DARUNAVIR (DRV)

GENERAL INFORMATION

- **Therapeutic class:** Protease inhibitor (PI). DRV should always be boosted, either with ritonavir (RTV/r) or cobicistat (COBI).
- **2016 WHO Guidelines:** Ritonavir-boosted, heat-stable DRV is an alternative option for second-line treatment, and remains an option for third-line treatment.
- Originator company and product brand name: Janssen; Prezista. Janssen (formerly known as Tibotec) is a subsidiary of Johnson & Johnson.
- First approved by the US Food and Drug Administration (FDA): June 2006.
- WHO Model List of Essential Medicines (EML): Not included in the 19th edition for adults or the 5th edition for children. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of FDCs and the development of appropriate new FDCs.
- World sales of originator product: 2015 (includes boosted co-forumation): US$1.81 billion; 2014: $1.83 billion; 2013: $1.67 billion; 2012: $1.4 billion; 2011: $1.2 billion; 2010: more than $1 billion reported.[1]

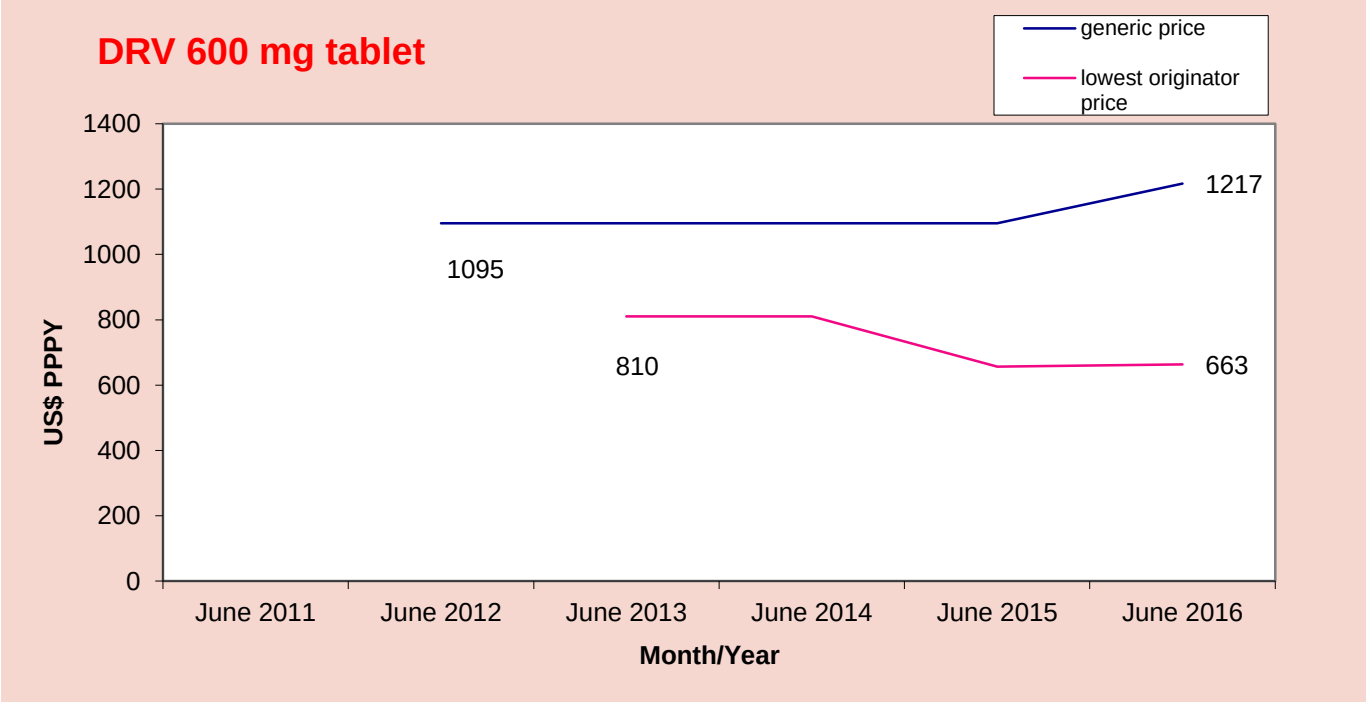
PRICE INFORMATION

Developing country prices in US$ per person per year (pppy), as quoted by companies.
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold.**

	Daily Dose	Janssen	Aspen	Hetero
DRV 75mg tablet	xx	**(0.114)**		
DRV 150mg tablet	xx	**(0.227)**		
DRV 400mg tablet	2*	438 (0.600)		973 (1.333)
DRV 600mg tablet	2**	663 (0.908)	658 (0.901)	1,217 (1.667)

* The dose of DRV must be boosted with RTV 100mg once a day.
** The dose of DRV must be boosted with RTV 100mg twice a day.

The price of generic DRV 600mg is almost twice as high as Janssen's access price ($1,217 pppy from Hetero vs. ¬¬$663 pppy from Janssen). Despite having multiple generic versions plus the originator darunavir formulations that are WHO-prequalified and/or US FDA-approved, the price of DRV has not decreased, due to lack of commercialisation of DRV by some generics which is likely related to small volume markets. DRV/r is likely to be used in only for third-line treatment until the price comes down. A search of the Global Fund Price and Quality Reporting database shows that from 2013-2015, Janssen supplied the majority of the DRV procured.



SPOTLIGHT ON ACCESS ISSUES

WHO guidelines recommend darunavir (DRV/r) as an alternative second-line treatment option. DRV/r is better tolerated than the other second-line options, ritonavir-boosted atazanavir (ATV/r) and ritonavir-boosted lopinavir (LPV/r)[2,3,4,5,6] but it is an alternative regimen because of its high price and the current lack of a heat-stable DRV/r fixed-dose combination (FDC). Generic producers are working on a heat-stable DRV/r (400mg/50mg) FDC.[7]

DRV/r cannot be used during rifampicin-based TB treatment due to a drug-drug interaction. However, modelling data suggest that increasing the dose of DRV/r (to 800/100mg twice-daily, or 1200/150mg twice-daily) might make it possible to co-administer it with rifampicin, pending results from a clinical trial.[8]

Paediatrics: The 2016 WHO guidelines include DRV/r as an alternative second-line option for children who are three to ten years of age (it is not recommended for use in children who are under three years of age). Paediatric formulations of 75mg and 150mg tablets and 100 mg/ml oral solution are available by the originator; there are two generic suppliers for the 75mg tablets and three generic suppliers for the 150mg tablets. Janssen has started a donation programme for qualifying countries (so far, Swaziland, Lesotho,

Zambia, and Kenya)[9] – although it does not provide ritonavir. The donation programme may make the low-volume paediatric market even less enticing for generics.

PATENT INFORMATION

(Note: Patent information may be updated in 2016 to fully reflect the evolving landscape of patents, other forms of intellectual property, licensing, and use of flexibilities for the particular drug.)

In most countries, the basic patent of DRV expired in 2013.[10,11] But secondary patents on DRV related to key intermediates and combinations with ritonavir (RTV/r) and tenofovir (TDF) will expire in 2025 in countries where they have been granted.[11]

Patent oppositions in India

The basic patent related to DRV[12] could not be applied for in India, because it did not grant product patents on pharmaceuticals in 1994. After the implementation of the TRIPS agreement in 2005, which obliged India to accept product patent applications, Janssen (Johnson & Johnson) applied for several secondary patents in India related to DRV.[13] Pre-grant oppositions were filed against all of these applications; several were rejected by the Indian patent office.[11,14,15,16] The patent application on the combination of DRV with TDF was withdrawn.[11,18]

A divisional patent application[19] concerning the combination of DRV with RTV has been abandoned by Janssen (J&J) after a pre-grant opposition by a generic manufacturer.[20] Other patent applications concerning RTV have been either rejected or abandoned after patent oppositions were filed by civil society organisations in India.[21]

Access challenges in other developing countries

In China, Janssen was granted patents related to racemic and pseudo-polymorphic forms of DRV,[11,22] and the same patent has been granted in South Africa.[11,23] The patent concerning the combination of DRV and RTV, and the combination of DRV, RTV and TDF has been withdrawn or lapsed in China, Brazil and South Africa, but it has been granted in other developing countries such as Mexico, Philippines and Turkey.[11]

In 2015, Brazil and other Mercosul countries engaged in joint negotiations for HIV drugs. One of their achievements was the regional price reduction for the 600mg dose of darunavir (to $1.26 per unit or $919.80 pppy).[24] However, the effects of the negotiation remain uncertain, given that price Brazil paid in 2016 is still the price that Janssen offered the country before the Mercosul deal ($2.98 per unit or $2175.40 pppy).[25] Civil society groups have been sending letters to the government claiming that the price must drop immediately, and that although there are 18 patent applications related to darunavir in Brazil, none of them block the use of generic versions.[26]

Voluntary licence

In September 2010, the US National Institutes of Health (NIH) licenced patents on DRV to the Medicines Patent Pool (MPP).[27] The move demonstrated political backing for the MPP, and it was also significant because all developing countries were covered in the geographical scope of the licence. However, the NIH patent will not clear the way for generic versions of DRV in all developing countries, due to additional patents held by Janssen. In December 2011, the company announced its decision not to enter into negotiations to licence its HIV drugs portfolio, including DRV, to the MPP.[28] In doing so, it has effectively made the NIH

licence useless for manufacture and export to countries where Janssen holds a patent.

Janssen is, however, engaging in bilateral voluntary licensing with two generic companies – Aspen in South Africa and Emcure in India,[29] – but only for packaging and distribution. The terms of the licences are not public.

In June 2011, Janssen announced that it had entered into a licence agreement with Gilead for the development and commercialisation of a new once-daily single tablet fixed-dose combination containing DRV and Gilead's cobicistat, and the agreement was amended in 2014.[30] Subject to regulatory approval, Janssen will be responsible for the formulation, manufacture, registration, distribution and commercialisation of the regimen of DRV/cobicistat combination worldwide.

REFERENCES

[1] Johnson and Johnson. Annual Report 2015 [Online] March 2016. [cited 2016 July 2]. Available from: http://files.shareholder.com/downloads/JNJ/1709744668x0x881109/474857DD-8E67-43B1-BB38-0A9712D93545/2015_annual_report_.pdf

[2] Bánhegyi D, Katlama C, da Cunha CA, et al. Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN. Curr HIV Res. [Online] 2012 Mar [cited 2016 June 16] Available from: 10(2):171-81.

[3] Lenox JL, Landovitz RJ, Ribaudo HJ, et al; for the AIDS Clinical Trials Group A5257. A Phase III Comparative Study of the Efficacy and Tolerability of Three Non-Nucleoside Reverse Transcriptase Inhibitor-Sparing Antiretroviral Regimens for Treatment-Naïve HIV-1-Infected Volunteers: A Randomized, Controlled Trial team. Ann Intern Med. [Online] 2014 October 7 [cited 2016 June 16]; 161(7): 461-471. Available from doi: 10.7326/M14-1084

[4] Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. AIDS. [Online] 2009 Aug 24[cited 2016 June 16] ;23(13):1679-88. Available from doi: 10.1097/QAD.0b013e32832d7350.

[5] Orkin C, DeJesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naïve patients in the ARTEMIS trial. HIV Med. [Online] 2013 Jan [cited 2016 June 16] ;14(1):49-59. Available from doi: 10.1111/j.1468-1293.2012.01060.x.

[6] Vitoria M, Hill AM, Ford NP, Doherty M, Khoo SH, Pozniak AL Choice of antiretroviral drugs for continued treatment scale-up in a public health approach: what more do we need to know? J Int AIDS Soc. [Online] 2016 Feb 2 [cited 2016 June 16] ;19(1):20504. Available from doi: 10.7448/IAS.19.1.20504

[7] UNAIDS, Clinton Health Access Initiative and UNTIAID. Press Release. (Online) November 30, 2015 [cited 2016 June 16] Available from: http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2015/november/20151130_PR_CHAI_UNITAID

[8] Dickinson L, Winston A, Boffito M, Khoo S, Back D, Siccardi M.Simulation of the impact of rifampicin on once-daily darunavir/ritonavir pharmacokinetics and dose adjustment strategies: a population pharmacokinetic approach. J Antimicrob Chemother. [Online] 2016 Apr [cited 2016 June 16];71(4):1041-5. Available from doi: 10.1093/jac/dkv439.

[9] Gabelnick T. Email communication with MSF. Elizabeth Glaser Pediatric AIDS Foundation June 2016.

[10] World Intellectual Property Organization, PATENTSCOPE. Hydroxythylamino sulfonamides useful as retroviral protease inhibitors. WO9404492 (A1)1994 Mar 3 [cited 2016 June 29]. Available from: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1994004492

[11] Medicines Patent Pool. ARV Patent Status Database. [Online]. Medicines Patent Pool [cited 2016 June 29]. Available from: http://www.medicinespatentpool.org/patent-data/patent-status-of-arvs/.

[12] World Intellectual Property Organization, PATENTSCOPE. [Online] Hydroxythylamino sulfonamides useful as retroviral protease inhibitors. WO9404492 (A1)1994 Mar 3 [cited 2016 June 29]. Available from: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1994004492

[13] India Patent Office Database. [Online] [cited 2016 July 11] Available from: http://ipindiaservices.gov.in/publicsearch/

[14] Patent Opposition Database. Darunavir (DRV) [Online] [cited 2016 June 29]. Available **from:** http://www.patentoppositions.org/en/drugs/4f1081df04a7f937af000004 .

[15] Rejection Decision of application for Patent no. 3598/ DELNP/ 2004 [Online] 2009 July 6 [cited 2016 June 30] Available from: http://www.patentoppositions.org/en/drugs/4f1081df04a7f937af000004/patent_office_decisions/51e917d024acb8000200001d .

[16] Rejection Decision of application for Patent no. 1647/DELNP/2000 [Online] 2009 March 29 [cited 2016 June 30] Available from: http://www.patentoppositions.org/en/drugs/521338be74cb5a000200002e/patent_office_decisions/5213270f74cb5a0002000025

[17] Rejection Decision of application for Patent no. 5301/DELNP/2006 [Online] 2010 November 30 [cited 2016 June 30] Available from: http://www.patentoppositions.org/en/drugs/4f1081df04a7f937af000004/patent_office_decisions/51e8ed4d24acb80002000008

[18] Indian Patent Office. Application No.7958/DELNP/2006 Abandoned U/S 21(1). [cited 2016 June 30] Ref. India Patent Office Database [Online] Available from: http://ipindiaservices.gov.in/publicsearch/.

[19] Indian Patent Office. Combination of Cytochome p450 dependent Protease Inhibitors, 2221/DELNP/2008. Ref. India Patent Office Database [cited 2016 June 29]Available from: http://ipindiaservices.gov.in/publicsearch/

[20] Opposition filed by Cipla on 2221/DELNP/2008 [Online] 2010 January 06 [cited 2016 June 29] Available from: http://www.patentoppositions.org/en/drugs/4f1081df04a7f937af000004/patent_oppositions/521320be74cb5a0002000021

[21] Patent Opposition Database. Ritonavir. [Online] [cited 2016 June 29] Available from: http://www.patentoppositions.org/en/drugs/4f1081fb04a7f937af000016

[22] World Intellectual Property Office, Patentscope, Pseudopolymorphic Forms Of A Hiv Protease Inhibitor, WO2003106461, [Online] 2003 December 24 [cited 2016 June 29] Available from: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2003106461 Equivalent Chinese patent publication no. CN100475819C

[23] Equivalent South Africa patent no. ZA200410154.

[24] Countries save up to 83% in the first joint purchase of medicines. [Online] November 16, 2015. [cited 2016 June 29] Available from: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20764-paises-economizam-ate-83-em-primeira-compra-conjunta-de-medicamentos

[25] Portal da Transparencia. (Portuguese) [Online] [cited 2016 June 29] https://transparencia.gov.br/despesasdiarias/empenho?documento=250005000012016NE801137

[26] Complemento À Carta Da Sociedade Civil Sobre Os Altos Preços Do Medicamento Antirretroviral Darunavir (Portugese) [Online] [cited 2016 June 30] Available from: http://deolhonaspatentes.org/wp-content/uploads/2015/10/Carta-Darunavir_complemento_final.pdf

[27] Medicines Patent Pool. US National Institutes of Health (NIH) First to Share Patents with Medicines Patent Pool As it Opens for Business. Press release. [Online] Geneva, 2010, September 30 [cited 2016 June 30] Available from: http://www.medicinespatentpool.org/wp-content/uploads/Medicines+Patent+Pool+NIH+license+PR+EMB+for+30+Sept+2010+FINAL-11.pdf

[28] Medicines Patent Pool. Statement on J&J's Decision on Negotiations with the Pool. Press release [Online] 2012 January 31 [cited 2016 June 20]. Available from: http://www.medicinespatentpool.org/statement-on-jjs-decision-on-negotiations/

[29] Johnson & Johnson. Tibotec Signs Multiple Agreements with Generic Manufacturers to Provide Access to New HIV Treatment. Press Release. [Online] 2011 January 27 [cited 2016 June 29]. Available from: http://www.investor.jnj.com/releasedetail.cfm?releaseid=545920

[30] Gilead. Press Release [Online] December 29, 2014 [cited 2016 June 29] Available from: http://www.gilead.com/news/press-releases/2014/12/gilead-announces-amended-agreements-with-janssen-to-develop-and-commercialize-tenofovir-alafenamidebased-single-tablet-regimens-for-hiv-treatment