PATENT SITUATION OF KEY PRODUCTS FOR TREATMENT OF HEPATITIS C

LEDIPASVIR

WORKING PAPER

Updated and revised version

June 2016

This report was prepared for the WHO Department of Essential Medicines and Health Products by Thomson Reuters and Pharmathen. 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/2016.04

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 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

[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.

[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.

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.

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 9313/DELNP/2011Form 3 dated 10 February 2016.

Patent 2, Indian Patent number 2644/MUMNP/2014 Form 3 dated 2 June 2016.

Patent 3, Indian Patent number 2496/MUMNP/2014 Form 3 dated 25 April 2016

Patent 6, Indian Patent number 3953/DELNP/2014 Form 3 dated 12 April 2016

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.)

LEDIPASVIR

Ledipasvir (formerly GS-5885) is a HCV treatment developed by Gilead Sciences Inc. (hereby referred to as the 'Sponsor'). Ledipasvir is an inhibitor of the HCV NS5A protein. It is marketed by Gilead as a fixed-dose combination with sofosbuvir. The application was approved by the United States Food and Drug Administration (FDA) in October 2014[7] and by the European Medicines Agency in November 2014. The updated WHO treatment guideline[8] from April 2016 recommends the use of ledipasvir in combination with sofosbuvir or ribavirin, as the preferred method of treatment for persons with HCV genotype 1, 4, 5 and 6 with or without cirrhosis.

CHEMICAL NAME

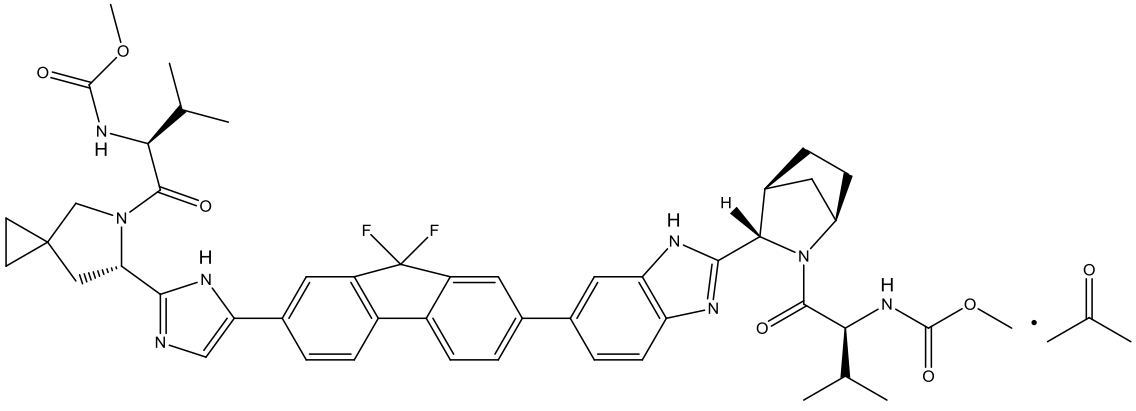
Systematic (IUPAC) name:

Methyl*N*-[(2*S*)-1-[(6*S*)-6-[5-[9,9-Difluoro-7-[2-[(1*S*,2*S*,4*R*)-3-[(2*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl]-3-azabicyclo[2.2.1]heptan-2-yl]-3*H*-benzimidazol-5-yl]fluoren-2-yl]-1*H*-imidazol-2-yl]-5-azaspiro[2.4]heptan-5-yl]-3-methyl-1-oxobutan-2-yl]carbamate acetone solvate

MOLECULAR FORMULA

$C_{49}H_{54}F_2N_8O_6 \cdot C_3H_6O$

MOLECULAR STRUCTURE



[7] (http://www.gilead.com/news/press-releases/2014/10/us-food-and-drug-administration-approves-gileads-harvoni-ledipasvirsofosbuvir-the-first-oncedaily-single-tablet-regimen-for-the-treatment-of-genotype-1-chronic-hepatitis-c, May 2016)

[8] 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).

SUMMARY

The ledipasvir Sponsor patent collection contains 7 different patents (patent families). Patent 1 is the primary patent, claiming the base compound. Patents 2, 3, 5, 6 and 7 are secondary patents, claiming formulation, method of use, and production processes. All patents were filed and remain in the name of the Sponsor entity, Gilead Sciences.

Patent 1 is the primary patent, claiming the base compound through a Markush claim along with various substituents. Where granted, this patent can prevent competitors from making ledipasvir. It is listed in the license agreement (see LICENCE AGREEMENTS) and the US Orange Book.

Patents 2 claims new crystalline solvate forms of ledipasvir for use in HCV treatment.

Patent 3 claims processes to make ledipasvir. Thus, if granted, the patent will require competitors to design around it and use other production processes. The chemical product itself is not protected.

Patent 5 claims combinations of different HCV drugs with ledipasvir, including sofosbuvir, and their formulations.

Patent 6 claims a pharmaceutical composition comprising ledipasvir in substantially amorphous form and sofosbuvir in substantially crystalline form.

Patent 7 is a formulation patent that claims amorphous solid dispersion formulations of ledipasvir with improved pharmacokinetic properties.

Note: Additional relevant combination patents

The searches revealed two patents that are relevant across all seven patent reports. Patent applications WO2013059630A1 and WO2013059638A1 by Abbvie inter alia claim the use of combinations of unnamed direct-acting antiviral agents (DAAs) for treating HCV, where the treatment is interferon- and ribavirin-free, and lasts 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.

LICENSE AGREEMENTS

Gilead Sciences signed licensing agreements with 11 Indian generic manufacturers. Under these agreements, the 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.[9] The license agreement contains information about sofosbuvir and

[9] Gilead, Chronic Hepatitis C Treatment Expansion, Factsheet: August 2015 (http://www.gilead.com/~/media/Files/pdfs/other/HCVGenericAgreementFactSheet.pdf, May 2016)

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.[10]

LEDIPASVIR PATENT SITUATION

PATENT 1: ANTIVIRAL COMPOUNDS

Patent application WO2010132601A1 is a primary patent disclosing the base compound of ledipasvir. The application claims a general structural formula, or Markush structure of new amide compounds for use in HCV-associated conditions. As the patent uses a Markush structure of antiviral agents, the claim is very broad. Thus this patent, if granted, serves as a blocking patent preventing competitors from making the product.

PATENT 2: SOLID FORMS OF AN ANTIVIRAL COMPOUND

Patent application WO2013184698A1 is a product and process patent, claiming new crystalline solvate forms of ledipasvir for use in HCV-infected individuals. The application also claims processes to manufacture amorphous and crystalline forms with specific X-ray diffraction peaks, along with the compositions and combinations comprising these forms.

Equivalent US8969588 is granted and protects crystalline ledipasvir acetone solvates. Crystalline ledipasvir monoacetonate is used in the reference product and is spray dried to form the amorphous dispersion used in the final formulation.

PATENT 3: SYNTHESIS OF ANTIVIRAL COMPOUND

Patent application WO2013184702A1 is a process patent, claiming processes for the preparation of ledipasvir. The disclosure also claims synthetic intermediate compounds of ledipasvir. The claims are moderately narrow, covering crystalline and amorphous forms of ledipasvir with specific X-ray diffraction peaks.

PATENT 4: COMBINATIONS FOR TREATING HCV

Patent application WO2012087596A1 is a formulation patent, claiming various formulations comprising a combination of ledipasvir with GS-9256, or tegobuvir. The application also claims methods of treatment with the said combinations for reducing the viral load in HCV-infected persons. The patent does not claim combinations of ledipasvir with sofosbuvir or daclatasvir. Currently ledipasvir is only sold in a combination tablet with sofosbuvir. Therefore, this patent is not relevant to the generic launch date of the combination of ledipasvir/sofosbuvir.

As per the WIPO ISR, the application is novel but not inventive in comparison to the closest prior art retrieved during the search. The combinations claimed in the instant

---

[10] (http://www.gilead.com/responsibility/developing-world-access/access%20partnerships, June 2016.)

application are not disclosed in the prior art, and thus are novel combinations. However, the prior art discloses various combinations; therefore, the invention should focus on new combinations with fewer side effects. Additionally, there is no experimental data to support synergy resulting from double, triple, or quadruple combinations. Thus, according to the ISR, the present invention cannot be regarded as inventive.

PATENT 5: METHODS FOR TREATING HCV

Patent application WO2013040492A2 is a formulation and method of use patent, claiming various combination compositions and a method of use for the combinations in HCV treatment. The combinations include sofosbuvir, PSI-7851 and ledipasvir. As the application claims the Markush structure of a group of compounds, the claim scope is broad. Currently ledipasvir is only sold in a combination tablet with sofosbuvir. Therefore, this patent is currently not relevant to the generic launch date of ledipasvir as an individual drug.

As per the WIPO ISR, the application is novel but lacks the inventive step in view of prior art. The invention lacks an inventive step as it would be obvious to a person skilled in the art to combine the diastereoisomer of the present invention, disclosed in the prior art, with other antiviral agents, thereby creating an alternative HCV therapy.

This patent is listed in the sofosbuvir report as Patent 7.

PATENT 6: COMBINATION FORMULATION OF TWO ANTIVIRAL COMPOUNDS

Patent application WO2014120981A1 applies to a pharmaceutical composition comprising ledipasvir in substantially amorphous form and sofosbuvir in substantially crystalline form. Sofosbuvir is present as a crystalline form in the combination product with ledipasvir. Therefore, this patent is relevant to the generic launch date of ledipasvir when sold in a combination tablet with sofosbuvir.

In the WIPO International Search Report the authority took the opinion that the combination of amorphous ledipasvir and crystalline sofosbuvir lacks any surprising technical effect such that the skilled individual could provide the claimed combination through routine design. Hence, according to the WIPO ISR no inventive step can be acknowledged.

This patent is listed in the sofosbuvir report as Patent 22.

PATENT 7: METHODS FOR TREATING HCV

Patent application WO2014120982A1 is a formulation patent that claims amorphous solid dispersion formulations of ledipasvir with improved pharmacokinetic properties.

In the WIPO International Search Report the authority took the opinion that no inventive step can be acknowledged since the claimed amorphous solid dispersion of ledipasvir has not shown any substantiated exceptional properties.

ANNEX – LEDIPASVIR PATENT SITUATION

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Subject Matter	Patent application WO2010132601 covers the base compound of ledipasvir.	Patent application WO2013184698 covers the new crystalline di-/mono-acetone solvate forms of ledipasvir useful for treating HCV infection.	Patent application WO2013184702 covers processes for the preparation of ledipasvir.	Patent application WO2012087596 covers various formulations comprising a combination of ledipasvir, with GS-9256, or tegobuvir or with other compounds.	Patent application WO2013040492 covers a composition and a method of treatment using a sofosbuvir, PSI-7851, or ledipasvir (and/or their respective salts and excipients). This patent is listed as Patent 7 in the sofosbuvir report.	Patent application WO2014120981 covers formulation comprising ledipasvir in substantially amorphous form and sofosbuvir in substantially crystalline form. This patent is listed in the sofosbuvir report as Patent 22.	Patent application WO2014120982 covers a solid dispersion wherein ledipasvir in amorphous form is dispersed in a polymer matrix.
Applicant	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.
Int'l Patent Publication Number	WO2010132601	WO2013184698	WO2013184702	WO2012087596	WO2013040492	WO2014120981	WO2014120982
Priority Number	US2009177972P	US2012655934P	US2012655935P	US2010425194P	US2011535885P	US201361759320P US201361772292P US201361828899P US201361870729P US201361897793P US201361907332P	US201361759310P US201361870721P

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Expected expiry[1]	11 May 2030	3 Jun 2033	3 Jun 2033	7 Dec 2031	13 Sep 2032	30 Jan 2034	30 Jan 2034
Listed in US Orange Book[11]	Yes US8088368 US8273341 US8822430 US8841278	No	No	No	No	No	No
PATENT STATUS							
ARIPO (AP)[2]	Pending grant AP201105987D0	Not filed[7]	Not filed[7]	N/A	Pending AP2014/007575	Pending[8] AP/P/2015/008630	N/A
Argentina (AR)	Pending AR76765A1	Pending[8] AR91259	Not filed[7]	Granted AR84237A1	Not filed[9]	Pending AR20140100352	N/A

[11] 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 product use; and certain other patents, FDA. Orange Book, 36th Edition 2016.

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Australia (AU)	Granted AU2010249043B2 Granted AU2013202666B2 Granted AU2014203349B2 Pending AU2015200984A1	Pending AU2013271768A1	Pending AU2013271772A1	Pending AU2011349844A1	Pending AU2012308295A	Pending AU2015202842B2	N/A
Brazil (BR)	Pending[8] BRPI1010795-9 Pending[8] BR122014012810-0 Pending[8] BR122014013631-5	Pending[8] BR1120140304009	Pending[8] BR1120140303657	N/A	Not filed[9]	Pending BR1120140119384	N/A
Canada (CA)	Granted CA2761258C Pending[8] CA2886322	Pending CA2875507A1	Pending CA2875508A1	Pending CA2822037A1	Pending CA2840242A1	Pending CA2852867A1	N/A
Chile (CL)	Pending[8] 2825-2011	Not filed[7]	Not filed[7]	No application identified	Pending CL2014000630A1	Pending CL2015002164	No application identified

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
China (CN)	Granted CN102596936B Pending CN103977406A Pending CN104230900A Pending CN104211689A Pending CN104211713A Pending CN104016971A	Pending CN104379584A Pending[8] CN105524050	Pending CN104520293A	N/A	Pending CN104244945A	Pending CN104144682A Pending[8] CN201610111865.4	N/A
China, Hong Kong SAR (HK)	Pending HK1162518A0 Pending[8] HK15108271.6	Pending[8] HK15105959.1	Pending[8] HK15109928.1	N/A	Not filed[9]	Not filed[7]	N/A
Colombia (CO)	Granted[8] CO5548	Not filed[7]	Not filed[7]	N/A	Granted CO6930366A2	Pending[8] CO15203177	N/A
Costa Rica (CR)	Not filed[7]	Not filed[7]	Not filed[7]	N/A	Pending CR20140177A	Pending[8] 2015-0453	N/A
Ecuador (EC)	Pending EC2011SP011517A	Not filed[7]	Not filed[7]	N/A	Not filed[9]	Pending[8] SP-2015-37311	N/A
Egypt (EG)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed	Pending EG2014030392	Pending EGPCT790/2014	N/A
Ethiopia (ET)	Not filed[7]	Not filed[7]	Not filed[7]	N/A	Not filed[9]	Not filed[7]	N/A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
EAPO (EA)[3]	Granted EA021974B1 Pending EA201490854A1 Pending EA201590073A1	Not filed[7]	Not filed[7]	N/A	Pending EA201490588A1	Pending EA201490806A1	N/A
EPO (EP)[4]	Granted EP2430014B1 Pending[8] EP14175539.7 Pending[8] EP15180635.3	Pending EP13729569A1	Pending EP2855454A1	Pending EP2654900A1	Pending EP2709613A2	Pending EP14704502.5	N/A
GCC[5]	Not filed[7]	Pending[8] GC2013/24562	Not filed[7]	N/A	Not filed[9]	Pending GC2014/26346	N/A
Georgia (GE)	Not filed[7]	Not filed[7]	Not filed[7]	N/A	Not filed[9]	Not filed[7]	N/A
India (IN)	Pending IN201109313P1 9313/DELNP/2011 Pending[8] 4889/DELNP/2014	Pending 2644/MUMNP/2014	Pending 2496/MUMNP/2014	N/A	Pending 2956/DELNP/2014	Pending 3953/DELNP/2014	N/A
Indonesia (ID)	Pending W00201104295 Pending[8] P00201502494	Not filed[7]	Not filed[7]	N/A	Pending ID2014/02133	Not filed[7]	N/A
Iran (Islamic Republic of) (IR)	Not filed[7]	Not filed[7]	Not filed[7]	N/A	Not filed[9]	Not filed[7]	N/A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Israel (IL)	Granted[8] IL233044 Pending IL216254D0 Pending[8] IL233042 Pending[8] IL233678 Pending[8] IL233679	Pending IL236004A	Pending IL235941A	N/A	Not filed[9]	Pending IL233419	N/A
Japan (JP)	Granted JP5582662B2 Granted JP5744283B2 Granted JP5745727B2 Pending[8] JP2015-91474	Pending JP2015516143	Pending JP2015518892	Granted JP2014505045B2	Pending JP2014526516A	Pending JP2015508418A	N/A
Jordan (JO)	Not filed[7]	Not filed[7]	Not filed[7]	N/A	Not filed[9]	Not filed[7]	N/A
Malaysia (MY)	Not filed[7]	Not filed[7]	Not filed[7]	N/A	Not filed[9]	Pending MYPI2015001926	N/A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Mexico (MX)	Granted[8] MX2011012058A Pending[8] MX/a/2014/005805 Pending[8] MX/a/2014/005933 Pending[8] MX/a/2014/006862	Pending[8] MX/a/2014/014563	Pending[8] MX/a/2014/014569	N/A	Pending MX2014003145A	Pending MX2014005955	N/A
Morocco (MA)	Not filed	Not filed	Not filed	Not filed	Pending 36906	Not filed	Not filed
New Zealand (NZ)	Granted NZ596444 Granted NZ619205 Pending[8] NZ706236	Not filed[7]	Not filed[7]	Granted NZ613370	Not filed[9]	Pending NZ625087	N/A
Nigeria (NG)	Not filed[7]	Not filed[7]	Not filed[7]	N/A	Not filed[9]	Not filed[7]	N/A
OAPI[6]	Granted 15651	Not filed[7]	Not filed[7]	N/A	Not filed[9]	Pending[8] 1201500300	N/A
Pakistan (PK)	Pending PK415/2010	Pending[8] PK2013/357	Not filed[7]	N/A	Pending PK880/2011	Pending PK0054/2014	Pending PK0052/82014

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Peru (PE)	Granted PE7305 Pending[8] 1982-2014/DIN Pending PE02022015 Status: N/A PE20120509A1	Not filed[7]	Not filed[7]	N/A	Pending PE10562014A1	Pending[8] 001594-2015/DIN	N/A
Philippines (PH)	Not filed[7]	Not filed[7]	Not filed[7]	N/A	Pending PH12014500557	Pending[8] PH1-2015-501710	N/A
Republic of Korea (KR)	Granted KR101546119B1 Granted KR101503752B1 Pending[8] KR1020147016501	Pending KR20150028971	Pending KR20150027158	N/A	Pending KR20140096029A	Pending KR20140119012A	N/A
Russian Federation (RU)	Not filed[7]	Pending[8] RU201408661	Pending[8] RU2014150435	N/A	Not filed[9]	Not filed[7]	N/A
Singapore (SG)	Granted SG176015A1 Pending SG10201402280Q	Pending SG11201408013W	Pending SG201408011S	N/A	Pending SG11201400664W	Pending SG11201503021X	N/A
South Africa (ZA)	Granted ZA201108436A	Not filed[7]	Not filed[7]	N/A	Pending ZA201402534	Pending ZA2015/05718	N/A
Thailand (TH)	Pending TH1101003118	Not filed[7]	Not filed[7]	N/A	Not filed[9]	Pending[8] TH1501004314	N/A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Tunisia (TN)	Not filed[7]	Not filed[7]	Not filed[7]	N/A	Not filed[9]	Not filed[7]	N/A
Ukraine (UA)	Granted[8] UA108610 Pending[8] UAa201413049	Not filed[7]	Not filed[7]	N/A	Not filed[9]	Pending[8] UAa201508402	N/A
The United States (US)	Granted US8088368B2 Granted US8273341B2 Granted US8575118B2 Granted US8669234B2 Granted US8822430B2 Granted US8841278B2 Pending US2014249074A1	Granted US8969588B2 Granted US9139570B2 Pending[8] US2015-0344488	Granted US9056860B2 Pending US2015232453A1	Pending US20130273005A1 Pending US2015141353A1	Pending US20130243726A1	Pending US14/868062	Pending US2014212487A
Uruguay (UY)	Pending[8] UY32629A	Pending UY34844A	Not filed[7]	Status: N/A UY33797A	Not filed[9]	Pending UY35299	Pending UY35298
Vietnam (VN)	Status: N/A VN32065A Pending 1-2011-03386[8]	Not filed[7]	Not filed[7]	N/A	Status: N/A VN1-2014-01180	Pending[8] VN1-2015-02805	N/A

[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.