MSF Briefing Document
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Barriers to Access and Scale-Up of Hepatitis C Treatment:
Spotlight on Daclatasvir

The international medical humanitarian organisation Médecins Sans Frontières/Doctors Without Borders (MSF) began introducing hepatitis C virus (HCV) treatment to several patients in India in 2013. MSF is in the process of scaling up treatment for HCV in at least eight additional countries, using direct-acting antiviral (DAA) medicines that have recently come to market with the potential to revolutionise treatment for people living with HCV.

Given the significant potential to improve HCV treatment using the drug daclatasvir, developed by Bristol-Myers Squibb (BMS), MSF puts forth the following concerns, comments and recommendations to make daclatasvir available and affordable in developing countries.

Background

In order to optimise treatment and take full advantage of the field of new DAA treatments, MSF needs not just one new DAA like sofosbuvir, but also another kind of DAA, such as an NS5A inhibitor. The combination of sofosbuvir with an NS5A inhibitor will maximise the potential to move from complex treatment regimens to more effective and better-tolerated, all-oral regimens. These regimens will eliminate the need for injectable pegylated interferon, potentially treat all genotypes of the disease, and will simplify protocols for treatment offered in remote settings and in the public sector. Such treatment regimens open the door for many more people living with HCV to receive life-saving treatment in developing countries.

One critical NS5A inhibitor that MSF seeks to procure for use in its treatment programmes is daclatasvir, which was developed by Bristol-Myers Squibb (BMS), and has been registered in 2014 as *Daklinza*® in the European Union, Brazil and Japan, and is under regulatory review in the US.

Daclatasvir, combined with other potent DAAs such as sofosbuvir, offers an interesting and robust combination, which fills all requirements for use in resource-limited settings: high efficacy, has a pan-genotypic profile and once-daily dosing. The combination can be used with or without ribavirin, can be co-formulated, and is very well tolerated. It can also be used for people with advanced liver disease, and shows very good results in people co-infected with HIV.

Key Access Considerations

MSF has the following comments and concerns with respect to scaling up access to daclatasvir for widespread use in developing countries.

1. BMS has no expanded access program or compassionate use mechanisms for daclatasvir.

Since the registration of daclatasvir by the European Medicines Agency (EMA) in June 2014 and the Japanese Ministry of Health, Labour and Welfare (MHLW) in July 2014, treatment providers and civil society organisations have awaited an announcement from BMS on how this DAA could be made available through a compassionate use/named-patient basis, or through expanded access programs to countries where it is not yet registered. Compassionate use programmes are governed by legislation in individual countries, to make medicines available on a named-patient basis or to groups of patients. Early access through this route could save more lives.

Not being able to access effective, well-tolerated treatment can be disappointing to people with chronic, life-threatening HCV infection and for their health care providers. BMS should immediately announce a

compassionate use programme that covers developing countries – particularly those that are high-burden – as a way to create access to daclatasvir in countries where registration is not yet filed, and to provide alternatives for patients who will not be able to take pegylated interferon/sofosbuvir/ribavirin or sofosbuvir/ribavirin regimens. This includes patients who are unable to tolerate pegylated interferon due to its severe side effects (e.g. those with advanced liver disease) and are not prescribed ribavirin due to renal disease or a low haemoglobin baseline. These patients need another drug to accompany sofosbuvir, as monotherapy is not recommended.

2. BMS has not announced a registration strategy to support treatment scale-up in developing countries.

Marketing authorisation of promising new DAAs is critical in developing countries to increase access to effective treatment. Gilead – the developer of another key DAA, sofosbuvir – has been filing for registration and receiving approval for sofosbuvir in a number of high-burden countries, including Egypt, India and Pakistan. Generic producers have also filed for registration or received approval in these countries and are also being encouraged to file for World Health Organization pre-qualification.

Registration of another DAA from the class of NS5A inhibitors, like daclatasvir, is imperative to expedite more tolerable and effective HCV treatment in developing countries, particularly where sofosbuvir is also registered. However, other than registration at the EMA and MHLW in 2014, and a New Drug Application filed at the US Food and Drug Administration in early 2015, BMS has not yet made public a strategy to register daclatasvir, even though more than 80 per cent of the global HCV patient population lives in low- and middle-income countries. To support long-term supply of daclatasvir and enable scale-up of treatment in these countries, filing registration dossiers in a broad range of high-burden countries must be a priority for BMS. If BMS delays registration applications, generic manufacturers should be encouraged to come forward for registration in developing countries so that precious time is not lost for patients.

3. BMS should refrain from implementing anti-diversion measures that undermine patient access.

MSF is deeply concerned with an anti-diversion programme that pharmaceutical company Gilead is instituting in all World Bank-classified low- and middle-income countries through its distributors and licensees (generic companies that have signed a voluntary licence with Gilead) to prevent what they characterise as the possible 'bulk diversion' or re-sale of DAAs marketed by Gilead or one of its licensees from low- or middle-income countries to high-income countries. Gilead's program violates patient privacy and autonomy, undermines confidentiality of patient data, introduces coercion and policing upon medical providers, potentially results in exclusions of patients in need that do not have proper identification or are migrants, and may result in treatment interruptions for patients – leading to treatment resistance and failure. Such a programme, the so-called Integrity Programme, is motivated solely by commercial interests and is unprecedented, as far as MSF is aware.

BMS has indicated to MSF that while it may introduce obligations upon licensees to prevent diversion – such as requirements to change the colour, packaging and brand name to distinguish the product – the company will not introduce invasive, coercive and unethical measures under the guise of preventing diversion.

4. BMS should refrain from implementing tiered pricing strategies, which restrict access to medicines.

A study authored by Hill et al. in 2014 indicates that the cost of manufacturing of daclatasvir may be no more than US$10 to $30 for a full three-month course of treatment.[1]

BMS has indicated that it will apply a strategy of 'tiered pricing' when it markets daclatasvir. Tiered pricing refers to the practice by companies of setting different prices for the same drugs sold in different countries,

[1] Hill A, et al. What is the minimum cost per person to cure HCV? 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention; Kuala Lumpur, Malaysia (2013). Available from: http://pag.ias2013.org/EPosterHandler.axd?aid=3142

with prices set according to a country's economic status. This allows companies to maximise profit in all countries as prices are set according to the highest price a country, or a particular segment of the market in that country, can pay. So while BMS is selling daclatasvir for an exorbitant $15,000 per bottle in the EU, prices may be lower in some middle- and low-income countries.

However, tiered pricing is a commercial strategy, not an access strategy for medicines. As opposed to robust generic competition, it leads to significantly higher prices in all low- and middle-income countries, especially compared to the cost of manufacturing. Tiered prices are almost always substantially higher than prices available with generic competition, even in low-income countries, and especially lead to reduced access in middle-income countries – where approximately 70 per cent of all people living with HCV reside.

5. BMS should ensure that intellectual property barriers do not restrict affordable access.

Patent barriers can prevent generic competition and the development of appropriate combinations (including fixed-dose combinations). Since it is highly likely that many governments and households will be unable to pay the high prices charged by BMS, the ability of governments, generic manufacturers and civil society to undertake technical work that is aimed at the early entry of price-busting generic competition through the use of legal flexibilities (patent oppositions and compulsory licensing) is critical for treatment access and scale-up.

MSF understands that BMS has approached multiple generic manufacturers to sign voluntary licences for daclatasvir. BMS has indicated that, unlike Gilead Sciences, it will not disclose its bilateral voluntary licences. BMS's lack of commitment to transparency is unfortunate since it undermines the ability of governments and treatment providers to offer their views on agreements that have a direct impact upon the public sector and other HCV treatment programmes. However, MSF understands that such a voluntary licence may be based upon a licence agreement already signed by BMS with the Medicines Patent Pool.

Previously, BMS indicated that its voluntary licence would include 90 countries, identical to the list of countries included under Gilead's voluntary licence, except that BMS will exclude Egypt. Inclusion of only 90 countries means that BMS is excluding a large number of middle-income countries with a high burden of HCV. In total, approximately 60 million people with HCV in middle-income countries will not have access to more affordable treatments under the restrictive geographic scope proposed by BMS. Furthermore, BMS has indicated that its licence agreement would create restrictions that limit the ability of generic manufacturers to sell their medicines to countries excluded from the licence agreement, even where BMS does not have patent protection for daclatasvir.

Although BMS has not provided full disclosure of its patent landscape for daclatasvir, a patent landscape recently released by the World Health Organization reveals that BMS has not filed or secured patents on daclatasvir in a substantial number of low- and middle-income countries,[2] including key countries where a large number of generic manufacturers are located. [3] Generic manufacturers should refuse to sign a licence agreement unless nearly all low- and middle-income countries (including all high-burden low- and middle-income countries) are included in the scope of the licence. Furthermore, a licence agreement must allow sales to excluded countries that have not granted patents which could interfere with generic competition for daclatasvir. In fact, generic manufacturers should be currently considering and moving forward with immediate production and sale of the drug as a licence agreement may not be required to introduce widespread generic competition.

Recommendations to expand access

Daclatasvir, when combined with other new DAAs, holds the promise to provide people living with HCV significantly improved treatment outcomes. However, it is essential that BMS takes crucial steps to ensure affordability and availability of daclatasvir across low- and middle-income countries. BMS also must not introduce measures, such as the recent anti-diversion programme introduced by Gilead, that undermine access to treatment or force patients and providers to comply with unethical rules and regulations.

[2] WHO. Patent Situation of Key Products for Treatment of Hepatitis C (2014). Available from: http://www.who.int/phi/implementation/ip_trade/daclatasvir_report_2014_09-02.pdf.
[3] See Annex for status of patent applications filed by BMS on daclatasvir in India.

MSF recommends BMS urgently take the following steps to ensure affordable access to daclatasvir:

1. Invest in clinical trials for some genotypes (GT4, 5, 6), increase information on the safety and efficacy of daclatasvir in decompensated liver disease, and continue to pursue trials to define the use of daclatasvir in other combinations (e.g. with novel NS5Bs);
2. Announce BMS compassionate use or expanded access program for developing countries, or enable the use of daclatasvir on a named-patient basis whenever requests arise, in order to ensure early access in all countries. Release a comprehensive and transparent schedule to register in all low- and middle-income countries. File for registration in high-burden countries including China, Thailand, Indonesia, Ukraine, Myanmar and Iran;
3. Introduce low prices for *Daklinza* in all low- and middle-income countries to ensure access in the public and private sectors;
4. Ensure any voluntary licence agreement that is negotiated on a bilateral basis is published. BMS should also publish a full patent landscape of daclatasvir worldwide; and
5. Negotiate voluntary licences that include nearly all low- and middle-income countries (including all high-burden countries), and that do not restrict sales of daclatasvir to excluded countries where there are no patents in force that actually block generic competition.

MSF recommends that generic manufacturers start production and sales of generic daclatasvir where possible, and reject any licence agreements which do not include terms and conditions with a broad geographic scope and opportunities to sell generic daclatasvir to countries that have not granted competition-blocking patents.

ANNEX: DACLATASVIR PATENT APPLICATIONS IN INDIA

	Patent No.	Applicant	PCT Filing Date/Status/Expiry	Coverage
1.	853/DELNP/2009 (equivalent to WO2008021927)	Bristol Myers Squibb Co	Filing Date – 9.8.2007 Status – Under examination Expiry – 9.8.2027 (if granted)	Covers daclatasvir in markush structure.
2.	806/DELNP/2010 (eq. to WO2009020828)	Bristol Myers Squibb Co	Filing Date – 31.7.2008 Status – Under examination Expiry – 31.7.2028 (if granted)	Form N-2 of dalcatasvir 2HCl. (Further characterized by unit cell & XRD.) Described as Crystalline form in the WHO report.
3.	854/DELNP/2010 (eq. to WO2009020825)	Bristol Myers Squibb Co	Filing Date – 31.7.2008 Status – Under examination Expiry – 31.7.2028 (if granted)	Preparation of a compound. Described as process for synthesizing daclatasvir in WHO report.
4.	3999/CHENP/2012 (eq. to WO2011059887, WO2011059850)	Bristol Myers Squibb Co	Filing Date – 2.11.2010 Status – Awaiting examination Expiry – 2.11.2030 (if granted)	Preparation of intermediates.
5.	3372/CHENP/2012 (eq. to WO2011046811)	Bristol Myers Squibb Co	Filing Date – 8.10.2010 Status – Awaiting examination Expiry – 7.10.2030 (if granted)	Formulation of daclatasvir + asunaprevir. Not an important combination.
6.	753/DELNP/2009 (eq. to WO2008021928)	Bristol Myers Squibb Co	Filing Date – 9.8.2007 Status – Under examination Expiry – 8.8.2027 (if granted)	Listed in the WHO report as derivatives of daclatasvir (salts, etc.).
7.	WO2012009394	Bristol Myers Squibb Co	Filing Date – 13.7.2011 Status – Not published Expiry – 12.7.2031 (if granted)	Listed in WHO report as method patent for screening of NS5A targeting compounds to inhibit HCV replication.
8.	WO2012018829	Bristol Myers Squibb Co	Filing Date – 2.8.2011 Status – Not published Expiry – 1.8.2031 (if granted)	Listed in WHO report as formulation comprising one or two HCV polymerase inhibitors and a pharmaceutically acceptable carrier.
9.	WO2013106520	Bristol Myers Squibb Co	Filing Date – 10.1.2013 Status - Not published Expiry – 9.1.2033 (if granted)	Listed in WHO report as formulation comprising a NS5A combination which provides synergistic anti-HCV activity.