PATENT SITUATION OF KEY PRODUCTS
FOR TREATMENT OF HEPATITIS C

LEDIPASVIR

WORKING PAPER

Prepared for the
World Health Organization (WHO) by
Thomson Reuters

August 2014
INTRODUCTION

The World Health Organization’s (WHO) 2014 Guidelines for the screening, care and treatment of persons with hepatitis C infection state that worldwide more than 185 million people are infected with the hepatitis C virus (HCV). Of these people, 350 000 to 500 000 die each year. An estimated one third of those who become chronically infected develop liver cirrhosis or hepatocellular carcinoma. HCV infection can be cured, but most people infected with the virus are unaware of their infection and so do not seek timely treatment. Furthermore, treatment remains unavailable for many who have been diagnosed. Several medicines are available to treat HCV, including pegylated interferon and ribavirin but treatment duration is long, involves weekly injections, and side effects are considerable. With the development of new direct-acting antivirals, the treatment landscape is rapidly changing. These new antivirals are expected to reach cure rates of more than 90% in persons with HCV infection across different genotypes, with fewer side effects and a shorter duration of treatment.¹ Two new compounds, simeprevir and sofosbuvir, have recently been approved in the United States and Europe and are recommended by the new WHO treatment guidelines. Many others are in various stages of development.

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, there is no such thing as a worldwide patent. 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 build a patent family. In the present study, patent families are based on the Derwent World Patent Index (DWPI).²

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.
The WHO Secretariat has mandated Thomson Reuters to carry out an analysis of the patent situation of seven new hepatitis treatments:

### International nonproprietary name | Sponsor
---|---
ABT-450 | AbbVie Inc.
daclatasvir | Bristol-Myers Squibb Company
dasabuvir | AbbVie Inc.
edipasvir | Gilead Sciences, Inc.
omitasvir | AbbVie Inc.
simeprevir | Janssen Pharmaceutical Companies of Johnson & Johnson
sofosbuvir | Gilead Sciences Inc.

The draft reports were shared with the respective sponsor companies before publication.

**OBJECTIVE**

The objective of the patent working papers was to:

1. identify the most relevant patents with respect to the medicines
2. identify in which countries these patents have been filed and granted

One will often find numerous patents relating to one medicine. These patents will cover different aspects and innovations around the same product. Not all however are equally relevant, as many will cover variations or production processes but would not prevent somebody else to produce the medicine, e.g. by using a different process.

These patent working papers identify the most relevant patents for each medicine. The patents are categorized in primary and secondary patents. The patent publication covering the base compound is considered the “primary patent” and patents on specific pharmaceutical formulations, method of use, product derivatives, and processes are considered “secondary patents”. Secondary patents are generally easier to circumvent (“to invent around”), meaning to make the medicine without infringing the secondary patents. For example, a patent on the aqueous solution would not prevent competitors to produce a tablet, and a combination patent would not prevent competitors to produce the combined products separately.

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<sup>3</sup> Initially two additional candidate medicines were included in the project (faldaprevir and deleobuvir), but development of these has been discontinued and 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/](http://www.who.int/phi/publications/category/en/)).

**HOW TO USE THIS WORKING PAPER?**

The working papers identify the relevant patents and provide 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 assess their possibilities for rendering the new treatments more affordable. The data is also essential to allow WHO to fulfil its mandate under Resolution WHA67.6 which requests WHO to assist Member States in ensuring equitable access to quality, effective, affordable and safe HCV treatments. Assisting countries in accessing the new hepatitis 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 to negotiate transfer of technology or license agreements, research ways to enhance or improve the current drug or treatment modality, and facilitate the development of generics.

Although being public domain information, patent information in many countries is difficult to retrieve, as is 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 in this working paper. 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. 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

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 a certain expertise to make full use of this study.

This study sets out relevant patents and patent applications in the countries included in this study as of March 2014 (see the Annex). 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 not 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 the many additional patents and application filed by various entities that may also relate to the compound.

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 WHO nor Thomson Reuters 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 provide a full assessment of the patent situation in a given country.

METHODOLOGY

Relevant patents and patent applications were identified by searching patent and non-patent databases, comprising Thomson Innovation, Newport, Thomson Pharma, Questel, Scientific Technology Network (STN) and Cortellis. Additional bibliographic details were collected from publicly available databases, comprising the United States Patent and Trademark Office (USPTO), Espacenet and relevant national patent office websites.
Legal status and oppositions, if any, were retrieved from respective patent offices (to the extent that information was available). Patent Offices in Brazil, African Regional Intellectual Property Organization (ARIPO), India, Russian Federation, and Ukraine have been directly contacted.

Litigation data were retrieved from WestLaw, PACER, and pharma-related publicly available sources. The study differentiates between patents held by Sponsors and non-Sponsors. Sponsors are the entities developing the medicines and are filing for or already hold market authorization. Non-Sponsor entities include other pharmaceutical companies, public research institutes and other applicants. The patent position of the Sponsors is assessed. Patents of non-Sponsor entities are included in the complete data collection in form of an Excel file that can be made available on demand. Please send any requests to: phidepartment@who.int.

Wherever available, the application submitted under the WIPO PCT is used as a primary source, both because it is generally the favoured priority application for the pharmaceutical industry, and also because the WIPO International Search Report (ISR) include examiner references that are coded for relevance and for which initial rejections (an indicator of possible novelty issues) can be identified.

Thomson Reuters´ technical experts analysed the claims and determined whether the scope of each of the claims are broad or narrow. 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 respective Annexes.

**GEOGRAPHIC SCOPE**

Family members of the Sponsor patent collection have been searched for in the following jurisdictions. It would have been beyond the scope of this study to include patent information of all WHO Member States, thus a 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 Viet Nam (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.\(^5\)

Information 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/](http://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/](http://www.who.int/topics/hepatitis/en/)

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**LEDIPASVIR**

Ledipasvir (formerly GS-5885) is an investigational drug for the treatment of HCV that is being developed by Gilead Sciences Inc. (hereby referred to as the ‘Sponsor’).

Ledipasvir is an inhibitor of the HCV NS5A protein and is being tested in interferon-free regimens with other direct-acting antiviral agents for hepatitis C. In February 2014, Gilead applied for market authorization with the United States Food and Drug Administration (FDA) and the European Medicines Agency for a once-daily fixed-dose combination of ledipasvir (90 mg) and the nucleotide analog polymerase inhibitor sofosbuvir (400 mg), for the treatment of chronic HCV genotype 1 infection in adults. Expected treatment duration would be eight or twelve weeks depending on prior treatment history and whether patients have already developed cirrhosis. The FDA has granted the combination priority review status and considers it a Breakthrough Therapy that may offer major advances in treatment over existing treatment options. The FDA is expected to make a decision on the application in October 2014.  

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**CHEMICAL NAME**

Systematic (IUPAC) name.

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

**MOLECULAR FORMULA**

C_{49}H_{54}F_{2}N_{8}O_{6}

**MOLECULAR STRUCTURE**

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SUMMARY

The search revealed patents filed with respect to ledipasvir by the Sponsor as well as a non-Sponsor.

The ledipasvir Sponsor patent collection comprises 5 different patents (patent families) with 47 family members published in 23 jurisdictions. The majority of these patent applications are still pending in the respective patent offices (see Patents 1 to 5 in the Annex).

**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.

**Patents 2 and 3** claim processes to make ledipasvir and thus if granted will require competitors to design around these patents and use other production processes. The chemical product itself is not protected.

**Patents 4 and 5** claim combinations of different HCV drugs with ledipasvir, and their formulations.

There is competition in the field by AbbVie, Inc., which filed formulation patents.

**Note:** The search also revealed two patents that are relevant for all seven reports. Patent applications WO2013059630A1 and WO2013059638A1 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 the treatment lasts between 8-12 weeks. The description and the dataset for these two patents can be found in the Working Paper on ombitasvir (Patents No 3 and 4). These patents are in litigation. Detailed information can be found in the Working Paper on sofosbuvir under Patent No 2.

LICENSE AGREEMENTS

In September 2014, Gilead Sciences has signed licensing agreements with seven Indian generic manufacturers (Cadila Healthcare Ltd., Cipla Ltd., Hetero Labs Ltd., Mylan Laboratories Ltd., Ranbaxy Laboratories Ltd., Sequent Scientific Ltd., Strides Arcolab Ltd.) who under these agreements can produce and sell generic sofosbuvir and the combination of ledipasvir/sofosbuvir in 91 countries. They can also combine sofosbuvir with other hepatitis treatments.⁸ The license agreements contain information about sofosbuvir patents.

A copy of the draft agreement is publicly available.⁹

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⁹ http://keionline.org/sites/default/files/GILD_Sof_License_Agmt_(FINAL).pdf
LEDIPASVIR PATENT SITUATION

SPONSOR PATENTS

Patent searches revealed five Sponsor patents (referred to as Patent 1 to 5 in the following analysis section and in the Annex).

Patent 1 is the primary patent, claiming the base compound. Patents 2 to 5 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

Patent application WO2010132601A1 (primary patent) discloses the base compound of ledipasvir. The application claims a general structural formula (Markush) of new amide compounds useful for treating disorders associated with HCV. This patent, if granted, serves as a blocking patent preventing competitors from making the product. The claims are very broad, using a Markush structure of antiviral agents.

As per the WIPO ISR, claims 1-19 are novel and inventive. However, according to the ISR, all remaining claims (claims 20 to 173), covering a large number of compounds, lack both novelty and inventive step, due to lack of support from the patent specification and in the light of prior art.

Prosecution at the USPTO

Three patents have been granted in the United States: US8088368B2, claiming the base compound by general structural formula; US8273341B2 (a division of US8088368B2), claiming a method of inhibiting HCV; and US8575118B2 (a continuation of US8273341B2 and a division of US8088368B2), claiming specific amide compounds not covered in the other two related patents. The examination report of US8088368B2 reveals that the application was allowed after the applicant cancelled and amended claims on Markush substrstents. The examination report of US8273341B2 reveals that the application was allowed after the applicant amended a claim 'A method of treating HCV' to 'A method of inhibiting HCV'. The examination report of US8575118B2 reveals that the application was allowed after the applicant cancelled claims already covered by the related patents, and limited claims to four specific compounds.

Patent 1 has been filed in various jurisdictions:

- The patent has been granted by the ARIPO, in South Africa, and the United States.
- The patent (or a related patent) is pending in Argentina, Australia, Canada, China, as well as China, Hong Kong SAR, the EAPO, the EPO, Israel, India, Japan, New Zealand, Singapore, and Ukraine.
- Legal status is not available for Colombia, Ecuador, Mexico, Peru, Uruguay, and Viet Nam.
Litigation / Opposition on Patent 1


PATENT 2

Patent application WO2013184698A1 is a product and process patent, claiming new crystalline solvate forms of ledipasvir useful for treating a subject suffering from HCV infection. The application also claims processes of manufacture of such amorphous and crystalline forms with specific X-ray diffraction peaks, and compositions and combinations comprising them.

The application has just recently been published and no written opinion on patentability is available at this stage.

As per the available information (details available in the Annex):

- The patent is pending at the EPO and the United States.

There are no litigation or opposition procedures reported.

PATENT 3

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

The application has just recently been published and no written opinion on patentability is available at this stage.

As per the available information (details available in the Annex):

- The patent is pending at the EPO and the United States.

There are no litigation or opposition procedures reported.

PATENT 4

Patent application WO2012087596A1 is a formulation patent, claiming various formulations comprising a combination of ledipasvir with GS-9256, or tegobuvir or with other compounds. The application also claims methods of treatment with the said combinations for reducing viral load in a person infected with HCV.
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 application are not disclosed in the prior art, thus the combinations are novel. However, the prior art discloses various combinations, therefore, the problem to be solved through the invention should be new combinations with fewer side effects. Further, no experimental data of synergism has been provided to support double, triple, or quadruple combinations. Thus, according to the ISR, the instant invention cannot be regarded as inventive.

As per the available information (details available in the Annex):

- The patent has been granted in Argentina.
- The patent is pending in Australia, Canada, the EPO, and the United States.
- Legal status is not available for Japan and Uruguay.

There are no litigation or opposition procedures reported.

**PATENT 5**

Patent application WO2013040492A2 is a formulation and method of use patent, claiming compositions and a method of using the combination for the treatment of HCV. Drug combinations are used, and the compositions include sofosbuvir, PSI-7851 and ledipasvir. Since the application claims a group of compounds of Markush structure, it gives the claims a broad scope.

As per the WIPO ISR the application is novel but lacks the inventive step in light 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 to provide an alternative HCV therapy.

As per the available information (details available in the Annex):

- The patent is pending in Australia, Canada, the EPO, and the United States.

There are no litigation or opposition procedures reported.

This patent is listed in the sofosbuvir report as Patent No. 7

**NON-SPONSOR PATENTS**

There is competition by AbbVie Inc., which has filed two formulation patent applications on ledipasvir.

Patents of non-Sponsor entities are included in the complete data collection in form of an Excel file that can be made available on demand. Please send any requests to: phidepartment@who.int.
# ANNEX – LEDIPASVIR PATENT SITUATION

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## PATENT STATUS

| ARIPO (AP)² | Granted Pub No: AP201105987D0 | N/A | N/A | N/A | N/A |

¹ Expected expiry is based on the priority dates and allows for up to 20 years of protection, which is the typical period for a patent.

² ARIPO (African Regional Intellectual Property Organisation)
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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, Luxembourg, 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.

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: Patent information was not available for this country at the time the patent searches were conducted, in March 2014.

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.

PUB NO: Patent publication number.

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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.