DOLUTEGRAVIR (DTG)

GENERAL INFORMATION

- **Therapeutic class:** Integrase inhibitor.
- **2016 WHO Guidelines:** Dolutegravir (DTG) was added as alternative first-line antiretroviral (ARV) option for adults, and for use in salvage treatment. For adolescents over 12 years old, DTG was added as an alternative first-line ARV. Before it can become a WHO-preferred first-line regimen, more data are needed in pregnancy and breast-feeding women, and during rifampicin-based TB treatment.
- Originator companies and product brand names: Viiv Healthcare (a Pfizer/GSK partnership founded in 2009 to develop and commercialise HIV medicines) and Shionogi; Tivicay (the DTG fixed-dose combination with abacavir [ABC] and lamivudine [3TC] is Trimeq).
- First approved by US Food and Drug Administration (FDA): For adults and adolescents in August, 2013. In 2016, this indication was expanded to include dolutegravir for children weighing at least 30kg.[1]
- WHO Model List of Essential Medicines (EML): Not yet included.
- World sales of originator product: In 2014, Shionogi reported global sales of US$372.2 million for dolutegravir singles and $75.2 million for DTG-containing FDC.[2,3]

PRICE INFORMATION

Prices not available/not quoted; generic versions are not yet available.

Dolutegravir-based treatment could lower the price of ART, since it is effective with only a 50mg dose. Many generic producers have DTG ready, and are working on FDCs, with the first USDFA approval of generic DTG expected in mid-2016. The launch price of Aurobindo's DTG was announced to be approximately on par with EFV 600mg, at $44 per person per year (pppy).[4] In meantime, ViiV is providing DTG at access prices that vary based on volumes and shipping in all least-developed countries (LDCs), low-income countries, and all sub-Saharan African countries.

SPOTLIGHT ON ACCESS ISSUES

Once-daily DTG has a higher resistance barrier and better tolerability than EFV.[5] Research is needed on DTG dosing[6] and efficacy during pregnancy (and breast-feeding), since women are recommended to increase their intake of calcium and iron, both of which reduce DTG levels.[7] The current recommendation is to

double the dose of DTG during rifampicin-based TB treatment,[8] but there is still limited clinical experience to validate this strategy in the context of real-life scale-up.

Paediatrics: The 2016 WHO guidelines include DTG as part of salvage treatment for children. DTG is recommended for children six years and older who weigh ≥30kg.

PATENTS

(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.)

Japanese company Shionogi and its licencee ViiV Healthcare have filed multiple patents on DTG, covering its main compound, intermediaries and synthetic processes. The base compound has been granted or filed in many countries, including India, Brazil, China, the Eurasian Patent Organization (EAPO), Egypt, Indonesia, OAPI, and South Africa.[9] The base compound patent will not expire before 2026.[9] Other patents will start expiring in 2029.[9]

India

The patent application for dolutegravir's main compound was filed in India on 10 November 2007 as Indian Application No. 3865/KOLNP/2007. Since 2013, three pre-grant oppositions have been filed in India by civil society organisations and other individuals against the grant of this Indian application[10] (which is equivalent to the international publication number under WIPO PCT, WO2006116764). GSK subsequently narrowed and amended its claims. The matter is still pending.

The final outcome of the opposition will determine the patentability of dolutegravir's main compound - as well as other patent applications related to ARVs with a similar chemical structure (the application also includes ViiV's new pipeline ARV, cabotegravir, which is being developed both as tablets and in a long-acting injectable formulation). This is because the application concerning DTG's base compound was filed under the so-called 'Markush claim', where millions of possible compounds are included in a single patent application without disclosing which ones will be put into development and production.

A number of evergreening patent applications have been filed in India, including a divisional application 485/KOLNP/2013 concerning the compound of DTG; an application that claims the DTG product, filed as 2071/KOLNP/2008; an application on the crystalline form of DTG and the process for the preparation of DTG, which was filed in 2011 as 1942/KOLNP/2011; an application on the intermediates of DTG, filed as 1971/KOLNP/201; and an application on crystalline intermediate compounds of DTG, filed as 886/CHENP/2013. All of these applications are pending for examinations now in India.

To date, the drug is not available from ViiV in India, as the company has neither applied for registration in the country, nor made DTG available under a 'compassionate use' programme.

MPP licence

On 1 April, 2014 the Medicines Patent Pool (MPP) and ViiV healthcare announced a new collaboration, comprised of two voluntary licences (VLs) on patents related to a paediatric formulation of DTG,[11] and the adult formulation of DTG, which includes the flexibility to develop FDCs with abacavir (ABC) and other compounds if there are no patents in force.[9] The licence on the adult formulation was amended in April 2016 to include more low- and middle-income countries.*[12]

The licence adopted a hybrid royalty structure. The paediatric licence agreement is royalty-free in 121 countries where the product is sold. The adult licence, after an amendment, includes 82 low-income countries (royalty-free) and 10 middle-income countries (Armenia, Egypt, India, Indonesia, Moldova, Morocco Philippines, Turkmenistan, Vietnam, and Ukraine), with a sliding royalty scheme, based on per-capita income;[11] it excludes certain middle-income countries, such as Brazil, China, Thailand, Malaysia, and Russia.

The licence adapted a market segmentation approach. Both public and private markets are included in the 82 royalty-free countries for the adult formulation, but in the 10 middle-income countries where there is a tiered royalty rate, ViiV only allows sales to the public sector market (defined to include non-profit organisations and public funding mechanisms that ViiV has authorised). In this licence, ViiV's public vs. private market division creates practical barriers for access in countries such as India, where the national treatment programme is still in the process of revising guidelines to include DTG, and generic versions are not available in the private market for people who may need immediate access.[13]

For countries outside of the licensed territories where there are currently no blocking patents on DTG (including Argentina and Venezuela), access to generic DTG would depend on a number of other factors. These include the future status of any relevant patent filing; the willingness of generics to supply outside the territories of the VL; regulatory barriers such as data exclusivity or the requirement of originator registration; and the actual process and speed of generic registration in these countries.

Although developing an ABC/DTG FDC has been covered by the adult licence, the licence would have an impact on development of an FDC that contains active ingredients other than ABC. For instance, ViiV holds a patent on the combination of ABC/3TC/DTG,[14] which will not expire until 2031. The patent has been filed widely in developing countries and has already been granted in some countries, such as South Africa and Ukraine.[9,15] Developing and importing the combination of ABC/3TC/DTG will be hindered in countries where this patent has been granted. In addition, this patent application has been filed in 20** out of the 82 royalty-free countries, and all of the 10 tiered-royalty countries including India; the patent has been granted in Ukraine. If the combination patent is granted in these countries, it could block the development of, and access to, a more affordable generic version of this FDC.

For countries that are not covered by the licence and where the DTG patent is not yet granted, the ABC/3TC/DTG combination patent application has been filed in seven countries (Albania, Bosnia, Colombia, Dominican Republic, Montenegro, Peru, Thailand). If the patent is granted - even where an active patent on DTG is not issued - these countries would be unable to secure a generic supply of a FDC containing ABC/3TC/DTG. In addition, for the Dominican Republic, Peru and Thailand, where there is also an ABC patent in place, generic access to ABC/3TC/DTG will not be possible if this combination patent is granted.[9]

*The 14 new countries included in the amendment are: Bolivia, El Salvador, Georgia, Guatemala, Guyana, Honduras, Kosovo, Micronesia, Nicaragua, Pakistan, Papua New Guinea, Syria, Uzbekistan, and West Bank of Gaza; the additional tiered royalty countries are: Ukraine, Morocco, Moldova, and Armenia.

**The 20 countries are: Botswana, Gambia, Gabon, Kenya, Lesotho, Liberia, Malawi, Mozambique, Namibia, Rwanda, Sao Tome and Principe, Sierra Leone, Somalia, Sudan, Swaziland, Tanzania, Tajikistan, Uganda, Zambia, and Zimbabwe.

REFERENCES

[1] Tivicay. Highlights of prescribing information. [Online] June 2016 [cited 2016 June 28]. Available from: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tivicay/pdf/TIVICAY-PI-PIL.PDF

[2] US Internal Revenue Service. Yearly Average Currency Rates. [Online]. [cited 16 June 2016] Available from: https://www.irs.gov/individuals/international-taxpayers/yearly-average-currency-exchange-rates

[3] US Internal Revenue Service. Yearly Average Currency Rates. [Online]. [cited 16 June 2016] Available from: https://www.irs.gov/individuals/international-taxpayers/yearly-average-currency-exchange-rates

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

[5] Walmsley S, Berenguer J, Khuong-Josses M, et al. Dolutegravir regimen statistically superior to efavirenz/tenofovir/emtricitabine: 96-week results from the SINGLE study (ING114467). (Online) CROI 2014 March 3-6 [cited 2016 9 June]. Boston MA. Abstract 543. Available from: http://www.croiconference.org/sites/all/abstracts/543.pdf

[6] Song I, Borland J, Arya N, Wynne B, Piscitelli S. Pharmacokinetics of dolutegravir when administered with mineral supplements in healthy adult subjects. J Clin Pharmacol. [Online] 2015 May; [cited 2016 May 30] 55(5):490-6. Available from doi: 10.1002/jcph.439.

[7] Mulligan N, Best MB, Capparelli EV et al; on behalf of the IMPAACT 1026s Protocol Team. Dolutegravir pharmacokinetics in HIV-infected pregnant and postpartum women. [Online] Conference on Retroviruses and Opportunistic Infections (CROI) 2016. February 22-25 [cited 2016 May 24] 2016. Boston, Massachusetts. Poster abstract 438.Available from: http://www.croiconference.org/sessions/dolutegravir-pharmacokinetics-hiv-infected-pregnant-and-postpartum-women-0

[8] Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. [Online] 2013 Jan 1; [cited 2016 May 30] 62(1):21-7. Available from doi: 10.1097/QAI.0b013e318276cda9.

[9] Medicines Patent Pool. ARV Patent status database. [Online] [cited 2016 June 26] Available from: http://www.medicinespatentpool.org/table/

[10] Patent Opposition Database. Dolutegravir. Opposition filed by Delhi Network of Positive People (DNP+) on 2013 February 22; Bengal Network of People Living with HIV/AIDS (BNP+) on 2015 December 2, and Sanjeev Sharma on 2016February 10. [Online]. [cited 2016 June 27] Available from: http://www.patentoppositions.org/en/drugs/52259e78a6f6740002000018

[11] Medicines Patent Pool. Medicines Patent Pool, ViiV Healthcare sign licence for the most recent HIV medicine to have received regulatory approval. Press release [Online]. April 1, 2014 [cited 2016 June 28]. Available from: http://www.medicinespatentpool.org/medicines-patent-pool-viiv-healthcare-sign-licence-for-the-most-recent-hiv-medicine-to-have-received-regulatory-approval/

[12] Medicines Patent Pool. License Agreement. [Online] April 22, 2016. [cited 2016 June 27]. Available from: http://www.medicinespatentpool.org/wp-content/uploads/Amended-and-Restated-ViiV-MPPF-Adult-Headlicence-dated-22-April-2016-Executed-copy.pdf

[13] MSF Access Campaign. Pharma company ViiV's attempts to secure patents for key HIV drugs dolutegravir and cabotegravir opposed in India. Press release. [Online] February 10, 2016.[cited June 27, 2016] Available from: http://www.msfaccess.org/about-us/media-room/press-releases/pharma-company-viivs-attempt-secure-patents-key-hiv-drugs-dolute.

[14] World Intellectual Property Organization. Patentscope. [Online] WO/2011/094150. January 24, 2011 [cited 2016 June 27]. Available from: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2011094150&recNum=45&maxRec=604&office=&prevFilter=&sortOption=&queryString=PA%3AGlaxoSmithKline&tab=PCT+Biblio

[15] World Intellectual Property Organization, Patentscope, WO/2011/094150, Antiviral Theraphy [Online] [cited 2016 July 11] Available from: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2011094150&recNum=45&docAn=US2011022219&queryString=PA:GlaxoSmithKline&maxRec=604