PATENT SITUATION OF KEY PRODUCTS FOR TREATMENT OF HEPATITIS C

SIMEPREVIR

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 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.

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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 situation, in August 2015

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[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.

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 6217/DELNP/2012 Form 3 dated 20 January 2014.

Patent 2, Indian Patent number 1505/MUMNP/2011 Form 3 dated 3 December 2013.

Patent 4, Indian Patent number 1520/MUMNP/2009 Form 3 dated 5 March 2014.

Patent 7, Indian Patent number 3860/DELNP/2006 Form 3 dated 23 July 2013.

Patent 9, Indian Patent number 1610/MUMNP/2009 Form 3 dated 17 December 2013.

Patent 10, Indian Patent number 722/MUMNP/2011 Form 3 dated 13 April 2011.

Patent 12, Indian Patent number 1885/MUMNP/2011 Form 3 dated 17 December 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.)

SIMEPREVIR

Simeprevir (formerly TMC435) is a second-generation HCV NS3/4A serine protease inhibitor marketed under the trade names Olysio, Galexos (in Canada) and Sovriad (in Japan). Simeprevir reaches high sustained virologic response when given in combination with pegylated interferon and ribavirin in patients with HCV genotype 1 infection. Simeprevir is considered a “second-generation compound” as it is a peptidomimetic compound, a small protein-like chain designed to mimic a peptide. It was developed by Medivir and Johnson & Johnson's pharmaceutical division, Janssen Pharmaceuticals Inc. (hereby referred to as the ‘Sponsor’).

The WHO *Guidelines for the screening, care and treatment of persons with hepatitis C infection* recommend simeprevir as an alternative treatment for HCV genotype 1 and 4 with or without cirrhosis in combination with sofosbuvir either with or without ribavirin.

Simeprevir was approved in 2013 for use in the United States, Japan and Canada as a combination treatment for chronic genotype 1 HCV infection. The Committee for Medicinal Products for Human Use of the European Medicines Agency has authorized use of simeprevir in the European Union in a combination treatment for chronic HCV.

On November 5, 2014, the U.S. 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 hepatitis C. The recommended treatment duration of simeprevir with sofosbuvir is 12 weeks for patients without cirrhosis or 24 weeks for patients with cirrhosis.

CHEMICAL NAME

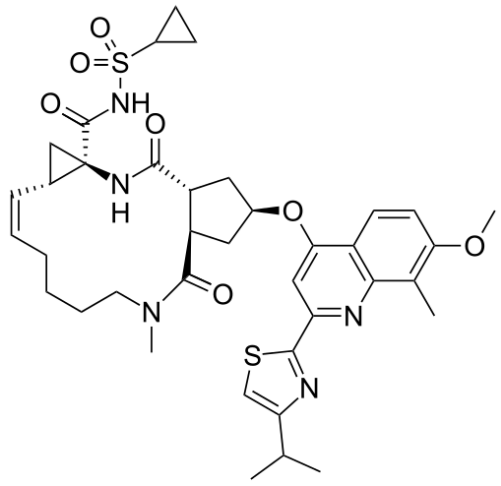
Systematic (IUPAC) name:

(2R,3aR,10Z,11aS,12aR,14aR)-N-(Cyclopropylsulfonyl)-2-{[2-(4-isopropyl-1,3-thiazol-2-yl)-7-methoxy-8-methyl-4-quinolinyl]oxy}-5-methyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14, 14a-tetradecahydrocycl openta[c]cyclopropa[g][1,6]diazacyclotetradecine-12a(1H)-carboxamide

MOLECULAR FORMULA

$C_{38}H_{47}N_5O_7S_2$

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	Process patent
Patent 3	Process patent
Patent 4	Process patent
Patent 5	Process patent
Patent 6	Process patent
Patent 7	Patent 7
Patent 8	Deleted due to no sign of development in the patent application procedure
Patent 9	Patent 9
Patent 10	Patent 10
Patent 11	Deleted due to no sign of development in the patent application procedure
Patent 12	Patent 12
Patent 13	Patent 13
Patent 14	Deleted as considered not/less relevant with respect to generic entry
Patent 15	New patent not contained in the previous report

SUMMARY

The simeprevir Sponsor patent collection comprises 12 different patents (patent families). The majority of these patent applications are still pending in the respective national and regional patent offices (see Annex).

Patent 1 is the primary patent, claiming the base compound. Patent 1 constrains the launch of generic products where granted and enforceable. Patents 2 to 15 are secondary patents, claiming formulation, and product derivatives/processes. All patents were filed and remain in the name of Sponsor entity Janssen Pharmaceuticals, except for patent 9, which was originally filed by Tibotec Pharmaceuticals, now part of Janssen Pharmaceuticals.

Patent filings that may be problematic to the launch of generic patents after expiry of the primary product patent (Patent 1) are 9, 10, and 12.

Patent 1 is the primary patent claiming the base compound through a Markush claim, other specific compounds, and a method of production. Where granted, this patent can serve to prevent competitors from making simeprevir.

Patents 2, 3, 4, 5, and 6 claim processes to make simeprevir as well as intermediate compounds. Thus, if granted, the patents will require competitors to design around these patents and use other production processes.

Patents 7 to 12 are formulation patents, claiming pharmaceutical compositions.

Patents 8 and 11 were deleted due to no sign of development in the patent application procedure.

Patent 14 was deleted as it was considered not/less relevant with respect to generic entry.

Patents 13 and 15 are combination patents, claiming a synergistic combination of TMC-647055 and simeprevir.

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 lasts between 8-12 weeks. The description and the dataset for these two patents can be found in the Working Paper on paritaprevir/ombitasvir/dasabuvir (Patents 6 and 7).

SIMEPREVIR PATENT SITUATION

SPONSOR PATENTS

PATENT 1

Patent application WO2007014926A1 relates to the base compound of simeprevir. The application claims a general structural formula of macrocyclic compounds which act as inhibitors of HCV infections. The application also claims a process for preparation of simeprevir and its method of use. It includes a pharmaceutical combination of simeprevir with ribavirin. This patent, if granted, serves as a blocking patent preventing any other competitor from making the product. The claims are very broad, covering a Markush structure of antiviral agents along with its process of preparation and method of use.

Prosecution at the USPTO

There are three patents granted in the United States: US8148399B2, US8153800B2 and US8349869B2. US8148399B2 relates to the base compound of simeprevir. US8153800B2 is a divisional of US8148399B2 and relates to the macrocyclic compounds as well as processes for preparing these compounds and compositions. US8349869B2 is a divisional of US8148399B2 and relates to a macrocyclic compound, it's N-oxide, pharmaceutically acceptable salt or stereoisomer. It claims a combination of the compound with interferon-α, pegylated interferon-α, and/or ribavirin.

As per the WIPO ISR, the invention is novel and not obvious in comparison to the closest prior art retrieved during the search. The application relates to novel macrocyclic compounds i.e., simeprevir. The closest prior art, WO2005010029A differs from the compounds of the present invention as the prior art claims a compound with a hydrazine functional group incorporated in the macrocyclic ring. The present invention substitutes this hydrazine functional group with an amino functional group to provide an alternative HCV inhibitor that is not obvious.

PATENT 2

Patent application WO2010072742A1 is a process patent. The application covers a process for the preparation of antiviral agents as well as intermediates for the preparation of bicyclic lactone amides, which are then converted into the desired products used for treating HCV infections, particularly simeprevir. The process claims are moderately narrow, claiming the process and various intermediates for preparation of antiviral compounds.

As per the WIPO ISR, the invention is novel and not obvious in comparison to the closest prior art retrieved during the search. Prior art patents claim a process of the formation of intermediates. However, the present invention provides a better alternative to the process by using an optically enriched salt to synthesize the intermediate compounds. Furthermore, the salt disclosed in the present application appears novel as well as the process of producing it.

PATENT 3

Patent application WO2011113859A1 covers a process for the preparation of intermediates useful in the preparation of macrocyclic compounds which are used for treating HCV infections, preferably simeprevir. The application also claims various intermediate compounds.

As per the WIPO ISR, the invention is novel and not obvious in comparison to the closest prior art retrieved during the search. A prior art claims a process for the formation of intermediates; however, the prior art claims only the racemic form of the intermediate compound, whereas the present invention claims an enantiomer in addition to the racemic form. Thus, the present invention provides an improved process for the preparation of intermediate compounds. Combining racemic forms with bromine to create an enantiomer form of the compound would not have been obvious to a person skilled in the art and therefore, the present invention is novel and inventive.

PATENT 4

The patent application WO2008092955A1 covers processes for preparing and further processing quinoline compounds to obtain the desired product, preferably simeprevir.

As per the WIPO ISR, the invention is novel and not obvious in comparison to the closest prior art retrieved during the search, because it provides an alternate sequence of the steps in the chemical reaction with better outcomes.

PATENT 5

Patent application WO2013041655A1 is a process patent, covering processes for the preparation of salts of intermediate compounds used in the synthesis of simeprevir. The claimed process is a multi-step synthesis involving a number of reactants.

As per the WIPO ISR, the invention is novel and not obvious in comparison to the closest prior art retrieved during the search. However, based on ISR, the application lacks sufficiency of disclosure as it does not provide suitable examples for the broad claims of the application. Thus, in accordance to the ISR, the application can be challenged in the national phase based on the WO2011113859 A1 prior art.

PATENT 6

Patent application WO2013061285A1 is a process patent, claiming an improved process for the preparation of intermediate compounds used in the synthesis of HCV inhibitor compounds, particularly simeprevir. The process is claimed to be a straightforward, quick and economic procedure to formulate intermediates for the production of simeprevir. The application also claims various new intermediate compounds.

As per the WIPO ISR, the patent appears to be novel but lacks an inventive step. The lack of an inventive step is the result of a technical issue involving the provision of an alternative process for the production of compound.

PATENT 7

This patent is listed in the US Orange Book with patent numbers US7671032.

Patent application WO2005073195A2 is a product patent, claiming simeprevir derivatives, their salts and prodrugs along with the compositions comprising them, as well as the use of the derivatives for the treatment or prevention of flavivirus infections including HCV infection. These compounds are stated to be useful as NS3 serine protease inhibitors. The application discloses a Markush structure of the general formula along with various substituents.

As per the WIPO ISR, the invention is novel and not obvious in comparison to the closest prior art retrieved during the search. The examination report of granted European patent EP1713823B1 reveals that the patent was allowed after the applicant limited substituents in the Markush structure and provided extra experimental data to support the claims. The examination report of the granted patent application US7671032B2 reveals that claims concerning various substituents in the Markush structure were withdrawn by the applicant in order to overcome obvious double-patenting based on co-pending US applications. The examination report of granted Indian patent IN200603860P1 reveals that the application was allowed after the applicant amended claims related to substituents in the Markush structure.

PATENT 9

Patent application WO2008092954A2 is a formulation patent, originally filed by Tibotec Pharmaceuticals, now part of Janssen Pharmaceuticals. The application claims a crystalline form of a substituted macrocyclic compound, preferably simeprevir, for use in HCV treatment. The application also claims a combination of the compound with a pharmaceutically acceptable excipient. The patent is not relevant to the current version of simeprevir sold by the Sponsor since the European Medicines Evaluation Report states that the crystalline form of the drug is poorly soluble. Therefore, an amorphous form of simeprevir was developed. The amorphous form of the sodium salt of simeprevir is patented under Patent 12. Therefore, Patent 9 and Patent 12 together cover both the crystalline and the amorphous form of simeprevir. Where granted Patent 9 and 12 are likely to prevent generic launch until expiry, unless alternative salts to the sodium salt are used that avoid the scope of Patent 9 and 12.

As per the WIPO ISR, the invention is novel, but lacks an inventive step in comparison to the closest prior art retrieved during the search. Lack of inventiveness is based on examiners objection that the polymorphs disclosed do not provide any advantage over the prior art and preparation of such forms is considered routine work for a chemist. The examination report of granted patent US8143402B2 reveals that the application was allowed after the applicant amended claims related to crystalline compounds.

PATENT 10

Patent application WO2010031829A1 is a formulation patent, claiming a combination of two compounds, simeprevir and a nucleoside, as well as a combination of these compounds with ribavirin or pegylated interferon. The combination is claimed to produce a synergetic effect to treat HCV infections.

As per the WIPO ISR, the application is novel and not obvious in comparison to the closest prior art retrieved during the search. The closest prior art claim HCV inhibitor compounds and their combinations, but the present invention claims a combination of specific HCV inhibitors, which makes it novel. This combination mediates a synergetic effect, making the invention non-obvious.

PATENT 12

Patent application WO2010097229A2 is a product patent, claiming a sodium salt of simeprevir in solid amorphous form, useful for the treatment of HCV infections. For the reasons described in Patent 9, this patent places constraints on the development of generic versions of simeprevir.

As per the WIPO ISR, the application lacks novelty and is obvious in comparison to the closest prior art (WO2007/014926A Patent 1 and WO2008/092954A Patent 9) which claim amorphous compounds, including sodium salts utilized as HCV inhibitors.

PATENT 13

Patent application WO2011128378A1 is a formulation patent, claiming a combination of a macrocyclic HCV protease inhibitor, a macrocyclic non-nucleoside HCV polymerase inhibitor, and a nucleoside HCV polymerase inhibitor. It is preferably a combination of TMC-647055 and simeprevir. The claims are limited to a combination of specific compounds. TMC647055 is a potent non-nucleoside inhibitor of the HCV NS5B polymerase currently developed by Janssen.

As per the WIPO ISR, the application is novel but lacks an inventive step in comparison to the closest prior art retrieved during the search. The closest prior art discloses the use of these compounds individually. Although a triple combination of the present application is not disclosed, the prior art also anticipates a synergetic effect of the claimed combination supported by data. Thus, according to the ISR, the application lacks inventiveness.

PATENT 15

Patent application WO2014033668A2 claims a combination compound comprised of simeprevir, ritonavir and TMC-647055 for treating HCV infection. As per the WIPO ISR, the application is novel and not obvious in comparison to the closest prior art retrieved during the search.

ANNEX - SIMEPREVIR PATENT SITUATION

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Subject Matter	Patent application WO2007014926A1 relates to the base compound of simeprevir.	Patent application WO2010072742 covers process for the preparation of antiviral agents as well as intermediates.	Patent application WO2011113859 covers process for the preparation of intermediates.	Patent application WO2008092955 covers processes for preparing quinoline compounds.	Patent application WO2013041655 is a process patent.	Patent application WO2013061285 covers an improved process for the preparation of intermediate compounds used in synthesis of HCV inhibitor compounds.	Patent application WO2005073195 covers peptidomimetic compounds useful as HCV neuroserpin-3 (NS-3) serine protease inhibitors.
Applicant	Janssen Pharmaceuticals Inc.	Janssen Pharmaceuticals Inc.	Janssen Pharmaceuticals Inc.	Janssen Pharmaceuticals Inc.	Janssen Pharmaceuticals Inc.	Janssen Pharmaceuticals Inc.	Janssen Pharmaceuticals Inc.
Int'l Patent Publication Number	WO2007014926A1	WO2010072742	WO2011113859	WO2008092955	WO2013041655	WO2013061285	WO2005073195
Priority Number	EP2005107074A	EP2008172691A	EP2010156681A	EP2007101571A	EP2011182375A	EP2011187025A	SE2004199A
Expected expiry[1]	27 Jul 2026	21 Dec 2029	15 Mar 2031	31 Jan 2028	20 Sep 2032	25 Oct 2032	27 Jan 2025
PATENT STATUS							
ARIPO (AP)[2]	Granted AP2406A	Not filed[7]	N/A	Not filed[7]	N/A	N/A	Not filed[7]
Argentina (AR)	Granted AR55359A1	Granted AR74863A1	N/A	Granted AR65137A1	N/A	N/A	Granted AR047793A1 Abandoned AR048401

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Australia (AU)	Granted AU2006274865B2	Granted AU2009331530B2	Pending AU2011229164A1	Pending AU2008209697A1	Pending AU2012311461A	Pending AU2012327934A	Granted AU2005207816B2 Granted AU2011203349B2
Brazil (BR)	Pending BRPI0614654A2	Pending[8] BRPI0923393-8	N/A	Pending BRPI0806853	N/A	N/A	Pending BRPI0506948
Canada (CA)	Granted CA2616580A1	Pending CA2745565A1	Pending CA2793129A1	Pending CA2677173A1	Pending CA2845720A1	N/A	Granted CA2552319C Granted CA2552317C
Chile (CL)	Pending CL2006/2007	Not filed[7]	N/A	Granted[8] CL49233	N/A	N/A	N/A
China (CN)	Granted CN101228169B Pending CN102627639A Pending CN103030636A	Granted CN102264715B	Pending CN103249708A	Pending CN101600713A Pending[8] CN103145699	Pending CN103906739A	N/A	Granted CN1914225B Granted CN1914224B
China, Hong Kong SAR (HK)	Granted HK1116771A1 Pending HK1174897A0 Pending HK1183872	Pending[8] HK1164839A	N/A	Granted HK1137442A1 Pending[8] HK1186458A	N/A	N/A	Granted HK1100881A1 Granted HK1104044A1
Colombia (CO)	Granted[8] CO1962	Not filed[7]	N/A	Not filed[7]	N/A	N/A	Granted[8] CO2461
Costa Rica (CR)	Pending[8] CR9783A	Not filed[7]	N/A	Not filed[7]	N/A	N/A	Rejected CR8540A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Ecuador (EC)	Pending[8] EC2008SP8150A	Not filed[7]	N/A	Not filed[7]	N/A	N/A	Status: N/A ECSP066725 Status: N/A ECSP066726
Egypt (EG)	Pending[8] EG2008010148	Not filed[7]	N/A	Not filed[7]	N/A	N/A	Pending[8] EG696/2006
Ethiopia (ET)	Not filed[7]	Not filed[7]	N/A	Not filed[7]	N/A	N/A	Not filed[7]
EAPO (EA)[3]	Granted EA15131B1	Not filed[7]	N/A	Not filed[7]	N/A	N/A	Granted EA14584B1
EPO (EP)[4]	Granted EP1912999B1 Granted EP2322516A1	Granted EP2382198B1	Pending EP2547645A1	Granted EP2121674B1	Status: N/A EP12762583A1	Status: N/A EP12790677A1	Granted EP1713823B1
GCC[5]	Pending[8] GCC6652	Not filed[7]	N/A	Not filed[7]	N/A	N/A	Not filed[7]
Georgia (GE)	Not filed[7]	Not filed[7]	N/A	Not filed[7]	N/A	N/A	Not filed[7]
India (IN)	Pending IN200710158P1 10158/DELNP/2007 Pending IN201206216P1 6216/DELNP/2012 Pending IN201206217P1 6217/DELNP/2012	Pending IN201101505P3 1505/MUMNP/2011	Pending IN201202371P3 2371/MUMNP/2012	Pending IN200901520P3 1520/MUMNP/2009	N/A	N/A	Granted IN200603860P1 3860/DELNP/2006
Indonesia (ID)	Pending WO0200800321	N/A	N/A	Not filed[7]	N/A	N/A	Not filed[7]

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Iran (Islamic Republic of) (IR)	Not filed[7]	N/A	N/A	Not filed[7]	N/A	N/A	Not filed[7]
Israel (IL)	Granted IL188227D0 Pending IL240244	Pending IL213246D0	Pending IL221242	Not filed[7]	Pending IL231024	N/A	Granted IL176921A
Japan (JP)	Granted JP04797067B2 Pending[8] JP523382/08	Rejected JP2012513381A	Status: N/A JP2013522273A	Granted JP5563830B2	N/A	N/A	Granted JP04902361B2 Granted JP5795619B2
Jordan (JO)	Pending JO236/2006	N/A	N/A	Not filed[7]	N/A	N/A	Not filed[7]
Malaysia (MY)	Granted MY144217A	N/A	N/A	Not filed[7]	N/A	N/A	Pending[8] MY146349
Mexico (MX)	Granted[8] MX284777B	Pending[8] MX2011006764A	Status: N/A MX2012010678A	Granted[8] MX280329B	N/A	N/A	Granted[8] MX270111B
Morocco (MA)	Not Filed[7]	N/A	N/A	Not filed[7]	N/A	N/A	Not filed[7]
New Zealand (NZ)	Granted NZ564550A	N/A	N/A	Not filed[7]	N/A	N/A	Granted NZ548740A
Nigeria (NG)	Granted NG2008/26	N/A	N/A	Not filed[7]	N/A	N/A	Not filed[7]
OAPI[6]	Granted OA14035	N/A	N/A	Not filed[7]	N/A	N/A	Not filed[7]
Pakistan (PK)	Pending PK0828/2006	N/A	N/A	Not filed[7]	N/A	N/A	Not filed[7]
Peru (PE)	Granted PE5701	N/A	N/A	Not filed[7]	N/A	N/A	Not filed[7]

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
Philippines (PH)	Granted PH12008500011B1	N/A	N/A	Not filed[7]	N/A	N/A	Granted PH12006501467
Republic of Korea (KR)	Granted KR1059419B1	Pending KR2011099048A	Pending KR2013034012A	Pending KR2009107038A	N/A	N/A	Granted KR1159575B1 Pending KR20120090077A
Russian Federation (RU)	Granted RU15131	Pending RU2011130895A	Pending RU2012143977	Granted RU2483067C2	N/A	N/A	Granted[8] RU014584
Singapore (SG)	Granted SG163617A1	N/A	N/A	Not filed[7]	N/A	N/A	Granted SG124176B
South Africa (ZA)	Granted ZA200800857	N/A	N/A	Not filed[7]	N/A	N/A	Granted ZA200607214A
Thailand (TH)	Pending TH0601003568	N/A	N/A	Not filed[7]	N/A	N/A	Pending[8] TH097320
Tunisia (TN)	Not filed[7]	N/A	N/A	Not filed[7]	N/A	N/A	Not filed[7]
Ukraine (UA)	Granted[8] UA95245	N/A	N/A	Not filed[7]	N/A	N/A	Granted[8] UA84189

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7
The United States (US)	Granted US8148399B2 Granted US8153800B2 Granted US8349869B2 Granted US8754106B2 Granted US9040562B2 Pending US2015218153A1	Pending US20110257403A1	Pending US20130005976A1	Granted US8212043B2 Granted US201000418891 Pending[8] US2012-0238746	N/A	N/A	Granted US7671032B2
Uruguay (UY)	Pending[8] UY29703A1	N/A	N/A	Not filed[7]	N/A	N/A	Not filed[7]
Vietnam (VN)	Granted[8] VN11211	N/A	N/A	Not filed[7]	N/A	N/A	Status: N/A VN10547

	Patent 9	Patent 10	Patent 12	Patent 13	Patent 15
Subject Matter	Patent application WO2008092954 covers a crystalline form of a substituted macro cyclic compound, preferably a variant of simeprevir.	Patent application WO2010031829 covers a combination of simeprevir and a nucleoside.	Patent application WO2010097229 covers a sodium salt of simeprevir in solid amorphous form.	Patent application WO2011128378 is a formulation patent. Preferably it is a combination of TMC-647055 and simeprevir.	Patent application WO2014033668 is a combination patent relates to simeprevir, ritonavir and TMC-647055 for treating HCV infection
Applicant	Janssen Pharmaceuticals Inc. (Tibotec Pharmaceuticals)	Janssen Pharmaceuticals Inc.	Janssen Pharmaceuticals Inc.	Janssen Pharmaceuticals Inc.	Janssen Pharmaceuticals Inc.
Int'l Patent Publication Number	WO2008092954	WO2010031829	WO2010097229	WO2011128378	WO2015033668
Priority Number	EP2007101563A	EP2008164612A	EP2009153964A	EP2010159825A	EP20120182551 EP20120185890
Expected expiry[1]	31 Jan 2028	17 Sep 2029	25 Feb 2030	12 Apr 2031	30 Aug 2033
PATENT STATUS					
ARIPO (AP)[2]	Not filed[7]	Pending AP201105608D0	Not filed[7]	N/A	N/A
Argentina (AR)	Granted AR65136A1	Granted AR73603A1	Not filed[7]	N/A	N/A
Australia (AU)	Granted AU2008209696B2	Lapsed AU2009294622A1	Pending AU2010219160A1	Pending AU2011239974A1	Pending AU2013311025A1
Brazil (BR)	Pending BRPI0806945	N/A	N/A	N/A	N/A
Canada (CA)	Pending CA2677170A1	Dead Application CA2737835A1	Pending CA2753667A1	Pending CA2796243A1	Pending CA2881052A1

	Patent 9	Patent 10	Patent 12	Patent 13	Patent 15
Chile (CL)	Pending[8] CL3212008A1	N/A	Not filed[7]	N/A	N/A
China (CN)	Pending CN101589040A Pending CN104230918A	Withdrawn CN102164602A	Granted CN102356080B Pending CN104478868A	Pending CN102844028A	Pending CN104780921A
China, Hong Kong SAR (HK)	Granted HK1137438	Pending HK1161833A0	Granted[8] HK1166315A0	Pending HK1180222A0	N/A
Colombia (CO)	Not filed[7]	Withdrawn CO6351740A2 Pending[8] CO11-032.140	Not filed[7]	N/A	N/A
Costa Rica (CR)	Not filed[7]	N/A	Not filed[7]	N/A	N/A
Ecuador (EC)	Not filed[7]	Pending[8] EC2011SP010902A	Not filed[7]	N/A	N/A
Egypt (EG)	Not filed[7]	N/A	Not filed[7]	N/A	N/A
Ethiopia (ET)	Not filed[7]	N/A	Not filed[7]	N/A	N/A
EAPO (EA)[3]	Not filed[7]	Pending EA201170456A1	Not filed[7]	Pending EA201291042A1	N/A
EPO (EP)[4]	Granted EP2118098B1	Withdrawn EP2341907A1	Pending EP2401272A2	Pending EP2558091A1	Pending EP2890378A2
GCC[5]	Not filed[7]	Pending[8] 14356	Not filed[7]	N/A	N/A
Georgia (GE)	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A
India (IN)	Pending IN200901610P3 1610/MUMNP/2009	Pending 722/MUMNP/2011	Pending IN201101885P3 1885/MUMNP/2011	N/A	N/A
Indonesia (ID)	Not filed[7]	N/A	Not filed[7]	N/A	N/A
Iran (Islamic Republic of) (IR)	Not filed[7]	N/A	Not filed[7]	N/A	N/A

	Patent 9	Patent 10	Patent 12	Patent 13	Patent 15
Israel (IL)	Pending[8] IL199215	Abandoned IL211599D0	Pending IL214398D0	Pending IL222105	Pending IL237049
Japan (JP)	Granted JP5523110B	Pending[8] JP2012502956A	Granted JP5711672B Pending JP2015143240	Status: N/A JP2013523866A	Pending JP2015-526504
Jordan (JO)	Not filed[7]	Pending[8] JO342/2009	Not filed[7]	N/A	N/A
Malaysia (MY)	Not filed[7]	N/A	Not filed[7]	N/A	N/A
Mexico (MX)	Granted[8] MX301070B	Pending[8] MX2011002896A	Pending[8] MX2011008999A	Status: N/A MX2012011963A	Pending MX2015002684A
Morocco (MA)	Not filed[7]	N/A	Not filed[7]	N/A	N/A
New Zealand (NZ)	Granted NZ577568A	Pending[8] NZ591611	Granted NZ594403A	Granted NZ602552	Pending NZ704565
Nigeria (NG)	Not filed[7]	N/A	Not filed[7]	N/A	N/A
OAPI[6]	Not filed[7]	N/A	Not filed[7]	N/A	N/A
Pakistan (PK)	Not filed[7]	Pending[8] PK855/2009	Not filed[7]	N/A	N/A
Peru (PE)	Not filed[7]	N/A	Not filed[7]	N/A	N/A
Philippines (PH)	Not filed[7]	Pending PH12011500575	Not filed[7]	N/A	N/A
Republic of Korea (KR)	Pending KR2009115929A	Pending KR2011054056A	Pending KR2011123273A	Pending KR2013057990A	Pending KR20150046083A
Russian Federation (RU)	Granted RU2533830C2	N/A	Granted RU2536868C2	N/A	N/A
Singapore (SG)	Granted SG153888B	Abandoned SG169689A1	Abandoned SG173772A1	Abandoned SG184524A1	N/A
South Africa (ZA)	Granted ZA200905377A	Granted ZA201102047A	Granted ZA201106303A	Pending ZA201208505	N/A
Tunisia (TN)	Not filed[7]	N/A	Not filed[7]	N/A	N/A
Thailand (TH)	Not filed[7]	Pending[8] TH0901004201	Not filed[7]	N/A	N/A

	Patent 9	Patent 10	Patent 12	Patent 13	Patent 15
Ukraine (UA)	Not filed[7]	Rejected UA201102963	Not filed[7]	N/A	N/A
The United States (US)	Granted US8143402B2	Pending[8] US13/119466	Pending US20110306634A1	Pending US20130028865A1	Pending US2015209366A1
Uruguay (UY)	Not filed[7]	Pending[8] UY32128A	Not filed[7]	N/A	N/A
Vietnam (VN)	Not filed[7]	Pending[8] VN28156A	Not filed[7]	N/A	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.

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 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.

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.

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.