values are not expected to have meaningful clinical consequences because to date in the development program for raltegravir, there had been no acute safety findings that were temporally associated with

peak concentrations, and raltegravir was found to be generally well tolerated in the clinical program with no dose-related toxicities so far detected.

In keeping with results of previous studies, administration with a high-fat meal slowed the rate of absorption from the chewable tablet; however, the extent of absorption was almost within bioequivalence criteria and the applicant believes that the differences are not clinically meaningful.

Based on the similarity in trough values, these results were taken as support of continued clinical development of both paediatric formulations. The applicant states that the effect of food on raltegravir pharmacokinetics is variable depending on the meal type and that administration of food leads to increased variability and that it is therefore unlikely that a recommendation to administered raltegravir with food would lead to consistent changes in the C_{12h} or other measures of exposure to raltegravir that would be likely to impact on efficacy or safety. The effects of food on the pharmacokinetic profile of raltegravir administered as either the adult tablet or the chewable tablet were thus not thought to be of clinical importance. The 400 mg tablet is registered for use in adult patients without food restriction.

Study P1066

Summary of Study P1066

Study P1066 (also known as IMPAACT or 022) is an ongoing multicentre, open label, non-comparative study in treatment-experienced children and adolescents aged ≥ 4 weeks to < 19 years of age with documented HIV-1 infection and HIV RNA $> 1,000$ copies/mL at screening. The aim was to evaluate the safety, tolerability, PK parameters and antiviral activity of raltegravir in combination with an optimised background regimen. The study evolved over the course of three versions of the protocol.

Raltegravir was administered orally as the adult tablet or chewable tablet. A third formulation, oral granules for suspension in water, was included in the study for use by patients aged ≥ 4 weeks to < 2 years. Data on the oral granule formulation are planned for inclusion in a future clinical study report. Patients enrolled in the study were stratified into six cohorts, four of which were relevant to this application:

Cohort I: ≥ 12 to < 19 years of age assigned to receive adult tablets

Cohort IIA: ≥ 6 to < 12 years of age assigned to receive adult tablets

Cohort IIB: ≥ 6 to < 12 years of age assigned to received chewable tablets

Cohort III: ≥ 2 to < 6 years of age assigned to receive chewable tablets

Stage I examined the pharmacokinetics, short-term tolerability, and safety of raltegravir in a limited number of patients to permit dose selection for further study in Stage II. The objective was to determine appropriate doses based on target ranges derived from adult studies. Testing, which ultimately determined choice of dose, was undertaken in the fasted state. Stage I enrolment opened with the oldest cohort and progressed sequentially to the younger cohorts. Patients enrolled in Stage I remained in this stage. Duration of treatment was at least 48 weeks.

Resultant pharmacokinetic data exhibited considerable inter-individual variability. The final doses chosen are those proposed for the dosage and administration section of the PI (see Table 3 below).

Table 3. Dosage and administration

Cohort	Age Group and Formulation	Final Recommended Dose
Cohort I	≥12 to <19 years of age receiving poloxamer film coated adult tablets	400 mg BID
Cohort IIA	≥6 to <12 years of age receiving poloxamer film coated adult tablets	400 mg BID if ≥ 25 kg
Cohort IIB	≥6 to <12 years of age receiving chewable tablets	Weight based dosing to approximate 6 mg/kg up to maximum dose of 300 mg BID
Cohort III	≥2 to <6 years of age receiving chewable tablets	Weight based dosing to approximate 6 mg/kg up to maximum dose of 300 mg BID

Population pharmacokinetic assessment was undertaken based on results of Stage I and on sparse sampling undertaken in Stage II. Variability was more pronounced in the results for those participants treated with the adult formulation than those taking the chewable tablet formulation. Modelling was undertaken using only results for the chewable tablet taken in the fasted state. Weight and to a lesser extent age were found to be significant covariates for apparent clearance and volume of distribution. These two variables were highly correlated. The finding would add support to use of weight in determining dosage requirements.

The objectives of Stage II were primarily to evaluate the safety and tolerability of raltegravir at the selected dose in combination with optimised background therapy at Week 24. The secondary objectives included assessment of efficacy in terms of the composite of HIV RNA < 400 copies/mL or ≥ 1-log drop from baseline and in terms of changes in CD4 cell count and CD4% over 24 and 48 weeks. The duration of chronic dosing in Stage II was 48 weeks on the Stage I selected dose.

The submission report focused primarily on the results generated by patients from Stage I and II who received only the selected dose, the Final Dose Population, (N = 96). Results for the All Treated Population (N = 126) were also reported. Enrolment numbers were unevenly spread throughout the cohorts, with 59 participants in Cohort I, 4 in Cohort IIA, 13 in Cohort IIB and 20 in Cohort III.

Complete data were currently available for Week 24 (the primary endpoint) for Cohorts I, IIA, IIB, and III; at Week 48 (a secondary time point) for Cohorts I, IIA and IIB and at Week 80 for Cohort I.

At Week 24 for all cohorts combined, 71.6% of patients achieved ≥ 1-log drop in HIV RNA or HIV RNA < 400 copies/mL and 53.7% of patients achieved HIV RNA < 50 copies/mL, based on Observed Failure (OF) approach. The mean change from baseline in CD4 cell count and percent were 119.0 cells/mm³ and 3.8%, respectively.

At Week 48, 77.5% of patients in Cohorts I, IIA, and IIB achieved ≥ 1-log drop in HIV RNA or HIV RNA < 400 copies/mL and 56.3% of patients achieved HIV RNA < 50 copies/mL. The mean change from baseline in CD4 cell count and percent were 155.1 cells/mm³ and 4.7%, respectively.

Overall, a total of 25 patients failed treatment by Week 24, and 34 patients failed by Week 48. Compliance data were insufficiently complete to be reliable. With respect to viral resistance, genotype and phenotype testing, though not always conducted simultaneously, were consistent. Of the 31 All Treated patients for whom any genotypic data were available, viruses from 10 (32.3%) across all cohorts displayed signature resistance mutations. No unexpected viral resistance associated mutations were detected. The findings were considered consistent with those observed in Phase II clinical studies in HIV infected adults.

With respect to safety, drug related serious clinical adverse events were reported for 1% of the Final Dose Population and Grade 3 and 4 laboratory adverse events were reported by 1%. The profile of clinical and laboratory adverse events for the All Treated population were similar to those of the Final Dose population. There were no discontinuations due to adverse events. One patient developed confirmed new Category C Acquired immune deficiency syndrome (AIDS) defining condition. One death due to pneumonia was considered unrelated to study drug. One serious adverse event, pancreatitis, resulted in discontinuation of raltegravir adult tablet treatment.

There were no events reported consistent with immune reconstitution syndrome, rhabdomyolysis or myositis or malignancy. Reports of rash and pruritus or psychiatric conditions were relatively common but attribution was confounded by baseline condition, by indication or by use of concomitant antiretroviral treatment. Headache and gastrointestinal disorders were also relatively common but generally less than Grade 3 in severity and did not lead to discontinuation of raltegravir therapy. Psychiatric events were also common but did not lead to discontinuation and in the main there were confounding issues including prior psychiatric diagnoses and situational stressors. Review of the literature and of post market information did not alter the safety profile.

Discussion of Study P1066

With reference to the TGA adopted EU guideline *Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population*², the disease process in adults and children is considered to be similar and the outcome of therapy is thought likely to be comparable. The applicant has supplied pharmacokinetic study P068 and for P1066 in the appropriate age ranges together with evaluation of safety in study P1066.

The guideline states that an approach based on pharmacokinetics is insufficient for medicinal products where blood levels are known, or expected not to correspond with efficacy, or where there is concern that the concentration-response relationship may differ between the adult and paediatric populations. In such cases, studies of the clinical or the pharmacological effect of the medicinal product would usually be expected. Efficacy was examined in the observational Study P1066.

Thus, it is concluded that the applicant has complied with the Guideline and the request for inclusion in the indication of use by children and adolescents aged at least two years and registration of the chewable tablet, is recommended.

It is noted that the application has been approved by the FDA. The dosage and administration section of the US product information specifies a lower weight limit of 10 kg, whereas the applicant includes instructions for children down to weight of 7 kg, that is, approximately 7 mg/kg (in comparison, a 25 kg child taking 300 mg would be taking 12 mg/kg). From the data available, the lightest patient studied intensively (Stage 1) weighed 11.8 kg. According to the Australasian Paediatric Endocrine Group growth charts, 7 kg is marginally below the third percentile for a 2 year old child; an ill child may well fail to thrive. Taking these matters into consideration, if the lower age limit is to be 2 years, it is recommended that the dosage advice for children down to 7 kg is allowed. In saying this it is also recommended that information is added to the *Dosage and Administration* section of the PI to the effect that for the chewable tablet formulation, dosage is based on approximation of 6 mg/kg, and it is recommended that rather than including the proposed dosage table as the dosage instruction as proposed, it is included as dosage guidance.

The inter individual and intra individual variability which has been consistently demonstrated in PK studies in both adults and children is considered problematic,

2 CPMP/ICH/2711/99 <<http://www.tga.gov.au/pdf/euguide/ich271199en.pdf>>

particularly as the variability increased when food is factored in. In the fasted state, the applicant has demonstrated less variability with the chewable formulation than the adult tablet which suggests that some of the problem of variability lies with the formulation of the adult tablet.

Literature review

A literature review was undertaken by the applicant up until 20 January 2011. Two relevant reports were discovered including 13 patients treated with adult formulation tablets; one case report and one small observational study as summarised below.

1. A Turkova, C Ball, S Gilmour-White, M Rela, and G Mieli-Vergani. (2009). A paediatric case of acute liver failure associated with efavirenz-based highly active antiretroviral therapy and effective use of raltegravir in combination antiretroviral treatment after liver transplantation. *J Antimicrob Chemother* **63**(3):623-5.
2. Thuret I, Chaix ML, Tamalet C, Reliquet V, Firtion G, Tricoire J, Rabaud C, Frange P, Aumaître H, Blanche S. (2009). Raltegravir, etravirine and r-darunavir combination in adolescents with multidrug-resistant virus. *AIDS* **23** (17):2364-6.

Table 4. Summary of results from the two published papers.

Reference (see list above)	Country	Number treated	Age range years	Effectiveness	Number AEs
Thuret I <i>et al</i> (2009)	France	12	12-17	92% favourable response (viral load <400 copies/mL at median 12 month follow-up)	No unusual events were observed during tolerance evaluation; no Grade 2 side effects were recorded; there was 1 report of a probable immune reconstitution inflammatory response
Turkova A <i>et al</i> (2009)	Belgium	1	~10	Viral load became undetectable within 2 weeks of treatment	None reported in association with raltegravir. LFTs were abnormal in association with mild graft dysfunction after a second liver transplant that occurred prior to initiation of raltegravir.

The patients reported by Thuret *et al.* had been perinatally HIV-infected and had received extensive ARV therapy for a median duration of 15 years. Raltegravir 400 mg bd was administered to all patients in addition to backbone therapy. One patient experienced

probable immune reconstitution syndrome. Virologic failure in one patient with a viral load more than 400 copies/mL was reported to be related to suboptimal adherence to treatment. Tolerability was stated to be “remarkable” with no clinical symptoms of intolerance related to raltegravir.

The case report was of a 9 year old patient treated with raltegravir/lamivudine and zidovudine after liver transplantation for acute liver failure 13 weeks after starting efavirenz-based ART. Within 2 weeks viral load became undetectable.

Post market experience

An estimate of off-label raltegravir use in the paediatric population could not be determined from available data. Raltegravir reports by age and gender from 27 September 2007 to 31 December 2010 and by System Organ Class were summarised in the clinical evaluation report.

The most common reports (number of events) were: drug exposure during pregnancy (4), intentional drug misuse (3), insomnia (2) and psychomotor hyperactivity (2). Of the 4 reports of pregnancy, 3 resulted in live births with no congenital anomalies. The outcome of the fourth pregnancy was unknown.

There was one report of flare of endogenous autoimmune thyroiditis considered by the reporter to be possible manifestation of Immune Reconstitution Syndrome (IRS) but considered by the Market Authorisation Holder (MAH), not be entirely consistent with IRS.

One patient had increase in liver enzymes associated with hepatic failure considered unlikely to be due to treatment as the patient recovered while still being treated with raltegravir.

The MAH conclusion was that the events reported were generally consistent with the Company Core Data Sheet for raltegravir and pose no new safety concerns.

The Post market Safety Update Report for 27 March 2011 to 26 September 2011 was reviewed contemporaneously. The reported changes made to the Company Core Data Sheet had either already been included in the current Product Information, or are addressed in another submission which is currently also under TGA evaluation.

List of questions

Question 1-Efficacy analysis

The applicant was requested to provide clarification regarding use of the Observed Failure approach to analysis of efficacy data stated to provide a more clinically meaningful estimate of the antiretroviral effect. The following is included in the sponsor’s submission: *“In general: the OF approach considers a virologic failure endpoint, which is focused on the antiretroviral effect of the treatment; and the NC=F approach considers a study failure endpoint, which depends on the conduct of the study.”*

It appears that the Observed Failure (OF) approach is dependent on definition of viral failure and this varies from study to study. For instance, in Study P1066, observed failure was dependent on the composite of results relating to drop HIV Ribonucleic acid (RNA) value log₁₀ drop from baseline *and* HIV RNA < 400 copies/mL. More frequently, in studies adhering to the TGA adopted EU guideline on the *Clinical Development of Medicinal Products for the Treatment of HIV Infection*³, the primary objective is assessed in terms of

3 EMEA/CPMP/EWP/633/02 <<http://www.tga.gov.au/pdf/euguide/ewp063302en.pdf>>

HIV RNA < 50 copies/mL. It also seems likely that the analysis included an investigator's assessment of relatedness of events to study treatment.

With regard to Study P1066, the following definitions were provided in the protocol. It can be seen that the choice of definition of treatment failure/success within this study was selective with the definitions appearing to differ subtly depending on the use of "or" or "and"

*Approaches to handling of missing values - Observed failure approach*⁴

-For binary endpoints, missing values were considered as failures for patients

- missing data due to discontinuation of study treatment for lack of efficacy or
- for non-treatment related reasons with last available HIV RNA value < 1-log₁₀ drop from baseline **and** ≥400 copies/mL;

Otherwise patients with missing values were excluded.

Virologic success:

*The primary definition of virologic success required participants to have achieved and maintained 1-log drop from baseline **or** viral loads of < 400 copies/ml. A secondary, more stringent definition of virologic success, which requires that subjects achieve and maintain viral loads of <50 copies/ml, will also be utilized.*

Virologic Failure:

- *A confirmed decrease from baseline plasma HIV RNA of < 1.0 log₁₀ and HIV RNA > 400 copies/mL at Week 24 or later. Confirmatory HIV RNA measurement must be performed within 1 to 4 weeks. OR*
- *Virologic REBOUND at Week 24 or later that is defined as:*
 - *confirmed HIV RNA > 400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA < 400 copies/mL OR*
 - *Confirmed >1.0 log₁₀ increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart). Nadir was defined as the lowest HIV RNA while on study drug.*

A confirmatory HIV RNA test was to have been done in 1 week (or up to 4 weeks) later to verify viral failure/relapse. Due to the difficulty of having paediatric patients commit and adhere to extra clinic visits, most patients did not have the confirmatory test within 1 to 4 weeks. Therefore, the next available test for the patient, which may have been within 1 to 4 weeks or longer, was used as confirmatory test to identify virologic failures.

Results using the OF approach are noted to be better than those using the NC=F approach; however, the NC=F approach would appear less susceptible to varying interpretation or definition and is more conservative. Thus when a PI includes OF analysis results of studies with different definitions of failure, comparative information is considered to have the potential to be misleading.

MSD response

The Study P1066 protocol did not specify the approaches to impute missing data for efficacy endpoints. A key issue for the analysis of virologic responses is the missing data imputation. Two missing data approaches were prospectively defined and used in all

⁴ This text is from the foot note of *table labelled Observed failure approach* and is the most detailed explanation of the approaches used. Other information is included in the protocol but there was not statistical analysis plan.

previous studies of raltegravir conducted by MSD, the Observed Failure (OF) approach and the Non-completer=Failure (NC=F) approach.

The following text summarises the differences between these two missing data approaches:

- Observed Failure (OF): Patients who prematurely discontinued assigned treatment due to lack of efficacy (including investigator's assessment of discontinuation due to lack of efficacy, or discontinuation due to other reasons other than adverse experiences and the last available HIV RNA value is a failure) were considered as failures thereafter. Patients who prematurely discontinued assigned treatment, for reasons other than lack of efficacy, were excluded from the analyses. Intermittent missing values were also excluded from the analyses.
- Non-Completer = Failure (NC=F): Patients who prematurely discontinued assigned treatment regardless of reasons were considered as failures thereafter. Intermittent missing values were assigned as failures unless immediately flanked by 2 successes.

In general: the OF approach considers a virologic failure endpoint, which is focused on the antiretroviral effect of the treatment, and the NC=F approach considers a study failure endpoint, which also depends on the conduct of the study.

It is true that the OF approach is dependent on the definition of viral failure and this varies from study to study. It is also acknowledged that recent Guidelines require an assessment of HIV RNA <50 copies/mL as the primary objective. However, for Study P1066, the primary definition of virologic success specified in the protocol required patients achieving 1-log drop from baseline or viral loads of <400 copies/mL. Therefore, patients with <1-log drop from baseline and viral load \geq 400 copies/mL were considered as failure and this criterion was used while doing imputation using the OF approach.

Results using the OF approach are always as good as or better than those using the NC=F approach. The sponsor will clarify in the label that the result is based on the OF approach. However, key results were also summarised in the Clinical Study Report and Common Technical Document using an NC=F approach as well as for the endpoint of HIV RNA <50 copies/mL individually and may be used for comparative purposes.

In a well-conducted study for a treatment with good safety profile, the non-treatment-related discontinuation (that is, lost to follow-up, withdrawn consent and so on) rate is low and discontinuation rate due to adverse experiences is low, response rates estimated by OF approach will be similar to NC=F approach. Indeed, these two approaches gave similar results in Study P1066 (only 1 patient difference in the denominator) as shown in Table 5.

Table 5. P1066 Virologic response at week 24 using different missing data approach (Final dose population)

Parameter	OF Approach (N=96)		NC=F Approach (N=96)	
	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of patients with \geq 1 log ₁₀ drop from baseline in HIV RNA or HIV RNA <400 copies/mL	68/95	71.6 (61.4, 80.4)	68/96	70.8 (60.7, 79.7)
Proportion of patients with HIV RNA <50 copies/mL	51/95	53.7 (43.2, 64)	51/96	53.1 (42.7, 63.4)

The overall pattern of efficacy was comparable to that observed in adults. In particular, in published Phase III studies of treatment-experienced HIV-infected adults, BENCHMRK-1 and -2, response rates (NC=F) for HIV RNA < 50 copies/mL in patients receiving raltegravir plus OBT were 62% at Week 48, and sustained (57%) at Week 96. The sponsor acknowledged that caution is warranted whenever comparing across studies as there may be many confounding factors making these comparisons difficult to interpret.

Only two reasons for discontinuation were considered as treatment-related: lack of efficacy or adverse experiences (either caused by study medication or other concomitant medication). The OF approach is affected by the investigator's report of reason for discontinuation but is not dependent on investigator's assessment of relatedness of adverse events to study medication.

Evaluator comment

The results for the NC = F analysis of HIV RNA < 50 copies/mL results in Table 5, above were for Week 24 and appear similar to the Week 96 results for adults quoted above.

It is reassuring that in this study, there was minimal loss of patient numbers affecting the denominator for the OF analysis but this is not always the case and may not be the case for studies with which this one will be compared if use of OF results becomes systemic. The minimal loss of patient numbers in this study is remarkable small. It is also reassuring to know that discontinuations due to adverse events were not based on investigators' decision regarding relatedness of the adverse event. However, it does appear that there is some scope for investigator interpretation of reason for discontinuation.

MSD stated the intention to clarify that the results was based on the OF approach; however in the PI included with the sponsor's (S31) response to a TGA request for information, no mention of the method of analysis could be found.

In conclusion, it is this evaluator's opinion that the most conservative evaluation of results should be included in the Product Information, that is, in this case the NC=F results, a method which has some legitimacy according to the TGA adopted EU Guideline: *Points to consider on missing data*⁵. This guideline does not mention the Observed Failure approach and literature on the subject of Observed Failure has been exceedingly difficult to locate.

Question 2-Dosage and administration

The applicant is requested to clarify how thoroughly the chewable tablet is to be chewed. How critical is thorough chewing? And to what extent can the response to this question be backed with data?

On examination of the protocol of Study P068, the instructions for chewing the paediatric tablet could not be located. With respect to Study P1066, the instructions appeared to evolve as follows. Protocol version 2: "Chew tablet in mouth before swallowing. The ingestion of food or liquids after chewing the paediatric tablet is permitted but not required". Protocol version 3: Instructions as for version 2 plus "If they prefer, subjects may swallow the chewable tablets whole."

MSD response

To ensure consistency in dosing administration, patients were required to chew the chewable tablet for the witnessed dose prior to intensive PK collection.

Loss of tablet integrity has been reported to result in a change of pharmacokinetic response for some drug compounds either due to:

- a. Differential drug release or solubilisation of the compound in the gastrointestinal lumen from the intact vs. dispersed formulation, or
- b. Significant intraoral absorption when tablet integrity is lost during chewing.

Neither mechanism appears likely for raltegravir.

5 CPMP/EWP/1776/99 <<http://www.tga.gov.au/pdf/euguide/ewp177699en.pdf>>

The proposed chewable tablet for raltegravir is an immediate release, fast disintegrating and fast dissolving formulation that results in rapid absorption of raltegravir in the gastrointestinal (GI) tract. The formulation does not include any solubility enhancers or release modifiers. Thus, a somewhat faster disintegration due to chewing is not expected to result in differential bioavailability.

Regarding the potential for intraoral absorption, raltegravir physicochemical properties suggest significant absorption would be unlikely. Raltegravir is not highly lipophilic therefore permeability in the oral tissue will be limited. As raltegravir is dosed as the potassium salt and small amounts of drug that may be released due to chewing in the saliva in the oral cavity will be dissolved quickly in an ionized form which would also be expected to have even lower permeability through the oral tissues.

To investigate this matter, crushed (mortar and pestle) and intact tablets (100 mg potency) were evaluated in the pentagastrin treated dog model. Crushed and intact tablets resulted in comparable total exposure (AUC from time 0 to 24 h (AUC_{0-24hr}), 41.2 ± 3.5 versus $45.4 \pm 4.4 \mu M \cdot hr$, $n=3$) as well as rate of absorption as judged by C_{max} (17.7 ± 4.9 versus $19.1 \pm 1.6 \mu M$), with fast time to peak plasma concentration (T_{max}) in the 0.5-1.0 hr range for both.

Based on these data, the raltegravir chewable tablet may be chewed or swallowed whole. It is not necessary to emphasise "thorough chewing" of these tablets in the labelling.

Evaluator comment

It appears that use of pentagastrin treated dog may be a useful animal model for predicting the absorption characteristics of poorly water-soluble drugs in humans; however, this method is not included in the TGA adopted (with notations) European Union clinical Guideline on the investigation of bioequivalence⁶. While the arguments above may be accepted for the 100 mg chewable tablet, information was not provided for the 25 mg tablet and there is some suggestion that dissolution differs for the two dose strengths of the chewable tablet. As the PK data has been based on results after chewing the tablet, it is recommended that this method of ingestion is the method included in the PI.

Clinical summary and conclusions

Benefit risk assessment

Benefits

HIV infection results in potentially life threatening illness which is controlled, but not cured, by use of highly active antiretroviral therapy consisting of combination of drugs with different mechanisms of action. Raltegravir has been registered for treatment of adult naive and treatment experienced adults based on controlled clinical of efficacy and safety in combination therapy. The mechanism of action of raltegravir in selectively inhibiting HIV-1 integrase catalysed strand transfer is unlikely to be different for adults and children.

⁶CPMP/EWP/QWP/1401/98 <<http://www.tga.gov.au/pdf/euguide/ewp140198rev1.pdf>>. Adopted by TGA with the following notation: "While this guidance suggests that the design and conduct of the study should follow EU regulations on Good Clinical Practice, sponsors should note that the EU Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) has been adopted in Australia with TGA annotations. The procedure for abridged applications claiming essential similarity to a reference product (ie, generics), which allows applications to be made to numerous Member States of the EU, based on bioequivalence with a reference product from one Member State, does not apply in Australia. An application for registration of a generic product in Australia should generally include a bioequivalence study versus a leading brand obtained in Australia."

Risks

The raltegravir safety profile has so far been studied only in a relatively small number of children. Safety in children, particularly the very young, who are still growing, developing and maturing may ultimately prove to have a different profile to that of adults.

Balance

The benefit risk balance is considered to lie on the side of benefit.

Recommendation

It is recommended that the paediatric chewable tablet formulation is registered for use in children and adolescents aged from 2 years according to the dosage regimen selected in Stage I of Study P1066. For the doses dependent on calculation by weight, it is recommended that the Dosage and Administration section of the PI includes the statement that dose is based on nearest approximation to 6 mg/kg and the proposed Table 15 [in the PI] is included as a guideline. It is further recommended that the *Dosage and Administration* section includes the instruction to chew the chewable tablet as PK studies were undertaken following witnessed chewing of the tablet.

With regard to reporting of efficacy results, it is recommended that the most conservative evaluation of results should be included in the PI, that is, in this case the NC=F results, a method which has legitimacy according to the TGA adopted EU Guideline: *Points to consider on missing data*⁵. This guideline does not mention the Observed Failure approach and literature on the subject of Observed Failure has been exceedingly difficult to locate. While accepting that on this occasion the results for the 2 methods of analysis were similar, it is considered a matter of principle that results should be based on a method of handling of missing data that is standard and included in the guidelines.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification (SS)

Subject to the evaluation of the clinical aspects of the SS by the Office of Medicine Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is summarised in Table 6 below.

Table 6. Summary of ongoing safety concerns

Important Identified Risks or Important Identified Drug Interactions	Immune reconstitution inflammatory syndrome Drug resistance Drug interaction with rifampin and other strong UGT1A1 inducers Extent of pharmacokinetic (PK) variability and impact, if any, on pharmacodynamics (PD)
Important Potential Risks	Malignancies Serious Rash Increase in liver enzymes Lipodystrophy/Fat maldistribution Increase in CK with clinical manifestations; myopathy, rhabdomyolysis Depression, suicidal ideation, suicidal behaviors
Important Missing Information	Potential exposure during pregnancy Long-term safety data <ul style="list-style-type: none"> • Populations studied • Populations insufficiently studied/not studied: <ul style="list-style-type: none"> ○ Exposure in children less than 2 years of age ○ Exposure in elderly patients ○ Exposure in patients with hepatitis B and/or C co-infection ○ Exposure in patients with severe hepatic impairment

OPR reviewer comment

It is recommended that the Important missing information: 'Use in lactation' be included as a new Ongoing Safety Concern. The RMP should be amended accordingly.

Pharmacovigilance plan

The sponsor states that routine pharmacovigilance activities⁷, consistent with the activities outlined in 3.1.2 *Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)*, are proposed to monitor all the specified Ongoing Safety Concerns, except for the Important identified risk: 'Extent of pharmacokinetic (PK) variability and impact, if any, on pharmacodynamics (PD)'.

Furthermore the sponsor proposes to monitor all the specified Ongoing Safety Concerns via the ongoing clinical trials program, except for the Important identified drug interaction: 'Drug interaction with rifampin and other strong UGT1A1 inducers' and the Important missing information: 'Exposure during pregnancy' and 'Exposure in patients with severe hepatic impairment'. Details of the protocol of these trials have been provided in Annex 5 of the RMP and the sponsor has stated planned dates for submission of interim and /or final data.

In addition the Important identified risks: 'Immune reconstitution inflammatory syndrome', 'Drug resistance' and 'Extent of pharmacokinetic (PK) variability and impact, if any, on pharmacodynamics (PD)'; the Important potential risks: 'Malignancies', 'Serious

⁷ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Rash', 'Increase in liver enzymes', 'Lipodystrophy/Fat maldistribution', 'Increase in CK with clinical manifestations; myopathy, rhabdomyolysis' and 'Depression, suicidal ideation, suicidal behaviours' and the important missing information: 'Exposure in children less than 2 years of age' will be further monitored during the planned Phase I, open-label, non-comparative study to evaluate the safety and PK of raltegravir in neonates less than 4 weeks of age born to HIV infected mothers. The sponsor has provided a brief synopsis of this study (Protocol 080) in Annex 5 of the RMP, which states that it will be initiated after demonstration of acceptable PK, safety and efficacy data in older children (children from 4 weeks to less than 18 years of age).

This statement would appear to refer to the ongoing clinical trial 022, a Phase I/II, multi-centre, open-label, non-comparative study of approximately 120 to 160 HIV-1 infected children and adolescents ages ≥ 4 weeks to < 19 years of age to evaluate the safety, tolerability, pharmacokinetic parameters and efficacy of raltegravir, which will also further monitor the Important missing information: 'Exposure in children less than 2 years of age'. The sponsor states that the planned date for submission of final data for the ongoing clinical trial 022 is 31 August 2017. As mentioned above, details of the protocol of this trial has been provided in Annex 5 of the RMP.

The Important potential risks: 'Malignancies', 'Increase in liver enzymes' and 'Lipodystrophy/Fat maldistribution'; and the Important missing information: 'Long-term safety data in Populations studied' will be further monitored by the ongoing observational post authorisation safety study in EuroSIDA (058). The sponsor reports that this study will be conducted for 5 years post-licensure and until at least 1,000 patient-years of exposure to raltegravir are accrued. Safety data on pre-specified clinical events of interest will be gathered and analysed on an ongoing basis and an update on the study's progress will be reported in the Periodic Safety Update Reports (PSURs) (for example, accumulated person-years of exposure). The results of this observational post authorisation safety study was presented in a report first provided based on one year of data accrual following the implementation of the project and then will be provided on an annual basis, until the final report provided at the end of the project.

The data from the ongoing observational post authorisation safety study in the US Managed Care Network (EPO8025.006) will be reported in a similar manner and will further monitor the Important potential risks: 'Malignancies', 'Serious Rash', 'Increase in liver enzymes', 'Lipodystrophy/Fat maldistribution' and 'Increase in CK with clinical manifestations; myopathy, rhabdomyolysis'; and the Important missing information: 'Long-term safety data in Populations studied'.

Details of these ongoing observational post authorisation safety studies were provided in Annex 5 of the RMP.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

In principle there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified Ongoing Safety Concerns. However, the ongoing clinical trials and ongoing post authorisation safety studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of these studies, as outlined in the RMP, will be expected in future PSURs.

At this stage no proper assessment of the planned neonatal study (Protocol 080) can be made. Nevertheless once the ongoing clinical trial 022 nears completion (first quarter of 2017?) and acceptable PK, safety and efficacy data in older children (children from 4 weeks to less than 18 years of age) have been demonstrated, it is expected that a draft protocol for the planned study will be submitted to the TGA for review.

It is also recommended that routine pharmacovigilance be used to monitor the Important missing information: 'Use in lactation', as a new Ongoing Safety Concern.

Risk minimisation activities

Routine risk minimisation activities⁸ will comprise labelling, including pharmacokinetic data, special warning and precaution statements, instructions for use, drug interactions and/or notification of undesirable effects for all the specified Ongoing Safety Concerns, although no such activity is proposed for the Important missing information: 'Long-term safety data in Populations studied'.

OPR reviewer comment

It is recommended that routine risk minimisation should also be applied to the Important missing information: 'Long-term safety data in Populations studied', particularly in relation to extending the use of raltegravir in adolescents and children from the age of 2 years (see below).

In addition the Australian Specific Risk Minimisation Plan of the Australian Specific Annex incorrectly refers to 'Creatine Kinase laboratory abnormalities' in the Adverse Effects' section for the Important potential risk: 'Increase in liver enzymes', rather than to 'Laboratory Abnormalities' in the same section. This should be corrected.

It is acknowledged that routine risk minimisation has already been proposed for the Important missing information: 'Use in lactation'.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows:

- For the Important identified risk: 'Drug resistance', the sentence: "*The use of other active antiretroviral agents in combination with Isentress is associated with a greater likelihood of treatment response (see Clinical Trials).*" in the 'Indications' section may also include advice that such a strategy will also minimise the development of drug resistance. This is consistent with the currently approved EU Summary of Product Characteristics (SmPC).
- For the Important identified risk: 'Extent of pharmacokinetic (PK) variability and impact, if any, on pharmacodynamics (PD)', precautionary advice that overall, considerable inter- and intra-subject variability was observed in the PK of raltegravir may be included and cross-referenced to the 'Pharmacokinetics' section. This is consistent with the currently approved SmPC.
- For the Important potential risk: 'Increase in CK with clinical manifestations; myopathy, rhabdomyolysis', the statement to use raltegravir with caution in patients at increased risk of myopathy or rhabdomyolysis located in the 'Adverse Effects' section should also be included in the 'Precautions' section and cross-referenced. This is consistent with the currently approved SmPC.
- For the Important missing information: 'Long-term safety data in Populations studied', the statement: "There are no safety data beyond 24 weeks of treatment", or words to that effect, should be included under the sub-heading: 'Paediatric Adverse Experiences' in the 'Adverse Effects' section of the PI.

It is also noted that for the Important identified drug interaction: 'Drug interaction with rifampin and other strong UGT1A1 inducers', the currently approved SmPC states: "*if co-*

⁸ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

administration with rifampin is unavoidable, a doubling of the dose of ISENTRESS can be considered". No such dosage adjustment advice is included in the draft PI.

In addition the clinical evaluator has recommended amendment to the draft Product Information.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified:

- It is recommended that the Important missing information: 'Use in lactation' be included as a new Ongoing Safety Concern. The RMP should be amended accordingly.
- In principle there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified Ongoing Safety Concerns. However, the ongoing clinical trials and ongoing post authorisation safety studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of these studies, as outlined in the RMP, will be expected in future PSURs.
- At this stage no proper assessment of the planned neonatal study (Protocol 080) can be made. Nevertheless once the ongoing clinical trial 022 nears completion (first quarter of 2017?) and acceptable PK, safety and efficacy data in older children (children from 4 weeks to less than 18 years of age) have been demonstrated, it is expected that a draft protocol for the planned study will be submitted to the TGA for review.
- It is recommended that routine pharmacovigilance be used to monitor the Important missing information: 'Use in lactation', as a new Ongoing Safety Concern.
- The sponsor's justification and conclusion that routine risk minimisation activities for the specified Ongoing Safety Concerns are sufficient appears reasonable. Nevertheless it is recommended that routine risk minimisation should also be applied to the Important missing information: 'Long-term safety data in Populations studied' - particularly in relation to extending the use of raltegravir in adolescents and children from the age of 2 years (see below).
- The Australian Specific Risk Minimisation Plan of the Australian Specific Annex incorrectly refers to 'Creatine Kinase laboratory abnormalities' in the Adverse Effects' section for the Important potential risk: 'Increase in liver enzymes', rather than to 'Laboratory Abnormalities' in the same section. This should be corrected.
- It is acknowledged that routine risk minimisation has already been proposed for the Important missing information: 'Use in lactation'.
- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows:
 - For the important identified risk: 'Drug resistance', the sentence: "The use of other active antiretroviral agents in combination with Isentress is associated with a greater likelihood of treatment response (see *Clinical Trials*)."

section may also include advice that such a strategy will also minimise the development of drug resistance. This is consistent with the currently approved SmPC.

- For the Important identified risk: ‘Extent of pharmacokinetic (PK) variability and impact, if any, on pharmacodynamics (PD)’, precautionary advice that overall, considerable inter- and intra-subject variability was observed in the PK of raltegravir may be included and cross-referenced to the ‘Pharmacokinetics’ section. This is consistent with the currently approved SmPC.
 - For the Important potential risk: ‘Increase in CK with clinical manifestations; myopathy, rhabdomyolysis’, the statement to use raltegravir with caution in patients at increased risk of myopathy or rhabdomyolysis located in the ‘Adverse Effects’ section should also be included in the ‘Precautions’ section and cross-referenced. This is consistent with the currently approved SmPC.
 - For the Important missing information: ‘Long-term safety data in Populations studied’, the statement: “There are no safety data beyond 24 weeks of treatment”, or words to that effect, should be included under the sub-heading: ‘Paediatric Adverse Experiences’ in the ‘Adverse Effects’ section of the PI.
 - It is also noted that for the Important identified drug interaction: ‘Drug interaction with rifampin and other strong UGT1A1 inducers’, the currently approved SmPC states: “*if co-administration with rifampin is unavoidable, a doubling of the dose of ISENTRESS can be considered*”. No such dosage adjustment advice is included in the draft PI.
- In addition the clinical evaluator has recommended amendment to the draft Product Information.
 - In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft Consumer Medicine Information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate’s overview and recommendations:

Quality

The bioavailability of the 100 mg chewable tablet was assessed in Study P068. The study showed that the 100 mg chewable tablets have considerably higher bioavailability at equal dose than the registered 400 mg conventional tablets. The C_{max} and AUC values of the chewable tablets are 3.22 and 1.78 times greater, respectively, than those of the conventional tablets. This is not surprising, as the conventional tablets were registered knowing that their bioavailability was sub-optimal. The PI includes a warning that because the formulations are not bioequivalent, the chewable tablets should not be substituted for the 400 mg tablet. The study also showed that despite the increased bioavailability of the chewable tablets, they still have sub-optimal oral bioavailability. The bioavailability of the chewable tablets relative to an oral granule formulation was below 70% for both C_{max} and AUC. Food delays the absorption of the chewable tablets, reducing C_{max} by 62% but has no significant effect on AUC.

The sponsor provided a justification for not conducting a bioavailability study on the 25 mg chewable tablet. The evaluator pointed out the following reasons why the justification might not be accepted:

- a. Raltegravir is poorly soluble over the physiological pH range; it is classified as BCS Class II (low solubility, high permeability).
- b. The formulations of the 25 mg and 100 mg chewable tablets are not direct scales.
- c. In water and in pH 1.2, 5.5 and 6.8 buffers, the 25 mg chewable tablets dissolve much more rapidly than the 100 mg chewable tablets.

The evaluator commented that although the formulations are not direct scales, they do contain identical coated granules, which are designed to inhibit drug release in the mouth. Chewing the tablets would be expected to release those granules rapidly and the granules would then be expected to behave similarly despite the presence of different levels of extra-granular excipients. Provided the tablets are chewed, the two strengths would be expected to be bioequivalent at equal dose.

This submission was considered by the PSC of the ACPM. The PSC was of the consensus that the PI should be amended to include a statement stipulating that the chewable tablets must be chewed and must not be swallowed whole in view of the results from Study P068. The company has agreed to amend the product labels and PI to this effect.

The PSC agreed that there should be no objections to registration on chemistry and quality control grounds, but recommended that the PI be amended to include the pKa and solubility data of the drug substance. The PSC made a number of comments about the submitted population pharmacokinetic data and considers that the proposed dosing recommendations, based on both age and body weight, were overly complicated and recommendations based on weight alone would appear to be more appropriate.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Two studies, Study 068 and P1066, were submitted and evaluated.

Study P068 was evaluated by the quality evaluator as discussed above. This study assessed the relative bioavailability of the chewable tablet, oral, and the registered 400 mg adult tablet. The effect of a high fat meal on the pharmacokinetic (PK) profile of the chewable tablet was also assessed. Twelve healthy adults each received four treatments randomised in a balanced, crossover design in Periods 1 to 4. Treatments A to C were administered in fasted conditions.

Treatment A: single dose of 400 mg adult formulation tablet (1 x 400 mg tablet).

Treatment B: single dose of 400 mg paediatric chewable tablet (4 x 100 mg tablets).

Treatment C: single dose of 400 mg oral granules in liquid suspension.

Treatment D: single dose of 400 mg chewable tablet (4 x 100 mg) following a high fat meal.

The results for AUC and C_{max} were well outside the accepted bioequivalence 90% CI of 80% - 125%. The lower limit of the 90% CI for C_{min} was below acceptance level.

The geometric means of $AUC_{0-\infty}$ were 19.2 $\mu\text{M}\cdot\text{h}$ for the adult tablet and 34.2 $\mu\text{M}\cdot\text{h}$ for the chewable formulation. The GMR (90% CI) was 1.78 (1.47, 2.15).

The geometric means of C_{max} were 5.0 μM for the adult tablet and 16.1 μM for the chewable tablet. The GMR (90% CI) was 3.22 (2.37, 4.38).

The geometric means for C_{12h} of 400 mg adult formulation and 400 mg chewable formulation were 149 nM and 134 nM respectively. The GMR (90% CI) was 0.90 (0.7, 1.18).

The chewable tablet was absorbed more rapidly than the adult tablet. The T_{max} is 4 hours and 0.5 hours for the adult tablet and chewable tablet, respectively.

Compared to the fasted state, administration of the chewable tablet with a high-fat meal led to an increase in C_{12h} . The GMR (90% CI) for fed/fasted was 2.88 (2.21, 3.75), a decrease in C_{max} with GMR (90% CI) equalling 0.38 (0.28, 0.52), a delay in T_{max} (median 0.5 hour in the fasted state and 1.0 hour in the fed state), and an $AUC_{0-\infty}$ with GMR (90% CI) of 0.94 (0.78, 1.14). There was considerable variability in individual results, and these findings are consistent with those of previous studies.

The evaluator noted that the inter-individual and intra-individual variability has been consistently demonstrated in PK studies in both adults and children. A high-fat meal slows the rate of absorption from the chewable tablet; however, the extent of absorption was almost within bioequivalence criteria and the differences are not considered clinically meaningful. The effects of food on the PK profile of raltegravir administered as either the adult tablet or the chewable tablet were thus not thought to be of clinical importance.

The evaluator also noted that in the development program for raltegravir, there had been no acute safety findings that were temporally associated with raltegravir peak concentrations and raltegravir was found to be generally well tolerated in the clinical program with no dose-related toxicities so far detected. It is therefore considered that the higher $AUC_{0-\infty}$ and C_{max} values are not expected to have meaningful clinical consequences.

Study P1066 is a multicentre, open label, non-comparative study in treatment-experienced children and adolescents aged ≥ 4 weeks to < 19 years of age with HIV-1 infection and HIV RNA $> 1,000$ copies/mL at screening. The study was to evaluate the safety, tolerability, PK and antiviral activity of raltegravir in combination with an optimised background regimen. Raltegravir was given as the adult tablet or chewable tablet. A third formulation, oral granules, was included for use by patients aged ≥ 4 weeks to < 2 years. Data on the granule formulation are planned for inclusion in a future study report. Patients enrolled were stratified into six cohorts, four of which were relevant to this application:

Cohort I: ≥ 12 to < 19 years of age assigned to receive adult tablets

Cohort IIA: ≥ 6 to < 12 years of age assigned to receive adult tablets

Cohort IIB: ≥ 6 to < 12 years of age assigned to received chewable tablets

Cohort III: ≥ 2 to < 6 years of age assigned to receive chewable tablets

Stage I examined the PK and short-term safety of raltegravir in a limited number of patients to allow dose selection for Stage II. The appropriate doses were to be determined based on achieving the target ranges derived from adult studies. Testing was undertaken in fasted state. Stage I enrolment opened with the oldest cohort and progressed to the younger cohorts. Duration of treatment was at least 48 weeks. The resultant PK data exhibited considerable inter-individual variability. The final doses chosen are those proposed for the *Dosage and Administration* section of the Product Information (PI; Table 15).

Population pharmacokinetic (PPK) assessment was undertaken based on results of Stage I and on sparse sampling in Stage II. Variability was more pronounced with the adult formulation than the chewable tablet formulation. Modelling was undertaken using only results for the chewable tablet taken in the fasted state. Weight and age were found to be

significant covariates for apparent clearance and volume of distribution. The findings support the weight-based dosage requirements. Based on the pharmacokinetic assessment, it is concluded that the children taking the doses selected for the Final Dose population achieved the target levels in adults at the approved raltegravir dose of 400 mg twice daily.

Stage II evaluated the safety and tolerability of raltegravir at the selected dose in combination with optimised background therapy at Week 24. The secondary objectives included assessment of efficacy in terms of the composite of HIV RNA < 400 copies/mL or ≥ 1 -log drop from baseline and in terms of changes in CD4 cell count and CD4% over 24 and 48 weeks. The duration of chronic dosing in Stage II was 48 weeks. The report focused on the results in patients who received only the selected dose, the Final Dose Population, (N = 96). Results for the All Treated Population (N = 126) were also reported. Enrolment numbers were unevenly spread throughout the cohorts, with 59 participants in Cohort I, 4 in Cohort IIA, 13 in Cohort IIB and 20 in Cohort III. Complete data were currently available for Week 24 (the primary endpoint) for Cohorts I, IIA, IIB, and III; at Week 48 data (a secondary time point) for Cohorts I, IIA and IIB and at Week 80 for Cohort I.

Week 24 results: for all cohorts combined, 71.6% of patients achieved ≥ -1 log drop in HIV RNA or HIV RNA < 400 copies/mL and 53.7% of patients achieved HIV RNA < 50 copies/mL, based on Observed Failure (OF) approach. The mean change from baseline in CD4 cell count and percent were 119.0 cells/mm³ and 3.8%, respectively.

Week 48 results: 77.5% of patients in Cohorts I, IIA, and IIB achieved ≥ -1 log drop in HIV RNA or HIV RNA < 400 copies/mL and 56.3% of patients achieved HIV RNA < 50 copies/mL. The mean change from baseline in CD4 cell count and percent were 155.1 cells/mm³ and 4.7%, respectively.

Safety aspects of Study P068 and P1066

Study P068: one participant experienced of somnolence following ingestion of both oral granules and chewable tablets; the event was considered study drug related. Overall, the various formulations of raltegravir were well tolerated.

Study P1066: Overall, a total of 25 patients failed treatment by Week 24 and 34 patients failed by Week 48. With respect to viral resistance, of the 31 All Treated patients for whom any genotypic data were available, viruses from 10 (32.3%) across all cohorts displayed signature resistance mutations. No unexpected viral resistance associated mutations were detected. The findings were consistent with those observed in Phase II clinical studies in HIV infected adults. Drug related serious adverse events (SAEs) were reported for 1% of the Final Dose Population and Grade 3 and 4 laboratory adverse events (AEs) were reported by 1%. The profile of clinical and laboratory AEs for the All Treated population were similar to those of the Final Dose population. There were no discontinuations due to AEs. One patient developed confirmed new Category C AIDS defining condition. One death due to pneumonia was considered unrelated to study drug. One SAE, pancreatitis, resulted in discontinuation of raltegravir adult tablet treatment. There were no events reported consistent with immune reconstitution syndrome, rhabdomyolysis or myositis or malignancy. Reports of rash and pruritus or psychiatric conditions were relatively common but attribution was confounded by other factors. Headache and gastrointestinal disorders were also relatively common but generally less than Grade 3 in severity and did not lead to drug discontinuation. Psychiatric events were also common but did not lead to discontinuation and in the main there were confounding issues including prior psychiatric diagnoses and situational stressors. Safety data in paediatric patients in this study is only available for 24 weeks.

Review of the literature and of post market information did not alter the safety profile.

Risk management plan

The RMP Version 7.0, dated 21 June 2011, was reviewed by the Office of Product Review (OPR).

Risk-benefit analysis**Delegate considerations**

Raltegravir, in combination with other antiviral agents, has been registered for treatment of adult HIV patients based on controlled clinical studies. The HIV disease process and the effects of antiviral therapy are likely to be similar between adults and children.

The applicant submitted a PK study (P068) in healthy adults and an uncontrolled PK, efficacy, and safety study (P1066) in paediatric HIV patients. The PK analysis in Study P1066 supports the selected doses for different age groups, as the final dose selected and administered to these paediatric patient led to mean AUC exposures that were comparable to the targeted adult mean AUC. The Week 24 efficacy analyses in Study P1066 demonstrated that raltegravir, administered at the selected dose, in combination with other antiviral agents, was effective in suppressing HIV RNA (<50 copies/mL and <400 copies/mL). No subject discontinued due to protocol defined virologic failure or adverse events.

The proposed dosing instructions for children include children down to weight of 7 kg. The evaluator noted that from the submitted data, the lightest patient studied intensively (Stage 1) weighed 11.8 kg, and according to the Australasian Paediatric Endocrine Group growth charts, 7 kg is marginally below the third percentile for a 2 year old child; an ill child may well fail to thrive. Taking these into consideration, if the lower age limit is to be 2 years, the dosage advice for children down to 7 kg should be allowed. The recommendation for the chewable tablets in paediatric patients 2 to 11 years is based on nearest approximation to 6 mg/kg and the proposed Table 15⁹ should be considered as a dosage guideline.

Product Information has been reviewed by the evaluators from clinical, quality and RMP evaluation areas, and a draft PI incorporating relevant changes should be submitted with the Pre-ACPM response. For the *Dosage and Administration* section of the PI, it is recommended adding a footnote to Table 15 stating that the dosage recommendations were derived from observed pharmacokinetic data in a clinical study in which a dose of 6 mg/kg was determined generally to most closely approximate the adult exposure from the 400mg bd which is known to be an effective dose.

Further changes to the PI may be required after the ACPM discussion.

Risk-management plan (RMP)

The RMP Version 7.0, dated 21 June 2011, with an Australian Specific Annex dated 24 October 2011, has been reviewed by the Office of Product Review (OPR). The evaluator has made a number of recommendations to amend some sections of the Product Information.

Specific issues for ACPM advice

The advice from ACPM is requested, specifically with the following aspects:

⁹ This refers to Table 15 of the PI and not of the AusPAR. Table 15 from the PI is shown as Table 1 in this AusPAR.

- What is the ACPM's view with regards to the proposed weight-based dosing recommendation using the chewable tablets for paediatric patients?
- What is the view of the ACPM with regards to the risk benefit balance for the use of raltegravir in paediatric HIV patients?

Proposed action

Pending the advice from the ACPM, the Delegate proposed the registration approval for the use of Isentress (raltegravir) 400 mg tablets, 25 mg and 100 mg chewable tablets, for the treatment of HIV-1 infection in children and adolescents from 2 to 18 years of age. The indications are as follows:

Isentress, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents and children from the age of 2 years.

The indication in adults is based on analyses of plasma HIV-1 RNA levels in controlled studies of Isentress (see Clinical Trials).

The indication in paediatric patients is based on the evaluation of safety, tolerability, pharmacokinetic parameters and efficacy of Isentress through at least 24 weeks in a multicentre, open label, non-comparative study in HIV-1 infected children and adolescents 2 to 18 years of age.

The use of other active antiretroviral agents in combination with Isentress is associated with a greater likelihood of treatment response (see Clinical Trials).

There are no study results demonstrating the effect of Isentress on clinical progression of HIV-1 infection.

The proposed dosage recommendation for children and adolescents from 2 to 18 years of age is considered acceptable with some amendments required.

Conditions of registration should include the implementation of Risk Management Plan Version, 7.0, dated 21 June 2011, with an Australian Specific Annex dated 24 October 2011.

Final approval is subject to the finalisation of the Product Information to the satisfaction of the TGA.

Response from sponsor

Merck Sharp and Dohme Australia Pty Limited (MSD) concurs with the evaluators' recommendations and the Delegate's proposed action to approve the extension of the indication of raltegravir to include treatment of HIV-1 infection in children and adolescents 2 to 18 years of age and to register the new formulation, chewable tablets (25 mg and 100 mg), for use in the paediatric population. The indication is as follows:

Isentress, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents and children from the age of 2 years.

The indication in adults is based on analyses of plasma HIV-1 RNA levels in controlled studies of Isentress (see Clinical Trials).

The indication in paediatric patients is based on the evaluation of safety, tolerability, pharmacokinetic parameters and efficacy of Isentress through at least 24 weeks in a multicentre, open label, non-comparative study in HIV-1 infected children and adolescents 2 to 18 years of age.

The use of other active antiretroviral agents in combination with Isentress is associated with a greater likelihood of treatment response (see Clinical Trials).

There are no study results demonstrating the effect of on clinical progression of HIV-1 infection.

The main clinical study (P1066) evaluated two raltegravir formulations (the adult film-coated tablet and a chewable tablet) in HIV-1 infected children aged between 2 to 18 years through 48 weeks of treatment (for the cohort that included the youngest patients, efficacy and safety data is presented after 24 weeks of treatment). The targeted pharmacokinetic parameters (AUC_{0-12h} and C_{12h}) were achieved allowing for selection of a final dose for each age group for one or both formulations. These doses provide pharmacokinetic exposures comparable to those seen in adults receiving the standard adult dose (400 mg twice daily), which is known to be effective.

This supports the outcome that weight based dosing is the most appropriate approach as also noted by the Delegate and hence has led to the dosing recommendations reproduced below. The chewable tablet formulation was developed specifically to allow dosing for younger patients who may not be able to swallow the 400 mg tablets. The chewable tablets have greater bioavailability compared to the adult 400 mg dose and are not considered interchangeable. The sponsor simplified/consolidated the dosing recommendations in the proposed PI as presented below as well as including the footnote to the table as suggested by the Delegate. The sponsor recognised that the clinical trial did not enrol children into the lowest band (7 to <10 kg), however, the dosing recommendations below would allow the doctor to treat these children with the chewable tablets, if clinically appropriate.

Children and adolescents:

- *6 years of age and older (if at least 25 kg in weight): One 400 mg tablet twice daily, orally*
- *2 to 11 years of age: Chewable tablets: weight based to maximum dose 300 mg, twice daily, as recommended in Table 15.*

Refer to Table 1 at the front of this AusPAR for the recommended dose for Isentress Chewable Tablets in Paediatric Patients 2 to 11 Years of Age.

Treatment of the paediatric cohorts with raltegravir has demonstrated an acceptable safety and efficacy profile at the recommended doses. As noted by the Delegate, the Week 24 efficacy analysis in Study P1066 demonstrated that raltegravir, administered at the selected dose, in combination with other anti-viral agents, was effective in suppressing HIV RNA (< 50 copies/mL and < 400 copies/mL). In addition, raltegravir demonstrated a durable immunological benefit, as measured by mean change from baseline in both CD4 cell count and percent. Results of a comprehensive review showed that the safety profile of raltegravir in paediatric patients 2 to 18 years receiving the adult tablet or chewable tablet was acceptable and did not raise any new safety concerns compared with data in adults and this was noted by the Delegate. Thus, the safety data in children are consistent with the established safety profile of raltegravir 400 mg (twice daily) in adults. This supports a favourable risk/benefit profile for raltegravir in the paediatric patient population.

In summary, raltegravir has been shown to be efficacious in the treatment of adult patients with HIV-1 and this application demonstrates that children with HIV-1 can also be effectively treated with raltegravir as part of a combination antiretroviral regimen. A chewable tablet has been specifically developed for younger children who may be unable to swallow the adult tablet. Treatment with the chewable tablet leads to raltegravir exposure (using weight based dosing) that is comparable to the adult dose of 400 mg twice daily, which is known to be efficacious. The safety profile is consistent with that

observed in adult patients and hence this presents a positive risk-benefit. This provides clinicians with further options to treat these children with HIV infection.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered this product to have an overall positive benefit-risk profile to support the extension of the patient population and the new dose form for the following indication:

Isentress in combination with other antiretroviral agents is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents and children from the age of 2 years.

This indication is based on analyses of plasma HIV-1 RNA levels in controlled studies of Isentress (see Clinical Trials.)

The indication in paediatric patients is based on the evaluation of safety, tolerability, pharmacokinetic parameters and efficacy of Isentress to at least 24 weeks in a multicentre, open label, non-comparative study in HIV-1 infected children and adolescents aged 2 to 18 years.

Isentress should not be used to treat HIV infection unless combined with other active anti retroviral agents.

There are no study results demonstrating the effect of Isentress on clinical progression of HIV-1 infection.

The proposed dosage recommendation for children and adolescents from 2 to 18 years of age is considered acceptable with some amendments required.

In making this recommendation the ACPM considered the data package to be deficient, particularly in relation to evidence in treatment-naive children; however, it noted the challenge of studies in this population group and the established role in treating adults with HIV infection.

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- *A statement in the Clinical trial / Precautions sections of the PI and relevant sections of the CMI to ensure clinicians are aware of the method of outcome analysis and that the clinical trials were conducted only in a treatment-experienced population. These documents should advise that while response in treatment-naive children is expected to match the experience in treatment-naive adults; clinicians should understand the limitations of the data.*
- *A statement in the Dosage and Administration / Precautions sections of the (PI/CMI) to ensure the dose of the chewable products is administered by chewing in accordance with the bioavailability profile of these products, together with a review of the information on dosing to ensure internal consistency.*
- *A statement in the Clinical Trial / Precautions sections of the PI / CMI to ensure clinicians are aware of the method of outcome analysis, and that the clinical trials were conducted only in a treatment-experienced population.*

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of the new strengths Isentress raltegravir 25 mg chewable tablet bottle and Isentress raltegravir 100 mg chewable tablet bottle; and the extension of indications for Isentress raltegravir tablet and chewable tablets. The new approved full indications for these therapeutic goods are now:

Isentress, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents and children from the age of 2 years.

This indication is based on analyses of plasma HIV-1 RNA levels in controlled studies of Isentress (see Clinical Trials).

The indication in paediatric patients is based on the evaluation of safety, tolerability, pharmacokinetic parameters and efficacy of Isentress through at least 24 weeks in a multicentre, open label, non-comparative study in HIV-1 infected, treatment-experienced children and adolescents 2 to 18 years of age.

The use of other active antiretroviral agents in combination with Isentress is associated with a greater likelihood of treatment response (see Clinical Trials.)

There are no study results demonstrating the effect of Isentress on clinical progression of HIV-1 infection.

Specific conditions applying to these therapeutic goods

The implementation in Australia of the raltegravir Risk Management Plan version 7, 21 June 2011, Australian Specific Annex dated 2 October 2011 included with submission PM-2011-03107-3-2, and any subsequent revisions, as agreed with the TGA and its Office of Product Review (Refer OPR Report 3 September 2012).

Attachment 1. Product information

The Product Information approved at the time this AusPAR was prepared is at Attachment 1. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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