PATENT SITUATION OF KEY PRODUCTS FOR TREATMENT OF HEPATITIS C

SOFOSBUVIR

WORKING PAPER

Updated and revised version

June 2016

World Health Organization

This report was prepared for the WHO Department of Essential Medicines and Health Products by Thomson Reuters (initial version) and Pharmathen (update). It is available for free download: http://www.who.int/phi/en/. If you have questions or feedback, please write to phidepartment@who.int.

WHO/EMP/PHI/2016.07

INTRODUCTION

The World Health Organization's (WHO) 2016 *Guidelines for the screening, care and treatment of persons with hepatitis C infection* states that more than 110 million people are infected with the hepatitis C virus (HCV) worldwide. Of these individuals, approximately 700,000 die from their infection annually and another 80 million progress to chronic infection within their lifetime. An estimated one third of those individuals who become chronically infected develop liver cirrhosis or hepatocellular carcinoma. HCV infection is curable, but most infected individuals are unaware of their illness and thus do not seek timely treatment. Furthermore, treatment remains unavailable for many who have been diagnosed. Several medicines available to treat HCV, such as pegylated interferon and ribavirin involve long treatment courses of weekly injections and considerable side effects. With the development of new direct-acting antivirals, the treatment landscape is rapidly changing. These new antivirals are reaching cure rates of over 90% in persons with HCV infection across different genotypes, with fewer side effects and shorter treatment courses. Since WHO issued its first guidelines on HCV treatment in 2014, more treatments have been approved. WHO published its updated treatment guidelines in April 2016.[1]

Resolution WHA67.6, adopted by the Sixty-Seventh World Health Assembly, requested the Director-General "to work with national authorities, upon their request, to promote comprehensive, equitable access to prevention, diagnosis and treatment for viral hepatitis" and "to assist Member States to ensure equitable access to quality, effective, affordable and safe hepatitis B and HCV treatments and diagnostics, in particular in developing countries". Ensuring access to new treatments is a challenging task. In order for countries to identify ways of increasing access and affordability of new HCV medicines, they need clarity about patent status. To assess whether a medicine is patent protected in a certain country requires expert knowledge and access to specialized databases that are not easily available. The WHO Global strategy and plan of action on public health, innovation and intellectual property provides WHO with a mandate to support efforts to determine the patent status of health products (element 5.1c). Despite the possibility of filing patents under the World Intellectual Property Organization (WIPO) Patent Cooperation Treaty (PCT) in 148 jurisdictions, worldwide patents do not exist. Patents are granted individually under each jurisdiction, depending on the national patent law and the outcome of the examination process. National patents that relate to the same basic patent (i.e. the same invention) are called family members and together constitute a patent family. In the present study, patent families are based on the Derwent World Patent Index (DWPI).[2] In 2014, the WHO Secretariat mandated Thomson Reuters to carry out an analysis of the patent situation of

[1] Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; 2016 (http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/, April 2016.)

[2] The Derwent World Patents Index (or DWPI) is a database containing patent applications. Each patent family is grouped around a basic patent, which is usually the first published example of the invention.

seven new hepatitis treatments.[3] The draft and updated reports were shared with the respective sponsor companies before publication. Due to the fast developing patent situation, in August 2015 WHO mandated another service provider, Pharmathen, to update and revise reports and the relevance of the different patents included in these reports.

International nonproprietary name	**Sponsor**
daclatasvir	Bristol-Myers Squibb Company
dasabuvir	AbbVie Inc.
ledipasvir	Gilead Sciences, Inc.
ombitasvir	AbbVie Inc.
paritaprevir	AbbVie Inc.
simeprevir	Janssen Pharmaceutical Companies of Johnson & Johnson
sofosbuvir	Gilead Sciences Inc.

OBJECTIVE

The objectives of the patent working papers are to:

1. identify the most relevant patents with respect to the medicines of interest
2. identify in which countries these patents have been filed and granted
3. identify secondary patents that might delay the entry of generic medicines

The patent working papers identify the most relevant patents for each medicine. The patents are categorized as primary and secondary patents. The patent publications on the base compound are considered “primary patents” and the patents on specific pharmaceutical formulations, methods of use, product derivatives, and processes are considered “secondary patents”. Secondary patents are generally easier to circumvent or “to invent around”, meaning that medicines can be formulated such that they do not infringe on the claims of the secondary patent. For example, a patent on an aqueous form of a medicine would not prevent competitors from producing a tablet form, and a combination patent would not prevent competitors from producing the combined products separately. The report highlights those secondary patents that may delay generic entry.

[3] Initially, two additional candidate medicines were included in the project (faldaprevir and deleobuvir), but development of these products has been discontinued. Thus, the patent landscapes were not finalized.

The following are different types of patents:

Product patents claim the chemical molecule/the active pharmaceutical ingredient. Product patents are usually the strongest patents as the patent holder can use product claims to prevent others from making, selling, or importing the chemical product.

Product-by-process patents define the product by its process of preparation.

Process patents claim a (new) production process for an active pharmaceutical ingredient.

Formulation patents relate to the specific dosage form (e.g. coated tablet, soft gel capsule, syrup etc.).

Combination patents claim the combination of new or existing medicines.

Patents on product derivatives claim a specific form or derivative (e.g. a salt of an existing compound).

Patents containing Markush claims refer to a chemical structure with multiple alternatives in a format such as "chemical compound A wherein X^1 is selected from a group consisting of a, b and c".

This list is simplified and not exhaustive. Detailed explanations can be found in Philip Grubb, Peter Thomsen, *Patents for Chemicals, Pharmaceuticals, and Biotechnology*, 5th Edition Oxford 2010, as well as in the patenting guidelines of the respective national or regional patent offices.

Interpretation of patentability criteria varies, in particular with respect to the so-called secondary patents. Some jurisdictions are more restrictive to prevent a proliferation of secondary patents covering minor modifications of existing medicines. In those jurisdictions, for example, India and Argentina, many of the secondary patents may not be granted as they do not fulfil their specific requirements. Further information can be found in the draft *Guidelines for the examination of pharmaceutical patents: developing a public health perspective* which provides detailed information on the different forms of patents in the pharmaceutical sector (www.who.int/phi/publications/category/en/).

HOW TO USE THIS WORKING PAPER?

Each working paper identifies the relevant patents and provides data where these patents have been filed or granted. They allow countries to carry out a first assessment on whether a medicine is patent protected and to explore affordable treatment schemes. The data is also essential to allow the WHO to fulfil its mandate under Resolution WHA67.6, which requests the WHO to assist Member States in ensuring equitable access to quality, effective, affordable and safe HCV treatments. Assisting countries in accessing the new HCV treatments at an affordable price requires knowledge about the patent situation in the respective jurisdictions as this determines the various options countries have.

The working papers can also help other interested parties negotiate the transfer of technology and license agreements, develop research methods to improve the current drug or treatment modality, and facilitate the development of generics.

Although considered public domain material, patent information in many countries is difficult to retrieve, as reflected by the gaps in the Annex. N/A indicates that no information could be retrieved for the relevant patents in the databases that were used. This can either signify that the information in the databases is not up-to-date or complete, or that the patents were not filed in these jurisdictions. While the latter may often be the case, certainty can only be achieved by checking the information with the local patent office. This can be done by using the patent numbers provided in this report, as they allow retrieval of information through national patent offices and/or national patent registries. The following WIPO page provides links to all national online patent search tools to search national patent registries: http://www.wipo.int/branddb/portal/portal.jsp.

For international patent searches Patentscope and Espacenet can be used:

https://patentscope.wipo.int/search/en/search.jsf

http://worldwide.espacenet.com/

LIMITATIONS

While endeavours have been made to make the content of this study accessible to the non-expert, the highly technical nature of the subject matter and the singularities of the patent system require certain expertise to make full use of this study.

Every effort has been made to obtain comprehensive and accurate information, including on the legal status of the patents. However, in many countries, patent information is not readily available or updated on a regular basis. In addition, some patent applications may have been published only after the searches were conducted, and thus may not be included in this study. As this study endeavours to identify the most relevant patents, it does not include all patents and applications filed by the Sponsor and other entities that also relate to the different treatments.

It should also be noted that this study is not a freedom-to-operate analysis. The information provides useful guidance, but only reflects the situation at a particular point in time. Neither the WHO nor Thomson Reuters or Pharmathen accept any responsibility for the accuracy of data, nor guarantee that it is complete or up-to-date. **Users are advised, before taking any investment or other legally relevant decision, to consult a local patent expert to assess the patent situation in a given country.**

METHODOLOGY

The initial working papers outline relevant patents and patent applications in countries included as of March 2014. Relevant patents and patent applications were identified by searching patent and non-patent databases comprised of Thomson Innovation, Newport, Thomson Pharma, Questel, Scientific Technology Network (STN) and Cortellis. For Patent 1 daclatasvir, the original data was kindly complemented by the Sponsor Bristol-Myers Squibb. The update of the original study includes patents published up to June 2016. Patents included in the original report were reviewed for relevance. Those considered less relevant or irrelevant were removed and new patents were added.

The annex includes information directly retrieved or received from the following patent offices: ARIPO, Brazil, Chile, Egypt, GCC, Georgia, Jordan, Malaysia, Morocco, OAPI, Peru, Philippines, Thailand, Tunisia and Vietnam. Additional information was received by the Medicines Patent Pool and Oscar Lizarazo from the National University of Colombia.

Information submitted under Section 8 of the Indian Patents Act 1970

Section 8 of the Patents Act on Information and undertaking regarding foreign applications requires the applicant for a patent to file a statement setting out detailed particulars of any applications in countries outside India in respect of the same invention and to update this information in writing, from time to time. The Patent Rules 2003 (as of March 2015) concretize that this information shall be filed by the applicant for a patent through the Form 3 within six months from the date of filing the application.

The data found for each of the patents listed in the Annex was compared to the latest Form 3 as submitted to the Indian Patent Office for the corresponding Indian family member. Any missing information was included in the Annex. For territories where no corresponding filing was identified in the data search and for which no corresponding filing was listed in Form 3 the information contained in the Annex was changed from “N/A” to “Not filed” with a reference to Form 3 as the source of information, provided that the respective Form 3 was dated at least 3 years after the International Patent Cooperation Treaty filing date.

The Form 3 for each patent filing in India can be found by searching on the Indian patent office website for the Indian patent and afterwards select view documents: http://ipindiaonline.gov.in/patentsearch/search/index.aspx

The following Form 3 lists where used to check and complete data in the annex:

Patent 1, Indian Patent number 6087/DELNP/2005 Form 3 dated 10 April 2015.

Patent 2, Indian Patent number 3658/KOLNP/2009 Form 3 dated 22 January 2016.

Patent 4, Indian Patent number 9149/CHENP/2012 Form 3 dated 14 September 2015.

Patent 5, Indian Patent number 4972/ KOLNP /2011 Form 3 dated 23 October 2015.

Patent 8, Indian Patent number 4542/DELNP/2014 Form 3 dated 7 December 2015.

Patent 22, Indian Patent number 3953/DELNP/2014 Form 3 dated 12 April 2016.

Patent 26, Indian Patent number 9170/CHENP/2012 Form 3 dated 23 April 2013.

Where available, the application submitted under the WIPO PCT is used as a primary source, both because a) it is generally the favoured priority application for the pharmaceutical industry, and b) the WIPO International Search Report (ISR) includes examiner references that are coded for relevance and for which initial rejections (an indicator of possible novelty issues) can be identified. Technical experts from the service providers analysed the claims. Where available, the outcome of the WIPO ISR on novelty and inventive step is described. It should be noted that quotes from the ISR are only examples and do not preclude objections or outcomes under national jurisdictions.

The expected time of expiration for all the patents was calculated and can be found in the Annex.

US ORANGE BOOK

The updated Annex indicates which of the listed patents are contained in the US Orange Book of the US Federal Drug Administration (FDA). The US Orange Book lists the patents as submitted by the holder of the authorization with respect to new medicines authorized by the FDA for the US market. Under FDA rules, the holder of the authorization has to notify certain patents, including formulation/composition patents and use patents for a particular approved indication or method of product use. Process patents, for example, do not need to be notified (FDA Orange Book, 36th Edition 2016).

GEOGRAPHIC SCOPE

Family members of the Sponsor patent collection have been searched for in the following jurisdictions. It is beyond the scope of this study to include patent information of all WHO Member States, thus selection was made taking into account disease burden, local manufacturing capacities and regional representation:

Argentina (AR), African Regional Intellectual Property Organization (AP), Australia (AU), Brazil (BR), Canada (CA), Chile (CL), China (CN), China, Hong Kong SAR (HK), Colombia (CO), Costa Rica (CR), Ecuador (EC), Egypt (EG), European Patent Office (EPO), Ethiopia (ET), Eurasian Patent Office (EAPO), Georgia (GE), India (IN), Indonesia (ID), Iran (Islamic Republic of) (IR), Israel, (IL), Japan, Jordan (JO), Malaysia (MY), Mexico (MX), Morocco (MA), New Zealand (NZ), Nigeria (NG), African Intellectual Property Organization (OA), Pakistan (PK), Patent Office of the Cooperation Council for the Arab States of the Gulf (GCC), Peru (PE), Philippines (PH), Republic of Korea (KR), Russian Federation (RU), Singapore (SG), South Africa (ZA), Thailand (TH), Tunisia (TN), Ukraine (UA), the United States of America (US), Uruguay (UY), and Vietnam (VN).

FURTHER RESOURCES

The WHO publication *How to conduct patent searches for medicines: a step-by-step guide* provides guidance on how to identify the patent status of medicines.[4] The draft *Guidelines for the examination of pharmaceutical patents: developing a public health perspective* provides detailed information on the different forms of patents in the pharmaceutical sector.[5] Material on the relationship between public health and intellectual property can be found in the document *Promoting Access to Medical Technologies and Innovation. Intersections between public health, intellectual property and trade*.[6] These publications as well as other relevant publications on issues related to public health and intellectual property can be found here: www.who.int/phi/publications/category/en/

More information on HCV and the recommended treatments can be found here: www.who.int/topics/hepatitis/en/

PATENT OPPOSITIONS AND LITIGATION

There are an increasing number of patent oppositions and litigation cases with respect to the new HCV drugs, sofosbuvir in particular. While the reports highlight some opposition and litigation cases, due to the high number of cases, it is beyond the scope of these reports to cover all these cases. Information on current opposition procedures can be found in relevant patent registers (see above) as well as on:

http://www.patentoppositions.org/

http://www.i-mak.org/

[4] How to Conduct Patent Searches for Medicines: A Step-by-Step Guide. Delhi: World Health Organization; 2010 (http://www.wpro.who.int/publications/PUB_9789290223757/en/, May 2016).
[5] Guidelines for the examination of pharmaceutical patents: developing a public health perspective. Geneva: World Health Organization; 2006 (http://apps.who.int/medicinedocs/documents/s21419en/s21419en.pdf, May 2016).
[6] Promoting Access to Medical Technologies and Innovation. Intersections between public health, intellectual property and trade. Geneva: World Health Organization, World Trade Organization, World Intellectual Property Organization; 2013 (http://www.who.int/phi/promoting_access_medical_innovation/en/, May 2016).

SOFOSBUVIR (GS-7977)

The drug sofosbuvir, previously known as GS-7977, was originally developed by Pharmasset as compound PSI-7977. PSI-7977 is the more active diastereoisomer form of the parent compound PSI-7851.

Sofosbuvir is a viral polymerase nucleotide inhibitor that was approved by the United States Food and Drug Administration (FDA) in December 2013, and by the European Medicines Agency in January 2014 for the treatment of HCV infection. The WHO *Guidelines for the screening, care and treatment of persons with hepatitis C infection*[7] recommends sofosbuvir in combination with other antiviral treatments as a preferred treatment option for all HCV genotypes 1-6. Sofosbuvir in combination with ribavirin was the first interferon-free HCV treatment. Sofosbuvir is considered the back-bone of new regimens for hepatitis C.

Sofosbuvir was invented by Pharmasset Ltd, which filed the first patent on the drug in 2003. In 2011, Gilead Sciences (hereby referred to as the Sponsor) acquired Pharmasset Ltd and further developed the drug. Today, sofosbuvir is marketed by the Sponsor under the brand names Sovaldi and Virunon. Sofosbuvir is a prodrug that is metabolized in the body to the active antiviral agent 2'-deoxy-2'-α-fluoro-β-C-methyluridine-5'-monophosphate, a nucleotide analogue inhibitor of the HCV polymerase, which is critical for viral RNA replication.

On December 6, 2013, sofosbuvir received approval from the U.S. FDA for treatment of individuals with chronic hepatitis C as a component of combination therapy.

On October 10, 2014, the US FDA-approved a fixed-dose combination pill (ledipasvir 90 mg and sofosbuvir 400mg) to treat chronic HCV genotype 1 infection.

On November 5, 2014, the US FDA-approved the use of simeprevir in combination with sofosbuvir as an all-oral, interferon- and ribavirin-free treatment option for patients with genotype 1 chronic HCV.

On July 24, 2015, the US FDA approved the use of daclatasvir in combination with sofosbuvir for patients with genotype 3 chronic HCV infection.

As of March 2015, Gilead Sciences is developing a fixed-dose oral combination of sofosbuvir and velpatasvir (GS-5816) as a tablet formulation for treating HCV genotypes 1-6.

[7] Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; 2016 (http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/, May 2016.)

CHEMICAL NAME

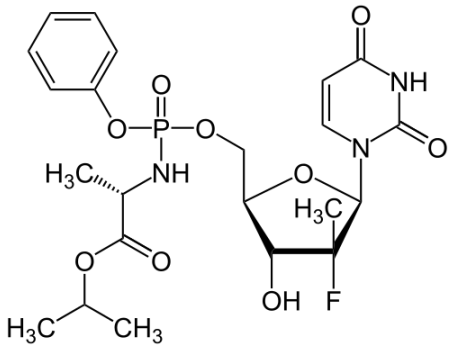
Systematic (IUPAC) name:

Isopropyl (2S)-2-[[[(2R,3R,4R,5R)-5-(2,4-dioxopyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydrofuran-2-yl]methoxy-phenoxy-phosphoryl]amino]propanoate

MOLECULAR FORMULA

$C_{22}H_{29}FN_3O_9P$

MOLECULAR STRUCTURE



Cross-reference list of the patent families in the original and updated report

The following table contains a list of cross-references that explains the changes that were made in this updated report.

Original Report	**Updated Report**
Patent 1	Patent 1
Patent 2	Patent 2
Patent 3	Process patent now patent 26
Patent 4	Patent 4
Patent 5	Patent 5
Patent 6	Deleted as considered not/less relevant with respect to generic entry
Patent 7	Patent 7
Patent 8	Patent 8
Patent 9	Deleted as considered not/less relevant with respect to generic entry
Patent 10	Deleted as considered not/less relevant with respect to generic entry
Patent 11	Deleted as considered not/less relevant with respect to generic entry
Patent 12	Deleted as considered not/less relevant with respect to generic entry
Patent 13	Process patent moved to 27
Patent 14	Deleted as considered not/less with respect to generic entry
Patent 15	Deleted as considered not/less with respect to generic entry
Patent 16	Deleted as considered not/less with respect to generic entry
Patent 17	Deleted as considered not/less relevant with respect to generic entry
Patent 18	Patent 18
Patent 19	Deleted as considered not/less with

	respect to generic entry
Patent 20	Family member of Patent 4
Patent 21	Patent 21
New Patents 22-25	New Patents 22-25

SUMMARY

The sofosbuvir Sponsor patent collection comprises 14 different patent families.

Patents 1 and 2 are primary patents. Patent 1 claims a generic compound for the active metabolite of sofosbuvir. Patent 2 relates to the sofosbuvir prodrug as marketed and claims the molecule per se in a specific compound claim. These patents constrain the launch of generic products where they are granted and enforceable. A number of family members of Patent 1 and Patent 2 are subject to pre-grant opposition and litigation cases that dispute their novelty and inventive step and are further explained in the working paper.

Patent 4 and 25 cover crystalline forms of sofosbuvir. The claims of Patent 4 as published cover all crystalline forms. It is expected that the claim scope will be reduced to specific crystalline forms in the patent examination process. However, reduction of the claim scope is not likely to occur in countries that do not practice substantial patent examination. If the claim scope remains broad as filed, generic companies may have issues developing products that do not infringe on the patent. According to the patentee, Patent 4 covers the most thermodynamically stable polymorphic form of sofosbuvir. Thus, to avoid infringing this patent, generic companies will have to develop a different stable molecular dispersion, liquid, or amorphous form. Care would have to be exercised to prevent conversion of the developed product to a stable form covered by Patent 4 to avoid patent infringement.

Sofosbuvir falls within Class III (Low Permeability, High Solubility) under the Biopharmaceutics Classification System (BCS)[8]. Therefore, any differences in dissolution between the polymorphic forms of the sponsor drug and the generic forms will have to be evaluated by the regulatory agencies when reviewing the market authorization for any generic versions. The US equivalent of Patent 4 is listed in the Orange Book. Patent 25 claims alternative stable crystalline forms. Patent 4 and 25 together may present difficulties for generic companies where these patent claims are granted.

Patent 5 is a product-by-process patent, claiming the sofosbuvir prodrug by a process of preparation. This patent, where granted, thereby prevents competitors from making sofosbuvir prodrug by the claimed process or from importing sofosbuvir manufactured by the claimed process.

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[8] See EMA European Public Assessment Report of sofosbuvir: November 2013: (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002798/WC500160600.pdf, May 2016.)

Patents 7 and 23 claim different combinations comprised of sofosbuvir and other anti-HCV drugs (ledipasvir, velpatasvir, ribavirin and PSI7851).

Patents 8 and 20 are formulation patents, claiming the pharmaceutical dosage form (pharmaceutical composition).

Patents 18 and 21 are method of use patents, claiming sofosbuvir and derivatives for use in HCV treatment.

Patent 22 covers a pharmaceutical composition comprised of amorphous ledipasvir and crystalline sofosbuvir.

Patent 24 claims the combination comprised of the amorphous form of velpatasvir and the crystalline form of sofosbuvir used for HCV treatment.

Patents 26 and 27 cover processes to make sofosbuvir. If granted, competitors will be required to design around these patents and use other production processes.

Additional patents have been filed by the Sponsor which are partly disclosed in the License Agreement (see LICENSE AGREEMENTS) as well as a huge number of non-Sponsor entities.

Note: Additional relevant combination patents

The searches revealed two patents that are relevant for all seven patent reports. Patent applications WO2013059630A1 and WO2013059638A1 by Abbvie inter alia claim the use of combinations of unnamed direct-acting antiviral agents for treating HCV where the treatment does not include administration of interferon or ribavirin and lasts between 8-12 weeks. These patents in principle also cover combinations of sofosbuvir with other antiviral treatments. The description and the dataset for these two patents can be found in the Working Paper on paritaprevir/ombitasvir/dasabuvir (Patents 6 and 7). These patents are in litigation.

PATENT OPPOSITION

In many countries, (pre-grant) oppositions have been filed against Patent 1 and Patent 2 since these are the primary patents on sofosbuvir, the backbone of the new HCV treatments. These oppositions are filed by third parties such as non-governmental organizations and generic competitors that challenge the legitimacy of a pending patent application. Countries where oppositions or inter parte observations have been filed include Argentina, Brazil, India, Russia, Thailand, Ukraine and the European Union.

On 13 January 2015, India initially rejected Gilead's application for Patent 1: 6087/DELNP/2005 on the basis of failure to meet section 3(d) of India's Patent Act[9] based on oppositions filed by the generic pharmaceutical company Natco and the non-for-profit organisation I-MAK.

Gilead appealed the decision and on 10 May 2016, the India patent office finally granted the patent. The decision is likely to be appealed. Patent 2 is still under examination in India and has several pre-grant oppositions filed by patient and public interest groups.

Information on current opposition procedures can be found at:

http://www.patentoppositions.org/

http://www.i-mak.org/

LICENCE AGREEMENTS

Gilead Sciences signed licensing agreements with 11 Indian generic manufacturers. Under these agreements, manufacturers can produce and sell generic sofosbuvir and the combination of ledipasvir/sofosbuvir and velpatasvir (GS5816) in 101 countries. They can also combine sofosbuvir with other hepatitis treatments. Gilead has also signed license agreements for in-country production and distribution with three local generic manufacturers in Pakistan and Egypt.[10] The license agreement contains information about sofosbuvir and ledipasvir patents. **Some but not all of the patents listed in the license agreement are included in this patent landscape.** Gilead has made available a copy of the draft agreement.[11]

[9] (http://ipindia.nic.in/ipr/patent/eVersion_ActRules/sections/ps3.html, May 2016)
[10] Gilead, Chronic Hepatitis C Treatment Expansion, Factsheet: August 2015 (http://www.gilead.com/~/media/Files/pdfs/other/HCVGenericAgreementFactSheet.pdf, May 2016)
[11](http://www.gilead.com/responsibility/developing-world-access/access%20partnerships, June 2016)

SOFOSBUVIR PATENT SITUATION

PATENT 1

Patent application WO2005003147A2 (primary patent) discloses the base compound of sofosbuvir Sofosbuvir as marketed is a “pro-drug” that upon administration, metabolizes into the base compounds claimed in Patent 1. The sofosbuvir base compound is a nucleoside derivative. The patent claims a general structural formula or Markush structure and specific compounds for this base compound. In addition to the claimed compositions, the patent also claims methods of treatment, the use of methyl nucleosides or a pharmaceutically acceptable salt, and a prodrug for the treatment of HCV infection in humans. It also claims the use of sofosbuvir for treatment of various other viral infections in humans. The patent has a broad scope. While the patent is not directly infringed upon by the manufacturing of a generic version of sofosbuvir, it would be indirectly infringed up when sofosbuvir is administered as the patent covers the active metabolite that is formed after administration of the treatment. Thus, the patent is relevant to the generic entry date. It is not listed in the USA Orange Book as only patents that protect the product as marketed are entitled to be listed in the Orange Book.

As per the WIPO ISR, the application has entered into the European national phase. The ISR report illustrates that claims 1-55 of WO2005003147A2 were subject to amendment in light of prior art.

Patent 1 is involved in a number of litigation procedures, including pre-grant oppositions.

PATENT 2

This patent is listed in the US Orange Book with patent numbers US8580765, US7964580, US8334270, US9085573.

Patent application WO2008121634A2 claims a Markush structure and several phosphoramidate prodrugs of nucleoside derivatives, their salts, hydrates, solvates, stereoisomers and crystalline forms and processes for their preparation. Methods of use are also claimed by administering the above to treat HCV. The compounds are disclosed as HCV NS5B polymerase inhibitors. WO2008121634A2 relates to the sofosbuvir pro-drug as marketed which, when administered, releases the active compound claimed in Patent 1.

As per the WIPO ISR, not all claims of WO2008121634A2 meet the novelty and inventive step requirement in light of prior art.

Patent 2 is involved in a number of litigation procedures, including pre-grant oppositions, for example several oppositions have been filed against the European Patent EP2203462 by generic companies as well as to the Médecins du Monde, a French NGO.

Oppositions are based on the grounds that the patent did not involve an inventive step (article 56 EPC), the invention was insufficiently disclosed (Article 83 EPC), and that it contained subject matter which extends beyond the content of the application as filed (Article 123(2) EPC), I-MAK, a United States-based not-for-profit group has filed a pre-grant opposition against Gilead’s Indian patent application (3658/KOLNP/2009) on the grounds of lack of novelty and obviousness. I-MAK also claims that sofosbuvir in IN200903658P2 is

merely a new form of a known substance that does not result in an enhancement of its efficacy. Lack of novelty is established based on Gilead Sciences' earlier patent WO2005/003147, which discloses both the parent structure of sofosbuvir and the stabilized phosphate prodrug form. I-MAK also filed a third party observation in China that led to the refusal of the patent application by the State Intellectual Property Office (CN101918425A).[12]

PATENT 4

This patent is listed in the US Orange Book with patent number US8618076.

Patent application WO2011123645A2 covers crystalline forms of sofosbuvir and a process for preparing sofosbuvir and one of its intermediates. The patent covers a crystalline structure of nucleoside phosphoramidates, a Markush structure of nucleoside phosphoramidates, and a preparation process for the active compound. Nucleoside phosphoramidates are used for the treatment of HCV infection. As per the WIPO ISR, several claims related to crystalline structures cannot be considered novel.

The patent as filed seeks to protect all crystalline forms. If all claims are granted, patent infringement would only be avoided through the creation of sofosbuvir variants in liquid, amorphous, or dispersion form. In areas where the claims will be reduced through the examination process and limited to the specific crystalline forms disclosed, alternative unclaimed crystalline forms could be used. Prosecution of this patent in markets of concern should be monitored.

The European Public Assessment Report (EPAR)[13] of the European Medicines Agency states that the Sponsor found eight polymorphic forms during development and that the most thermodynamically stable crystalline form is the one marketed. The EPAR confirms that a polymorphic purity specification has been set. Sovaldi, however, is not a pure polymorph, but has a small amount of a related polymorphic form present. Patent 4 is highly relevant as it claims all the polymorphic forms that the Sponsor identified, including the one used by the marketed product.

PATENT 5

This patent is listed in the US Orange Book with patent number US8633309.

The patent application WO2010135569A1 contains product-by-process claims. A product-by-process claim is directed to a product that is defined by its process of preparation. This application claims diastereoisomeres of two specific nucleoside phosphoramidate pro-drugs, their solvates, and polymorphic forms, as well as processes for their preparation and novel intermediates. As per the WIPO ISR, the application does not meet the requirement for unity of invention, i.e. it relates to a group of closely related inventions rather than one invention.

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[12] Zosia Kmietowicz, China rejects patent on hepatitis C drug sofosbuvir BMJ 2015;350:h3429

[13] November 2013 (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002798/WC500160600.pdf, May 2016)

The subject matter of independent claims 1, 18-21 and dependent claims 2-6 of WO2010135569A1 is new as it shows novelty and involves inventive steps.

PATENT 7

Patent application WO2013040492A2 relates to combinations of therapeutic molecules (sofosbuvir, ledipasvir, PSI-7851) exhibiting synergistic effects, oral formulation, tablet formulation, dosing regimens, and methods of use for treating HCV infection. Daclatasvir and velpatasvir are not included as combination treatment options with sofosbuvir in this patent filing.

As per the WIPO ISR, the subject matter of several claims (1, 2, 10,11, 15-16, 19-21, 24, 33-38) is not inventive in view of prior art.

Where granted, this patent potentially constrains the combination consisting of sofosbuvir/ledipasvir administered as two separate tablets and also a composition consisting of said combination in a single tablet. If granted, the patent could constrain the use of sofosbuvir when administered as a tablet in combination with another separate tablet containing one or more of the other active ingredients claimed, for example, ledipasvir (see claim 10 of the WO2013040492A2). If claim 10 or its equivalents are not granted, then the patent scope is limited to tablets that contain two or more of the active ingredients claimed.

This patent is listed in the ledipasvir report as Patent 5.

PATENT 8

This patent is listed in the US Orange Book with patent number US8889159.

Patent application WO2013082003A1 claims a pharmaceutical composition comprised of anywhere from 25%wt (percentage by weight) to 35%wt of sofosbuvir and at least one excipient for the treatment of HCV infection, a unit dosage form of about 400 mg of sofosbuvir, and a method to prepare a tablet of sofosbuvir. Provided that the percentage by weight of sofosbuvir can be altered, then this patent filing can be circumvented when needed. However, the claim on the unit dosage form would be difficult to circumvent if granted as 400mg is the only approved dose strength of sofosbuvir. Thus, a generic product would be required to use this dosage strength. Though such patent claims are generally rejected, they are likely to be granted in countries where patent examination is weak or where substantial patent examination is not practiced, such as South Africa.

PATENT 18

Patent application WO2011156757A1 claims a dosing regimen comprised of the combination of an anti-HCV agent or its pharmaceutically acceptable salts, and ribavirin (but not interferon). It also claims instances in which the combination exhibits synergistic effects in treating HCV infection. Also claimed are compositions and kits. The anti-HCV compounds are selected from an NS3 protease inhibitor, a NS4B inhibitor, a nucleoside NS5B polymerase inhibitor (here sofosbuvir), a non-nucleoside NS5B polymerase inhibitor, a NS5A inhibitor, or an HCV entry inhibitor.

A WIPO ISR is not available. The examination history of this PCT application reveals that the constituency application is believed to have been withdrawn because of non-payment of filing fee/search fee in time.

PATENT 21

Patent application WO2013066748A1 covers a composition and a method of treatment of HCV infection using sofosbuvir and ribavirin.

An International Search Report (ISR) is yet to be published.

PATENT 22

Patent application WO2014120981A1 is directed at a composition comprised of ledipasvir in a substantially amorphous form and sofosbuvir in a substantially crystalline form.

As per the WIPO ISR, since the combination of the amorphous ledipasvir and crystalline sofosbuvir does not require appreciable technical effort and can be performed by a skilled individual through routine design, no inventive step can be acknowledged.

This patent is listed in the ledipasvir report as Patent No. 6.

PATENT 23

Patent application WO2014185995 relates to combination of sofosbuvir with other anti-HCV compounds, including velpatasvir, ledipasvir, GS-9190 and tegobuvir.

PATENT 24

Patent application WO2015030853 claims a pharmaceutical composition comprised of amorphous velpatasvir and crystalline sofosbuvir, used for HCV treatment. The amorphous form improves the aqueous solubility. Gilead Sciences is developing a fixed-dose oral combination of the NS5B inhibitor sofosbuvir and velpatasvir, a pan-genotypic NS5A inhibitor (phase 3, as of March 2015), as tablet formulation.

PATENT 25

Patent application WO2015099989 is directed toward crystalline solid forms of sofosbuvir.

Gilead observed eight polymorphic forms of sofosbuvir as discussed in relation to Patent 4. The marketed form is the most thermodynamically stable polymorphic form, containing a small amount of a metastable form. A specific patent covering the most thermodynamically stable polymorphic form can be important if it is found that other metastable forms exist specifically if these metastable forms remain unstable in a formulation preventing conversion to another polymorphic form that would infringe on this patent or another form with different physical properties. The prosecution of this patent should be monitored.

Sofosbuvir falls within Class III (Low Permeability, High Solubility) under the Biopharmaceutics Classification System (BCS)[14]. Therefore, any differences in dissolution between the polymorphic forms of the sponsor drug and the generic forms will have to be evaluated by the regulatory agencies when reviewing the market authorization for any generic versions.

PATENT 26

Patent application WO2011123668A2 is a process patent with some claims referring to a compound in the form of a Markush structure. The process comprises the preparation of sofosbuvir containing phosphorus. The process allows enantiomers or diastereomers of compounds to have improved pharmacokinetic parameters relative to the active substance. Thus, claims are broad in nature and competitors may have to invent around this process.

As per the WIPO ISR, several process-related claims cannot be considered novel.

PATENT 27

Patent application WO2012012465A1 is a process patent claiming methods for preparing diastereomerically pure phosphoramidate prodrugs (Markush structure).

As per the WIPO ISR, all 36 claims meet the requirement of novelty and industrial applicability. However, claims 1-7 of the present application lack inventive steps.

[14] See EMA European Public Assessment Report of sofosbuvir: November 2013: (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002798/WC500160600.pdf, May 2016.)

ANNEX – SOFOSBUVIR PATENT SITUATION

	Patent 1	Patent 2	Patent 4	Patent 5	Patent 7	Patent 8	Patent 18
Subject Matter	Patent application WO2005003147A2 discloses the base compound of sofosbuvir (primary patent).	Patent application WO2008121634A2 relates to the sofosbuvir prodrug as marketed.	Patent application WO2011123645A2 is a process patent for the preparation of the active compound.	Patent application WO2010135569A1 is a product by process patent.	Patent application WO2013040492A2 covers a composition and a method of treatment using a sofosbuvir, PSI-7851, or ledipasvir. This patent is the same as Patent 5 in the ledipasvir report.	Patent application WO2013082003A1 claims a pharmaceutical composition comprising sofosbuvir and at least one excipient.	Patent application WO2011156757A1 claims a dosing regimen comprising the combination of an anti-HCV agent or its pharmaceutically acceptable salts, Ribavirin.
Applicant	Pharmasset Ltd.	Pharmasset Ltd.	Pharmasset Ltd.	Pharmasset Ltd.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.
Int'l Patent Publication Number	WO2005003147A2	WO2008121634A2	WO2011123645A2	WO2010135569A1	WO2013040492A2	WO2013082003A1	WO2011156757A1
Priority Number	US2003474368P	US20070909315P US20070982309P US20080053015	US2010319513P	US2009179923P	US2011535885P	US2011564500P	US2010353460P
Listed in US Orange Book[15]	No	US8580765, US7964580, US8334270, US9085573	US8618076	US8633309	No	US8889159	No
Expected expiry[1]	20 Apr 2024	25 Mar 2028	30 Mar 2031	19 May 2030	13 Sep 2032	26 Nov 2032	9-Jun-31

[15] The US Orange Book lists the patents as submitted by the holder of the authorization in line with Federal Drug Administration (FDA) Form 3542. This includes formulation/composition patents; use patents for a particular approved indication or method of using the product; and certain other patents, FDA. Orange Book, 36th Edition 2016.

	Patent 1	Patent 2	Patent 4	Patent 5	Patent 7	Patent 8	Patent 18
PATENT STATUS							
ARIPO (AP)[2]	Not filed[7]	Not filed[7]	Granted AP2012006543D0 Patent No: AP 3515	Not filed[7]	Examined and objection to patentability issued. Awaiting Applicants response AP2014007575	Examined and objection to patentability issued. Awaiting Applicants response AP2012007699	No application identified
Argentina (AR)	Pending AR82068A2 Pending AR82067A2 Pending AR82066A2 Pending AR82064A2 Pending AR44566A1	Pending AR66898A1	Pending AR80870A1	Pending AR82937A1	Not filed[9]	Pending AR089578	Pending AR084393A1
Australia (AU)	Granted AU2004253860B2	Granted AU2012241173B2 Granted AU2008232827B2 Pending AU2014215983 Pending AU2014233579	Granted AU2011235112B2	Granted AU2010249481B2 Pending[8] AU2016200676A1	Pending U2012308295A1	Pending AU2012346217	N/A

	Patent 1	Patent 2	Patent 4	Patent 5	Patent 7	Patent 8	Patent 18
Brazil (BR)	Pending BR200410846A	Pending PI0809654-6 Pending PI0823519-8	Pending BR1120120249231 Pending[8] BR1220130046216	Pending[8] BRPI1012781-0 Pending[8] BR1220130075569	Not filed[9]	Pending BR1120140127395	N/A
Canada (CA)	Pending CA2734066A1 Pending CA2734055A1 Pending CA2734052A1 Pending CA2733842A1 Granted CA2527657C	Granted CA2682230C	Pending CA2794669A1 Pending[8] CA2849694	Pending CA2819700A1	Pending CA2840242A1	Pending CA2856529	N/A
Chile (CL)	Not filed[7]	Granted CL2008000902A1	Pending[8] CL716-2011	Rejected CL201000520 Pending CL2013000903 Pending[8] CL2013000904	Pending CL2014000630A1	Pending CL2014001397	No application identified
China (CN)	Granted CN100503628C	Rejected CN101918425A Pending CN104402955A	Pending CN102858790A	Pending CN102459299A Pending CN104292256A	Pending CN104244945A	Pending CN104039319	N/A

	Patent 1	Patent 2	Patent 4	Patent 5	Patent 7	Patent 8	Patent 18
China, Hong Kong SAR (HK)	Pending HK1155752A0 Pending HK1155751A0 Pending HK1155458A0 Pending HK1155457A0	Pending HK1150450A0 Pending HK11105202.0 Pending HK15106528.1 Pending HK15106529.0	Pending HK1178171A0 Pending[8] HK13110269.8	Pending HK1169414A0 Pending HK1182114A0 Pending HK1182938A0	Pending HK1194692A	Pending HK1202268A1	N/A
Colombia (CO)	Granted CO5660270	Granted CO6260023	Rejected CO6630167A2	Rejected CO6470789A2	Granted CO6930366A2	Rejected CO6970603	N/A
Costa Rica (CR)	Not filed[7]	Not filed[7]	Pending CR20120532A	Not filed[7]	Pending CR20140177A	Pending CR20140273	N/A
Ecuador (EC)	Not filed[7]	Not filed[7]	Pending[8] SP-12-12282	Not filed[7]	Not filed[9]	Pending EC2014-5678	N/A
Egypt (EG)	Not filed[7]	Not filed[7]	Pending 1659/2012	Rejected 2011111955	Pending 392/2014	Pending 864/2014	Not filed
Ethiopia (ET)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[9]	Not filed[7]	N/A
EAPO[3] (EA)	Not filed[7]	Not filed[7]	Pending EA201290993A1	Pending EA201171417A1 Pending EA201370186A1	Pending EA201490588A1	Pending EA201490903	N/A

	Patent 1	Patent 2	Patent 4	Patent 5	Patent 7	Patent 8	Patent 18
EPO[4] (EP)	Pending EP2604620A1 Pending EP2345661A1 Pending EP2345659A1 Withdrawn EP2345658A1 Pending EP2345657A1 Pending EP1633766A2	Granted EP2203462B1 Pending EP2792680A1 Pending EP2801580A1 Pending EP2824109A1 Pending EP2826784A1 Pending[8] EP2933260A1	Granted[8] EP2552930A2 Pending[8] EP2609923A3	Pending EP2432792A1 Pending[8] EP2913337A1 Pending[8] EP2910562A1	Pending EP2709613A2	Pending EP2785340A1	Closed EP11726033
GCC[5]	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[9]	Pending GC2012-22917	No application identified
Georgia (GE)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[9]	Not filed[7]	No application identified
India (IN)	Pending IN201102079P1 2079/DELNP/2011 Pending IN201101871P1 1871/DELNP/2011 Pending IN201101870P1 1870/DELNP/2011 Granted IN200506087P1 6087/DELNP/2005	Pending IN200903658P2 3658/KOLNP/2009	Pending 9149/CHENP/2012	Pending 4972/KOLNP/2011	Pending 2956/DELNP/2014	Pending 4542/DELNP/2014	N/A

	Patent 1	Patent 2	Patent 4	Patent 5	Patent 7	Patent 8	Patent 18
Indonesia (ID)	Granted ID28288 Pending ID201101419 Pending ID201101420 Pending ID201101421 Pending ID201101422	Not filed[7]	Pending W0020124454	Not filed[7]	Pending P00201402133	Pending P00201403478	N/A
Iran (Islamic Republic of) (IR)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[9]	Not filed[7]	N/A
Israel (IL)	Granted IL211375A Granted IL210367A Granted IL172259A	Granted IL222810D0 Granted IL217228 Granted IL201239	Pending IL222099	Granted IL216492 Pending[8] IL239115 Pending[8] IL237471	Not filed[9]	Pending IL232889	N/A

	Patent 1	Patent 2	Patent 4	Patent 5	Patent 7	Patent 8	Patent 18
Japan (JP)	Abandoned JP2011201882A Inactive[8] JP2011190263A Granted JP05266357B2 Granted JP04958158B2	Granted JP05318085B2 Granted JP5539419B2 Pending JP2015024998A Granted JP5774749B2 Pending JP2016023187A[8]	Pending JP2013523767A Pending[8] JP2015205903A	Granted[8] JP5885659B2 Granted[8] JP5909535B2	Pending JP2014526516A	Pending JP2014-533733	N/A
Jordan (JO)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[9]	Not filed[7]	N/A
Malaysia (MY)	Granted MY138477A	Granted MY147409A Pending PI2013700348 Pending PI2013700240	Not filed[7]	Pending MY2011005625P	Not filed[9]	Pending MY2014001520P	N/A
Mexico (MX)	Granted MX275935B	Granted MX296818B Pending MX201200289A	Pending MX2012011171A Pending[8] MX2014005752A	Granted MX320108 Granted MX324805	Pending MX2014003145A	Pending[8] MX2014006373A	N/A
Morocco (MA)	Not filed	Not filed	Not filed	Not filed	Pending 36906	Pending 37130	Not filed

	Patent 1	Patent 2	Patent 4	Patent 5	Patent 7	Patent 8	Patent 18
New Zealand (NZ)	Granted NZ543867A	Granted NZ599206A Granted NZ579880A	Granted NZ603232	Granted NZ596635 Pending[8] NZ709926 Pending[8] NZ623602	Pending NZ623396	Pending NZ625532	N/A
Nigeria (NG)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[9]	Not filed[7]	N/A
OAPI[6]	Not filed[7]	Not filed[7]	Granted OA16103	Not filed[7]	Pending 1201400117	Pending 1201400229	No application identified
Pakistan (PK)	Not filed[7]	Not filed[7]	Pending 233/2011 Pending 748/2012	Not filed[7]	Pending 880/2011	Pending 803/2012	No application identified
Peru (PE)	Not filed[7]	Not filed[7]	Pending PE20130183A1	Not filed[7]	Pending PE10562014A1	Pending PE20140749	N/A
Philippines (PH)	Granted PH12005502136	Pending PH2009501847 Pending PH12014502771	Not filed[7]	Pending PH12011502433 Pending PH12014502684 Pending PH12015502237	Pending PH2014500557	Pending PH2014501133	No application identified
Republic of Korea (KR)	Granted KR100883703B1	Granted KR101432860B1 Granted KR101525293B1 Granted KR101527701B1	Pending KR20120138242A	Granted[8] KR101603817B1 Granted[8] KR101599183B1 Pending[8] KR10-2015-7008852	Pending KR20140096029A	Pending KR1020147016699	N/A

	Patent 1	Patent 2	Patent 4	Patent 5	Patent 7	Patent 8	Patent 18
Russian Federation (RU)	Granted RU2358979C2	Granted RU2478104C2 Pending RU2012152811A	Not filed[7]	Not filed[7]	Not filed[9]	Not filed[7]	N/A
Singapore (SG)	Granted SG117252	Granted SG155711	Pending SG184324A1	Pending SG176197A1 Pending[8] SG10201500835WA	Pending SG11201400664W	Granted SG11201402609R	N/A
South Africa (ZA)	Granted ZA200509521A	Granted ZA200906647 Granted ZA201200310	Granted ZA201207799A Pending ZA201400249	Granted ZA201108749 Pending[8] ZA201301620	Pending ZA201402534	Pending ZA201403903 Pending ZA201404061	N/A
Tunisia (TN)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[9]	Not filed[7]	No application identified
Thailand (TH)	Pending TH079569	Pending TH801001634	Pending TH1201005189	Pending TH10010000775	Not filed[9]	Pending TH1401002830	N/A
Ukraine (UA)	Not filed[7]	Not filed[7]	Pending[8] UA201212444 Pending[8] UA201311603	Not filed[9]	Not filed[9]	Pending UA201405757	N/A

	Patent 1	Patent 2	Patent 4	Patent 5	Patent 7	Patent 8	Patent 18
The United States (US)	Granted US8415322B2 Granted US7429572B2 Pending US20080253995A1 Pending US20080070861A1 Pending US20090004135A1 Pending US20090036666A1 Pending US20120245335A1	Granted US8580765B2 Granted US8334270B2 Granted US7964580B2 Granted US8906880B2 Granted US8735372B2 Granted US8957046B2 Granted US9085573B2 Pending US2015231166A1	Granted US8859756B2 Granted[8] US8618076B2	Pending US20130165401A1 Granted US8629263B2 Granted US8633309B2 Granted US8642756B2 Pending US20140121366A1	Pending US20130243726A1 Pending US2015150896A1	Granted US8889159B2	Abandoned US20110306541A1
Uruguay (UY)	Not filed[7]	Not filed[7]	Pending UY33311A	Not filed[7]	Not filed[9]	Pending UY34474A	Pending UY33445A
VietNam (VN)	Not filed[7]	Not filed[7]	Pending VN33365A	Not filed[7]	Pending VN39534	Pending VN1-201401861	N/A

	Patent 21	Patent 22	Patent 23	Patent 24	Patent 25	Patent 26	Patent 27
Subject Matter	Patent application WO2013066748A1 covers a composition and a method of treatment of HCV infection using sofosbuvir and ribavirin.	Patent application WO2014120981A1 claims compositions comprising substantially amorphous ledipasvir and substantially crystalline sofosbuvir. This patent is listed in the ledipasvir report as Patent No. 6.	Patent application WO2014185995A1 claims combination of sofosbuvir with other compound such as velpatasvir, ledipasvir, GS-9190 and tegobuvir.	Patent application WO2015030853A1 claims composition comprising amorphous velpatasvir GS-5816 and crystalline sofosbuvir.	Patent application WO2015099989A1 claims crystalline solid forms of sofosbuvir.	Patent application WO2011123668A2 is a process patent.	Patent application WO2012012465A1 is a process patent claiming methods for preparing diastereomerically pure phosphoramidate prodrugs (Markush structure).
Applicant	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Pharmasset Ltd.	Gilead Sciences Inc.
Int'l Patent Publication Number	WO2011156757A1	WO2013066748A1	WO2014185995A1	WO2015030853A1	WO2015099989A1	WO2011123668A2	WO2012012465A1
Priority Number	US2010353460P	US2011553481P	US201361824266P US201361919108P	US201361870712P US201361898690P US201361907308P	US201361920371P	US2010319548P	US2010365621P
Expected expiry[1]	9-Jun-31	25-Oct-32	30-Jan-2034	30-Jan-2034	08-Dec-2034	30-Mar-2031	18-Jul-2031
Listed in US Orange Book[16]	No	No	No	No	No	No	No
PATENT STATUS							
ARIPO[2] **(AP)**	No application identified	Pending[8] AP/P/2015/008630	N/A	N/A	N/A	Examined and objection to patentability issued. Awaiting Applicants response AP201206535	Ending AP201306665D0

[16] The US Orange Book lists the patents as submitted by the holder of the authorization in line with Federal Drug Administration (FDA) Form 3542. This includes formulation/composition patents; use patents for a particular approved indication or method of using the product; and certain other patents, FDA. Orange Book, 34th Edition 2014.

	Patent 21	Patent 22	Patent 23	Patent 24	Patent 25	Patent 26	Patent 27
Argentina (AR)	Pending AR088580A1	Pending AR20140100352	N/A	N/A	N/A	Pending AR80819A1	N/A
Australia (AU)	Pending AU2012332827A1	Pending AU2015202842	N/A	N/A	N/A	Pending AU2011235044A1	Granted AU2011282241B2
Brazil (BR)	N/A	Pending BR1120140119384	N/A	N/A	N/A	N/A	N/A
Canada (CA)	Pending CA2853495A1	Pending CA2852867	N/A	N/A	N/A	Pending CA2794671A1	Pending CA2804375A1
Chile (CL)	No application identified	Pending[8] CL2164-2015	No application identified	No application identified	No application identified	Abandoned for lack of payment CL2011000718	Pending CL2013000076A1
China (CN)	Pending CN104244947A	Pending CN104144682A Pending[8] CN201610111865.4	N/A	N/A	N/A	Pending CN102906102A Pending CN104017020A	Pending CN103052646A
China, Hong Kong SAR (HK)	N/A	Not filed[7]	N/A	N/A	N/A	Granted HK1181775A0	Pending HK1182394A0
Colombia (CO)	N/A	Pending CO15203177	N/A	N/A	N/A	Rejected CO6630166A2	Rejected CO6680607A2
Costa Rica (CR)	N/A	Pending[8] CR2015-0453	N/A	N/A	N/A	Pending CR20120534A	Pending CR20130063A
Ecuador (EC)	N/A	Pending[8] SP-2015-37311	N/A	N/A	N/A	Pending[8] SP-12-12283	Pending ECSP13012451
Egypt (EG)	Not filed	Pending EGPCT790/2014	N/A	N/A	N/A	Pending[8] EG1671/2012	N/A

	Patent 21	Patent 22	Patent 23	Patent 24	Patent 25	Patent 26	Patent 27
Ethiopia (ET)	N/A	Not filed[7]	N/A	N/A	N/A	N/A	N/A
EAPO[3] (EA)	N/A	Pending EA201490806	N/A	N/A	N/A	Pending EA201290988A1	Pending EA201390133A1
EPO[4] (EP)	Closed EP2776024A1	Pending EP14704502.5	N/A	N/A	N/A	Granted EP2552931B1	Granted EP2596004B1 Pending EP2805960A1
GCC[5]	Pending GC2012-22601	Pending GC2014-26346	N/A	N/A	N/A	No application identified	No application identified
Georgia (GE)	No application identified	Not filed[7]	N/A	N/A	N/A	No application identified	No application identified
India (IN)	N/A	Pending 3953/DELNP/2014	N/A	N/A	N/A	Pending 9170/CHENP/2012	N/A
Indonesia (ID)	N/A	Pending[8] IDP00201504713	N/A	N/A	N/A	Pending[8] W00201204457	N/A
Iran (Islamic Republic of) (IR)	N/A	Not filed[7]	N/A	N/A	N/A	N/A	N/A
Israel (IL)	N/A	Pending IL233419	N/A	N/A	N/A	Pending IL222174	Pending IL224045
Japan (JP)	Pending JP2014532657A	Pending JP2015508418	N/A	N/A	N/A	Pending JP2013527145A	Pending JP2013537527A
Jordan (JO)	N/A	Not filed[7]	N/A	N/A	N/A	N/A	N/A
Malaysia (MY)	N/A	Pending[8] MY2015001926	N/A	N/A	N/A	N/A	N/A
Mexico (MX)	N/A	Pending MX2014005955	N/A	N/A	N/A	Pending MX2012011324A	Pending MX2013000656A

	Patent 21	Patent 22	Patent 23	Patent 24	Patent 25	Patent 26	Patent 27
Morocco (MA)[9]	Not filed	Not filed	Not filed	Not filed	Not filed	Not filed	Granted MA34471B1
New Zealand (NZ)	N/A	Pending NZ625087	N/A	N/A	N/A	Pending[8] NZ603239	Granted NZ606141
Nigeria (NG)	N/A	Not filed[7]	N/A	N/A	N/A	N/A	N/A
OAPI[6]	No application identified	Pending[8] 1201500300	N/A	N/A	N/A	Granted OA16115	Granted 16292
Pakistan (PK)	No application identified	Pending PK20140054	N/A	N/A	N/A	Pending[8] PK231/2011	No application identified
Peru (PE)	N/A	Pending[8] PE001594-2015/DIN	N/A	N/A	N/A	Pending PE20130151A1	Pending PE20130807A1
Philippines (PH)	No application identified	Pending[8] PH1-2015-501710	N/A	N/A	N/A	No application identified	Pending PH2013500033
Republic of Korea (KR)	N/A	Pending KR20140119012A	N/A	N/A	N/A	Pending KR20130064064A	Pending KR2013130690A
Russian Federation (RU)	N/A	Not filed[7]	N/A	N/A	N/A	N/A	N/A
Singapore (SG)	N/A	Pending SG11201503021X	N/A	N/A	N/A	Pending SG184323A1	Pending SG186831A1
South Africa (ZA)	N/A	Pending[8] ZA2015/05718	N/A	N/A	N/A	Granted ZA201207800	Granted ZA201300135A
Tunisia (TN)	No application identified	Not filed	N/A	N/A	N/A	No application identified	No application identified
Thailand (TH)	N/A	Pending[8] TH1501004314	N/A	N/A	N/A	Pending TH1201005229	N/A
Ukraine (UA)	N/A	Pending[8] UAa201508402	N/A	N/A	N/A	Pending[8] UA201212443	Pending UA201301999A
United States (US)	Pending US2013109647A1	Pending[8] US2016120892A1	Pending US2014343008A	Pending US2015064253A	Pending US2015175646A	Granted US8859756B2	Granted US9090642B2

	Patent 21	Patent 22	Patent 23	Patent 24	Patent 25	Patent 26	Patent 27
Uruguay (UY)	Pending UY34420A	Pending UY35299	N/A	Pending UY35300	Pending UY35917	Pending[8] UY33310	N/A
VietNam (VN)	N/A	Pending[8] VN1-2015-02805	N/A	N/A	N/A	Pending VN32717A	Pending VN33756A

[1] If granted and not subject to patent term extension.

[2] **The African Regional Intellectual Property Organization (ARIPO) includes the following countries:** Botswana, Ghana, Gambia, Kenya, Liberia, Lesotho, Malawi, Mozambique, Namibia, Sudan, Sierra Leone, Swaziland, the United Republic of Tanzania, Uganda, Zambia and Zimbabwe.

[3] **The Eurasian Patent Organization (EAPO) includes the following countries:** Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Russian Federation, Tajikistan and Turkmenistan.

[4] **The European Patent Office (EPO) includes the following countries:** Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Luxemburg, Latvia, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Romania, San Marino, Serbia, Slovenia, Slovakia, Spain, Sweden, Switzerland, The former Yugoslav Republic of Macedonia, Turkey and the United Kingdom.

[5] **The Patent Office of the Cooperation Council for the Arab States of the Gulf** (**Gulf Cooperation Council - GCC) includes the following countries**: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and United Arab Emirates.

[6] **The African Intellectual Property Organization (OAPI) includes the following countries:** Benin, Burkina Faso, Cameroon, Central African Republic, Chad, The Congo, Equatorial Guinea, Gabon, Guinea, Guinea Bissau, Côte d'Ivoire, Mali, Mauritania, Niger, Senegal and Togo.

[7] No family member for this patent is listed in the matching Form 3 of the respective patent filling in India. Please see the methodology section for further information

[8] Information stems from the matching Form 3 of the respective patent filling in India. Please see the methodology section for further information.

[9] No patent or patent application listed in the Gilead draft licence agreement: (http://www.gilead.com/responsibility/developing-world-access/access%20partnerships, June 2016.)

GLOSSARY

INTERFERENCE PROCEEDING: An interference proceeding is a proceeding to determine the priority issues of multiple patent applications. Based on the (previous) first-to-invent system of the United States, a party which has failed to file a patent application on time is allowed to challenge the inventorship of another party which has a granted or pending patent.

N/A: N/A indicates that no information could be retrieved for the relevant patents in the databases that were used. This can either mean that the information in the databases is not up-to-date or complete, or that the patents were not filed in these jurisdictions. While the latter may often be the case, certainty can only be achieved by checking the information with the local patent office. This can be done by using the patent numbers provided in this report, as they allow retrieval of information through national patent offices and/or national patent registries.

NOTICE OF ALLOWANCE: During a USTPO examination, if it appears to the examiner that the applicant is entitled to a patent under the law, a notice of allowance is sent to the applicant. The notice of allowance specifies a sum constituting the issue fee which must be paid within a given time from the date of mailing of the notice of allowance to avoid abandonment of the application.

PATENT FAMILY MEMBER: All patent publications that relate to the same basic patent (that is, invention) are members of this patent family. In the present study patent families are based on the Derwent World Patent Index (DWPI).

PENDING or GRANTED: Indicates a patent's legal status.

PRIORITY NO: Earliest application number.

SPONSOR: The term "Sponsor" refers to the entities that are developing the medicines and are holding or filing for market authorization. Note that a Sponsor is not necessarily the patent assignee or applicant.

THE WIPO INTERNATIONAL SEARCH REPORT (ISR): After an applicant files a PCT application with WIPO, a search is conducted by an authorised International Searching Authority (ISA) to find the most relevant prior art documents regarding the claimed subject matter. The search results in an International Search Report (ISR), together with a written opinion regarding patentability.