Report on New Patented Drugs – Isentress

Under its transparency initiative, the PMPRB publishes the results of the reviews of new patented drugs by Board Staff, for purposes of applying the Board's *Excessive Price Guidelines* (Guidelines) for all new active substances introduced after January 1, 2002.

Brand Name:	Isentress
Generic Name:	(*raltegravir potassium*)
DIN:	02301881 (400 mg tablet)
Patentee:	Merck Frosst Canada Ltd.

Indication – as per product monograph:

In combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

Date of Issuance of First Patent Pertaining to the Medicine:	February 13, 2007
Notice of Compliance with Conditions (NOC/c):	November 27, 2007
Date of First Sale:	November 28, 2007
ATC Class:	J05AX Antiinfectives for System Use; Antivirals for system use; Direct Acting Antivirals; Other antivirals

APPLICATION OF THE GUIDELINES

Summary

The introductory price of Isentress was found to be within the Guidelines because the cost of therapy did not exceed the cost of therapy of existing drugs in the therapeutic class comparison and did not exceed the range of prices of the same medicine in the comparator countries listed in the *Patented Medicines Regulations (*Regulations) in which Isentress was sold.

Scientific Review

Isentress is a new active substance and the PMPRB's Human Drug Advisory Panel (HDAP) recommended that Isentress be classified as a category 3 new medicine (provides moderate, little or no therapeutic advantage over comparable existing medicines).

The Therapeutic Class Comparison (TCC) test of the Guidelines provides that the price of a category 3 new drug product cannot exceed the prices of other comparable drugs that treat the same disease or condition. Comparators are generally selected from among existing drug products in the same 4th level of the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system that are clinically equivalent in addressing the approved indication. See the PMPRB's *Compendium of Guidelines, Policies and Procedures* for a more complete description of the Guidelines and the policies on TCCs.

The HDAP recommended Fuzeon (*enfuvirtide*), Aptivus (*tipranavir*) plus Norvir Sec (*ritonavir*), Aptivus (*tipranavir*) plus Norvir Liquid (*ritonavir*), Prezista (*darunavir ethonolate*) plus Norvir Sec (*ritonavir*), and Prezista (*darunavir ethonolate*) plus Norvir Liquid (*ritonavir*) as appropriate comparators. Fuzeon shares the same 4th level ATC class as Isentress and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. Aptivus and Prezista, two protease inhibitors, which do not share the same 4th level ATC class as Isentress, are both indicated for treatment-experienced patients infected with HIV. They are included in treatment guidelines and review documents as treatment options for treatment-experienced adult patients.

The Guidelines provide that the dosage recommended for comparison purposes will normally not be higher than the maximum of the usual recommended dosage. The recommended comparable dosage regimens for Isentress and the comparable drug products were based on their respective product monographs and supported by clinical literature.

Price Review

Under the Guidelines, the introductory price of a category 3 new drug product will be presumed to be excessive if it exceeds the prices of all of the comparable drug products based on the TCC test or if it exceeds the range of prices of the same medicine sold in the seven countries listed in the Regulations.

The introductory price of Isentress 400 mg tablet was within the Guidelines as the cost per treatment did not exceed the cost per treatment of the comparator medicines as shown in the table below.

Introductory Period (November to December 2007)

Trade name (Generic name)	Strength	Dosage Regimen (Daily)	Unit Price	Treatment Cost (Daily)
Isentress (*raltegravir*)	400 mg	2 tablets	$13.5000[(1)]	$27.0000
Fuzeon (*enfuvirtide*)	108 mg	2 vials	$39.7600 [(1)]	$79.5200
Aptivus (*tipranavir*) + Norvir Sec (*ritonavir*)	250 mg + 100 mg	4 capsules + 4 capsules	$8.2500[(1)] + $1.3625[(1)]	$38.4500
Aptivus (*tipranavir*) + Norvir Liquid (*ritonavir*)	250 mg + 80 mg/mL	4 capsules + 5 mL	$8.2500[(1)] + $1.0898[(1)]	$38.4490
Prezista (*darunavir ethonolate*) + Norvir Sec (*ritonavir*)	300 mg + 100 mg	4 tablets + 2 capsules	$6.9600[(1)] + $1.3625[(1)]	$30.5650
Prezista (*darunavir ethonolate*) + Norvir Liquid (*ritonavir*)	300 mg + 80 mg/mL	4 tablets + 2.5 mL	$6.9600[(1)] + $1.0898[(1)]	$30.5645

Sources:
(1) Régie de l'assurance maladie du Québec, Juin 2007

In 2007, Isentress was being sold in three countries listed in the Regulations, namely Sweden, Switzerland and the United States. In compliance with the Guidelines, the price of Isentress in Canada did not exceed the range of prices in those countries, it was the lowest.

The publication of Summary Reports is part of the PMPRB's commitment to make its price review process more transparent.

Where comparators and dosage regimens are referred to in the Summary Reports, they have been selected by the HDAP for the purpose of carrying out the PMPRB's regulatory mandate, which is to review the prices of patented medicines sold in Canada to ensure that such prices are not excessive.

The PMPRB reserves the right to exclude from the therapeutic class comparison list any drug if it has reason to believe it is being sold at an excessive price.

In its Summary Reports, the PMPRB will also refer to the publicly available prices of comparators provided such prices are not more than 10% above a non-excessive price in which case no price will be made available. As a result, the publication of these prices is for information purposes only and should not be relied upon as being considered within the Guidelines.

The information contained in the PMPRB's Summary Reports should not be relied upon for any purpose other than stated and is not to be interpreted as an endorsement, recommendation or approval of any drug nor is it intended to be relied upon as a substitute for seeking appropriate advice from a qualified health care practitioner.

References – Isentress

1. Anonymous. 48-week data on raltegravir in naïve patients. AIDS Patient Care Stds 2007; 21(9):703.

2. Anonymous. Anti-HIV agents. Raltegravir (Isentress) – results after one year. Treatment Update 2007;19(6):8-9. Available from: http://www.catie.ca/tu.nsf/df739470490ae50d8525717f0061769d/4b79c66afb9fb9108525738c00727756!OpenDocument.

3. Bartlett JG. Modifying HIV antiretroviral therapy regimens. Up To Date Online, November 17, 2006. Accessed online at: www.utdol.com.

4. Cahn P, Sued O. Raltegravir: a new antiretroviral class for salvage therapy. Lancet 2007;369:1235-6.

5. Correll T, Klibanov OM. Integrase Inhibitors: A new treatment option for patients with human immunodeficiency virus infection. Pharmacotherapy 2008;28(1):90-101.

6. Croxtall JD, Lyseng-Williamson KA, Perry CM. Raltegravir. Drugs 2008;68(1):131-8.

7. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents . January 29, 2008. Available from: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

8. Gazzard B, Bernard AJ, Boffito M, Churchill D, Edwards S, Fisher N, et al; Writing Committee, British HIV Association. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006). HIV Med. 2006 Nov; 7(8): 487-503. Available: http://www.bhiva.org/files/file1001303.pdf

9. Grinsztejn B, Nguyen B-Y, Katlama C, *et al.* Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomized controlled trial. Lancet 2007;369:1261-9.

10. Grinsztejn B, Nguyen B, Katlama C, *et al.* 48 week efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus [abstract]. Available from: http://www.abstractsonline.com/viewer/viewAbstract.asp?CKey={E1164EA8-563F-4689-97C7-43C74D768231}&MKey={D52CF5B5-E7A0-40B1-B430-CE0AC26BBA9E}&AKey={32093528-52DC-4EBE-9D80-29DAD84C92CE}&SKey={5F5FCA3D-1CD2-4AA3-A93F-73B4E8E75F71}.htm

11. Hammer SM, Saag MS, Schechter M, et al. Treatment for adults HIV infection: 2006 recommendations of the Internation AIDS Society-USA panel. JAMA 2006; 296: 827-43.

12. Jones J, Taylor B, Wilkin TJ, Hammer SM. Advances in antiretroviral therapy. Topics HIV Medicine 2007;15(2):48-82.

13. Markowitz M, Nguyen BY, Gottuzzo E, *et al*. Rapid and durable antiretroviral effect of the HIV-1 integrase inhibitor raltegravir as part of combination therapy in treatment-naïve patients with HIV-1 infection. J Acquir Immune Defic Syndr 2007;46(2):125-133.

14. Merschman SA, Vallano PT, Wenning LA, *et al.* Determination of the HIV integrase inhibitor, MK-0518 (raltegravir), in human plasma using 96 well liquid-liquid extraction and HPLC-MS/MS. J Chormatography B 2007;15-24.

15. Murray JM, Emery S, Kelleher AD, *et al.* Antiretroviral therapy with the integrase inhibitor raltegravir alters decay kinetics of HIV, significantly reducing the second phase. AIDS 2007;21:2315-21.

16. Public Health Agency of Canada. HIV/AIDS Epi Updates, August 2006. Surveillence and Risk Assessment Division, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada. 2007.Available from : http://www.phac-aspc.gc.ca/publicat/epiu-aepi/epi-06/index.html

17. Raltegravir, Produced by London New Drugs Group, on behalf of HIV Drugs and Treatments sub-group of the London HIV Consortium, April 2008.

18. Repchinsky C. Compendium of Pharmaceuticals and Specialties. Canadian Pharmacists Association. Ottawa, ON. 2007.

19. Savarino A. In-Silico docking of HIV-1 integrase inhibitors reveals a novel drug type acting on an enzyme/DNA reaction intermediate. Retrovirology;2007:4:21.

20. Sax PE. Therapeutic options for treatment-experienced patients: a focus on resistance testing andoptimizing background therapy. AIDS Read. 2006 May; 1(5): 265-75, 277-8.

21. WHO Collaborating Centre for Drug Statistics Methadology. ATC Codes 2008 [database online]. Available from: http://www.whocc.no/atcddd/