

5.11 RALTEGRAVIR, Tablet 600 mg (as potassium), Isentress HD[®], Merck Sharp & Dohme (Australia) Pty Limited

1 Purpose of Application

- 1.1 The submission sought to list a once-daily formulation of raltegravir (2 × 600 mg tablets taken once daily [QD]) for the treatment of HIV infection in combination with other antiretroviral therapy. Raltegravir 400 mg tablets (taken as one tablet twice daily [BID]) are currently PBS-listed.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	HIV infected patients (including treatment naïve patients and treatment-experienced patients, and patients who are virologically suppressed on raltegravir 400 mg twice daily)
Intervention	Raltegravir 600 mg tablets (to be taken as raltegravir 1200 mg QD in combination with other antiretroviral therapy)
Comparator	Raltegravir 400 mg tablets BID
Outcomes	Proportion of patients achieving HIV RNA <40 copies/mL
Clinical claim	In HIV infected patients, raltegravir 1200 mg once-daily (taken as 2 × 600 mg tablets) is no worse than raltegravir 400 mg twice-daily at achieving viral suppression

Source: Developed during evaluation

- 1.2 The submission claimed that treating HIV-infected patients on a once-daily regimen of raltegravir is non-inferior in both efficacy and safety to a twice-daily regimen of raltegravir and will improve adherence.

2 Requested listing

- 2.1 The submission sought a Section 100 (Highly Specialised Drugs Program) listing for raltegravir 600 mg tablets (to be taken as raltegravir 1200 mg QD in combination with other antiretroviral therapy) for the treatment of HIV-1 infection in patients who are antiretroviral treatment-naïve or who are treatment-experienced, or patients who are virologically suppressed on an initial regimen of raltegravir 400 mg twice daily.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RALTEGRAVIR Tablet, 600 mg	120	5	\$1311.56	ISENTRESS® Merck Sharp & Dohme (Australia) Pty Ltd
Category / Program:	Section 100 - Highly Specialised Drugs (Community Access)			
PBS Indication:	HIV-1 infection			
Treatment phase:	Initial			
Restriction:	STREAMLINED			
Treatment criteria:	N/A			
Clinical criteria:	The treatment must be in combination with other antiretroviral agents			
Population criteria:	HIV-1 infection			

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RALTEGRAVIR Tablet, 600 mg	120	5	\$1311.56	ISENTRESS® Merck Sharp & Dohme (Australia) Pty Ltd
Category / Program:	Section 100 - Highly Specialised Drugs (Community Access)			
PBS Indication:	HIV-1 infection			
Treatment phase:	Continuing			
Restriction:	STREAMLINED			
Treatment criteria:	N/A			
Clinical criteria:	Patients must have previously received PBS-subsidised therapy for HIV infection; AND The treatment must be in combination with other antiretroviral agents.			
Population criteria:	HIV-1 infection			

2.2 The submission presented a cost minimisation evaluation of raltegravir 1200 mg (2 × 600 mg tablets) QD, compared to raltegravir 400 mg BID. The sponsor agreed in the Pre-Sub-Committee Response (PSCR) it would be acceptable to align the listings of the 400 mg and 600 mg raltegravir tablets.

2.3 Treatment would be continuous (unless loss of virologic suppression occurs).

2.4 No Special pricing arrangement was proposed.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

3.1 TGA status at time of PBAC consideration: The submission was made under TGA/PBAC Parallel Process. The TGA Clinical Evaluation Report became available during the evaluation. The sponsor advised that this form of raltegravir would not require consideration by the Advisory Committee on Medicines (ACM), and that no Delegate's Overview would be prepared, instead a Proposed Regulatory Action would

be provided in lieu of an Overview. However, the TGA Delegate's Proposed Regulatory Action was not available prior to the PBAC meeting.

- 3.2 Raltegravir 600 mg tablets have not been previously considered by the PBAC.
- 3.3 Raltegravir 400 mg twice daily (BID) was recommended for listing at the March 2008 PBAC meeting for the treatment of HIV infected patients who have failed, or have resistance to, three different antiretroviral regimens which have included at least one non-nucleoside reverse transcriptase inhibitors (NNRTI); at least one nucleoside reverse transcriptase inhibitors (NRTI); and at least one protease inhibitor (PI).
- 3.4 A recommendation was made at the March 2010 PBAC meeting to extend the listing for raltegravir 400 mg to treatment-naïve patients infected with HIV.
- 3.5 The ESC noted there are three Integrase Strand Transfer Inhibitors (InSTI) listed on the PBS (raltegravir, elvitegravir, dolutegravir). In treatment naïve patients, InSTIs are used in combination with a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs). The raltegravir 400 mg BID recommended regimen in the US treatment guidelines¹ is in combination with tenofovir and emtricitabine, both of which are administered QD.

For more detail on PBAC's view, see section 7 "PBAC outcome"

4 Population and disease

- 4.1 HIV-1 infected patients who weigh >40 kgs and are being treated with other antiretroviral agents.
- 4.2 Antiretroviral therapy (ART) is commenced in all HIV-1 infected patients. The Australian commentary on international clinical guidelines (ASHM anti-retroviral guidelines) recommends starting regimens in treatment-naïve patients with one of three ART regimens options including an InSTI plus two nucleoside reverse transcriptase inhibitors (NRTIs). Raltegravir 400 mg is an InSTI that is PBS listed for treatment-naïve patients and treatment-experienced patients.

5 Comparator

- 5.1 The submission nominated raltegravir 400 mg BID as the comparator. This is an appropriate comparator. However, other InSTI agents may also be appropriate comparators as they may be replaced by raltegravir 1200 mg QD in practice. Dolutegravir was recommended for listing at the November 2013 PBAC meeting on the basis of a cost-minimisation versus raltegravir 400 mg BID; with daily treatment costs as of April 2017 of \$22.97 and \$21.86, respectively.

For more detail on PBAC's view, see section 7 "PBAC outcome"

¹ Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Department of Health and Human Services. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed 09 June 2017, pp F3-F4

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on one head-to-head, non-inferiority trial comparing raltegravir 1200 mg QD (n=531) to raltegravir 400 mg BID (n=266) in treatment-naïve HIV-1 infected patients (Trial PN292).

6.4 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
PN292	Internal study report title: Evaluation of the Safety and Efficacy of Reformulated Raltegravir (MK-0518) 1200 mg Once Daily in Combination With TRUVADA in Human Immunodeficiency Virus (HIV)-1 Infected, Treatment-Naive Participants (MK-0518-292). Merck Research Laboratories. Clinical Study Report, version 1, 2016	Date: 12 May 2016

Source: Table 2-3, p.29 of the submission and PN292 CSR, p.1.

6.5 The key features of the direct randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)
PN292	797	R, DB, MC 48 weeks	Low	HIV infected treatment naïve	Proportion achieving HIV RNA <40 copies/mL

DB=double blind; MC=multi-centre; R=randomised.

Source: compiled during the evaluation

Comparative effectiveness

6.6 Table 4 presents the comparative effectiveness results from Trial PN292.

Table 4: Results of HIV RNA <40 copies/mL% in Trial PN292

Trial	Raltegravir 1200 mg QD n/N (%)	Raltegravir 400 mg BID n/N (%)	Relative risk (95% CI)	Risk difference (95% CI)
PN292	472/531 (88.9%)	235/266 (88.3%)	1.01 (0.95, 1.06)	0.510 (-4.20 , 5.22)

Source: Table 2-12, p.51 of the submission

6.7 No statistically significant differences between raltegravir 1200 mg QD and raltegravir 400 mg BID were observed with respect to the outcome of the proportion of patients achieving HIV RNA to <40 copies/mL. The analysis also met the pre-specified non-inferiority margin of the trial (-10%); with non-inferiority margins of -12% on the proportion of patients achieving HIV RNA to <50 copies/mL having been previously accepted by the PBAC. Additionally, a similar time for onset of action and duration of response were also observed between the two regimens.

Comparative harms

6.8 The clinical adverse event data showed the adverse event profiles of the two treatments are similar, with no statistically significant differences observed in any adverse event reported.

Clinical claim

6.9 The submission's clinical claim is that:

- “once daily raltegravir 1200 mg, taken with Truvada[®] as backbone therapy, has non-inferior efficacy compared to raltegravir 400 mg BID, taken with Truvada[®] as backbone therapy, in the treatment of HIV-1 infection” (p.69 of the submission).
- The submission further claimed that its analysis of safety demonstrated raltegravir QD is well tolerated and has a safety profile comparable to raltegravir 400 mg BID.

6.10 The therapeutic conclusion regarding efficacy was supported in HIV-1 infected patients who are treatment-naïve and treated in combination with Truvada[®] as a backbone therapy which was derived from the results of a single, randomised, head-to-head, double-blind, non-inferiority trial over 48 weeks. The primary outcome was based upon an objective laboratory test of HIV RNA <40 copies/mL. The pre-specified threshold of HIV RNA <40 copies/mL and a non-inferiority margin of the lower 95% CI of -10% are at, or slightly stricter, than thresholds previously accepted by the PBAC. Secondary efficacy outcomes, including both clinical measures and laboratory tests, were supportive of the submission's conclusion of non-inferiority. Safety data from the key trial, Trial PN292, also supported non-inferiority. The TGA Periodic Safety Update Report (PSUR) information in the submission did not identify any new safety concerns, although the information available for raltegravir 1200 mg QD is limited.

6.11 Clinical data were presented in treatment-naïve patients only. The PSCR noted that the TGA clinical evaluator had accepted the proposed indication, which did not differentiate between treatment-naïve and treatment-experienced patients. The ESC considered that there was no reason to exclude treatment-experienced patients from raltegravir 600 mg, as the use of raltegravir 400 mg tablets has been shown to be effective in these patients.

6.12 The submission did not present evidence of the comparative safety of raltegravir 1200 mg QD versus raltegravir 400 mg BID when used in combination with background therapies other than Truvada[®].

6.13 The PSCR argued that the efficacy profile of raltegravir is established with alternative backbone therapy in the real world, and there is no reason to assume this form of raltegravir would have a different effect. The ESC noted that the submission only presented evidence with tenofovir disoproxil fumarate with emtricitabine (Truvada[®]). The ESC further noted that raltegravir 400 mg BID in combination with tenofovir plus emtricitabine is a ‘recommended regimen option’ in the US treatment guidelines². The

² Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Department of Health and Human Services. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed 09 June 2017, pp F3-F4

other raltegravir combination included in the guidelines (raltegravir plus abacavir and lamivudine) is recommended as an ‘other regimen option’ as there is no randomised trial supporting this combination. A summary of the regimens from the US guidelines is presented in Table 5 below. The PBAC considered that use of raltegravir did not need to be limited to use in combination with tenofovir disoproxil fumarate with emtricitabine (Truvada®).

Table 5: Summary of US Guidelines on evidence for integrase inhibitors and NRTI backbone therapies

	ABC/3TC (incl. Kivexa)	TDF/FTC (incl. Truvada)
RAL	'Other options' (one grade below 'alternative options') 1 tablet bd + another tablet daily	Recommended, 1 tablet bd + another tablet daily
EVG	-	Recommended, 1 tablet daily
DTG	Recommended, 1 tablet daily	Recommended, 2 tablets daily

Abbreviations: ABC/3TC: abacavir/lamivudine; TDF/FTC: tenofovir/emtricitabine; RAL: raltegravir; EVG: elvitegravir; DTG: dolutegravir. Source: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Department of Health and Human Services. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>, Table 6 pp F3-F4

6.14 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.15 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.16 Given the claim of non-inferior efficacy and safety, a cost-minimisation approach was appropriate.

6.17 The equi-effective doses were estimated as raltegravir 1200 mg QD and raltegravir 400 mg BID, each as continuous therapy. These estimates were derived from the results of the randomised head-to-head Trial PN292. The PBAC considered these estimates are reasonable for treatment naïve and treatment-experienced patients.

6.18 The proposed cost for a maximum quantity of 120 tablets for each formulation is \$1,311.56. Each formulation comprises 60 tablets per pack and is taken as 2 tablets per day (raltegravir 1200 mg taken as 2 x 600 mg once-daily; and raltegravir 400 mg taken as 1 x 400 mg twice daily), thus producing the same daily treatment cost.

Drug cost/patient/year: \$7,978.66.

6.19 Treatment is ongoing for each formulation. The annual cost per patient was derived as:

$$\$7,978.66 = (\$1,311.56/120 \text{ tablets}) \times 2 \times 365 \text{ days (based on the cost of the 400 mg twice daily regimen)}$$

Estimated PBS usage & financial implications

6.20 This submission was not considered by DUSC. A market share was used by the submission based upon the assumption that raltegravir 1200 mg QD would substitute for all of the raltegravir 400 mg BID (Table 6).

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed ^a	4,716	6,115	4,957	4,018	3,257	2,640
Estimated cost of raltegravir 1200 mg						
Cost to PBS/RPBS	\$6,184,661	\$8,020,452	\$6,501,141	\$5,270,373	\$4,271,489	\$3,462,518
Co-payments	\$98,393	\$127,590	\$103,430	\$83,844	\$67,956	\$55,078
Cost to PBS/RPBS less co-payments	\$6,086,268	\$7,892,861	\$6,397,710	\$5,186,529	\$4,203,533	\$3,407,440
Estimated cost offset for raltegravir 400 mg						
Cost to PBS/RPBS less co-payments	\$6,086,268	\$7,892,861	\$6,397,710	\$5,186,529	\$4,203,533	\$3,407,440
Net financial implications						
Net cost to PBS/RPBS	0	0	0	0	0	0

^a The submission assumes direct substitution of raltegravir 1200 mg QD would for raltegravir 400 mg BID
Source: Table 4-3, p.80 of the submission

6.21 Some marginal growth in the cost to PBS/RPBS may be expected from listing of raltegravir 1200 mg QD due to simpler administration. Thus the submission's estimates of usage may be underestimated as no allowance was made to account for an increased adherence (to translate to an increased supply of raltegravir 1200 mg QD) as the submission argued that simplified dosing will be associated with improved adherence. The consequences of this (if any) are likely to be modest.

Quality Use of Medicines

6.22 In the proposed product information (PI), it is noted that the two formulations of raltegravir (600 mg and 400 mg) are not interchangeable as the formulations have different pharmacokinetic profiles. Similarly, the chewable tablets used in paediatric patients may not be substituted for by either the 400 mg tablet or 600 mg tablet regimens. Additionally, the TGA Clinical Evaluation Report which became available during the evaluation concluded "that patients with greater severity at baseline should be commenced on 400 mg twice daily before changing to 1200 mg once daily after responding".

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

7.1 The PBAC was of a mind to recommend raltegravir 600 mg tablets be listed on the PBS for the treatment of HIV infection on a cost-minimisation basis compared with raltegravir 400 mg tablets, noting that raltegravir 600 mg tablets should be available only under special arrangements under Section 100 – Highly Specialised Drugs Program (Community Access). However, the PBAC deferred making a final recommendation pending the TGA Delegate's Proposed Regulatory Action.

- 7.2 The PBAC considered that the restriction for raltegravir 600 mg tablets should be aligned with that for raltegravir 400 mg tablets, and for other single agent integrase inhibitors listed on the PBS.
- 7.3 The PBAC accepted raltegravir 400 mg twice daily as the appropriate comparator.
- 7.4 The PBAC considered the results of the clinical trials supported the clinical claim of non-inferior comparative efficacy and non-inferior comparative safety compared with the twice daily 400 mg form of raltegravir.
- 7.5 The PBAC accepted cost-minimisation on the basis of equi-effective doses of raltegravir 1,200 mg once daily (two 600 mg tablets) and raltegravir 400 mg twice daily.
- 7.6 The PBAC noted there was a downward trend on the use of single agent integrase inhibitors in combination with backbone NRTI therapy, as the use of triple therapy fixed dose combination therapies continue to increase.
- 7.7 The PBAC advised that the 600 mg form of raltegravir should not be treated as substitutable at a pharmacy level (“a” flagged) with any other form of raltegravir given the different pharmacokinetics of the 600 mg form.
- 7.8 The PBAC advised that raltegravir 600 mg tablets are not suitable for prescribing by nurse practitioners at this time.
- 7.9 The PBAC recommended that the Early Supply Rule should apply, similar to existing listings for anti-retroviral therapies for HIV infection.

Outcome:

Deferred

Addendum to the July 2017 PBAC Minutes:

**5.11 RALTEGRAVIR,
Tablet 600 mg (as potassium),
Isentress HD[®],
Merck Sharp & Dohme (Australia) Pty Limited**

Out-of-session, between its July 2017 and November 2017 meetings, the PBAC decided to recommend to the Minister (under section 101(3) of the *National Health Act 1953* (“the Act”) that a new form be determined for raltegravir.

A note of the PBAC’s decision follows:

Background

Subsequent to the July 2017 PBAC meeting, the sponsor supplied additional regulatory documents from the Therapeutic Goods Administration (TGA), including the Delegate’s Proposed Regulatory Action (in lieu of the Delegate’s Request for ACM Advice/Delegate’s Overview) and TGA Letter of Registration for the 600 mg form of raltegravir.

The PBAC recalled that it was of a mind to recommend listing at the July 2017 meeting and recommended, out of session, the Section 100 (Highly Specialised Drugs Program – Community Access), Authority Required (STREAMLINED) listing of raltegravir 600 mg tablets (as 1,200 mg once daily) for the treatment of Human Immunodeficiency Virus (HIV) infection, in combination with other anti-retroviral agents, on a cost minimisation basis with raltegravir 400 mg tablets twice daily.

The PBAC noted the receipt of the additional TGA regulatory documents, and further noted that raltegravir 600 mg was registered in the Australian Register of Therapeutic Goods (ARTG) on 23 August 2017. The Committee recalled it had no other outstanding issues to consider regarding the submission when considered at its July 2017 meeting, and therefore was satisfied to recommend listing of raltegravir 600 mg tablets on a cost-minimisation basis of equi-effective doses of raltegravir 1,200 mg once daily (two 600 mg tablets) and raltegravir 400 mg twice daily.

The PBAC reaffirmed that per its advice at the July 2017 meeting, it was appropriate to align the restriction for raltegravir 600 mg tablets with the existing listings for raltegravir 400 mg tablet, that the Safety Net Early Supply Rule should apply, the 600 mg form of raltegravir should not be treated as substitutable at the pharmacy level (‘a’ flagged) with the 400 mg form of raltegravir and that nurse practitioner prescribing was not appropriate, similar to existing listings for HIV therapies.

Outcome:

Recommended

8 Recommended listing

Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
RALTEGRAVIR Tablet 600 mg (as potassium), 60	120	5	Isentress® HD	Merck, Sharp and Dohme (Australia) Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program (Community Access)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	HIV infection
PBS Indication:	HIV infection
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must be antiretroviral treatment naïve, AND The treatment must be in combination with other antiretroviral agents.

Category / Program	Section 100 – Highly Specialised Drugs Program (Community Access)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	HIV infection
PBS Indication:	HIV infection
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised therapy for HIV infection AND The treatment must be in combination with other antiretroviral agents.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.