PATENT SITUATION OF KEY PRODUCTS
FOR TREATMENT OF HEPATITIS C

DACLATASVIR

WORKING PAPER

Update 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.

WHO/EMP/PHI/2016.03

INTRODUCTION

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

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

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

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

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

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

OBJECTIVE

The objectives of the patent working papers are to:

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

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

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

The following are different types of patents:

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

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

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

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

Combination patents claim the combination of new or existing medicines.

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

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

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

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

HOW TO USE THIS WORKING PAPER?

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

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

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

For international patent searches Patentscope and Espacenet can be used:

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

http://worldwide.espacenet.com/

LIMITATIONS

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

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

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

METHODOLOGY

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

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

Information submitted under Section 8 of the Indian Patents Act 1970

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

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

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

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

Patent 1, Indian Patent number 853/DELNP/2009 Form 3 dated 24 September 2015.

Patent 2, Indian Patent number 854/DELNP/2010 Form 3 dated 27 January 2016.

Patent 3, Indian Patent number 753/DELNP/2009 Form 3 dated 19 December 2014.

Patent 4, Indian Patent number 806/DELNP/2010 Form 3 dated 19 October 2015.

Patent 5, Indian Patent number 3372/CHENP/2012 Form 3 dated 3 October 2012.

Patent 8, Indian Patent number 4845/CHENP/2014 Form 3 dated 17 July 2015.

Patent 9, Indian Patent number 3999/CHENP/2012 Form 3 dated 17 October 2012.

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.)

DACLATASVIR

Daclatasvir (formerly BMS-790052; tradename: Daklinza) has been developed and is marketed by Bristol-Myers Squibb (hereby referred to as the 'Sponsor').

Daclatasvir belongs to a class of new direct acting antiviral agents (DAAs) that inhibit the non-structural HCV protein NS5A. It has been tested in combination regimens with pegylated interferon and ribavirin, as well as with other DAAs including asunaprevir and sofosbuvir.[7] In August 2014, the European Medicines Agency approved daclatasvir for use in combination with other drugs for the treatment of chronic HCV infection in adults across genotypes.[8] On July 24, 2015, the US FDA approved the use of daclatasvir in combination with sofosbuvir for patients with genotype 3 chronic hepatitis C infection.

Daclatasvir was not in the initially recommended WHO guideline issued in 2014 because the drug was not finalised at the time. It is included in the new guideline[9] from 2016 as a preferred treatment for patients with HCV genotype 1, 3 and 4, with or without cirrhosis, taken with another DAA.

CHEMICAL NAME

Systematic (IUPAC) name.

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate dihydrochloride

MOLECULAR FORMULA

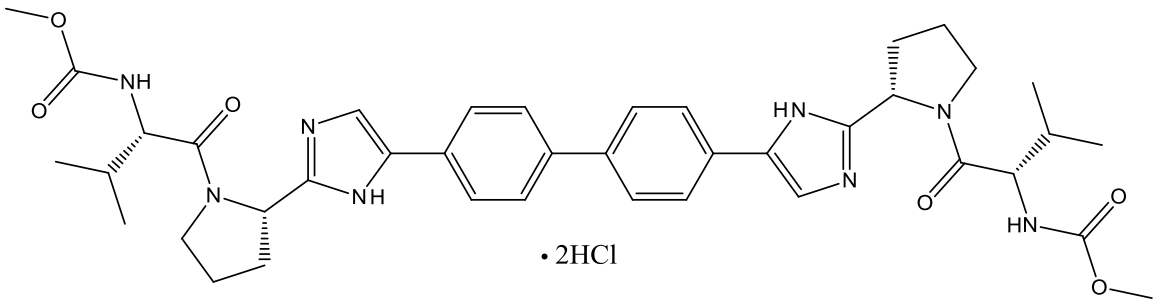
$C_{40}H_{50}N_8O_6 \cdot 2HCl$

[7] December 2011 (http://www.hivandhepatitis.com/hepatitis-c/hepatitis-c-topics/hcv-treatment/3378-aasld-Daclatasvir-with-pegylated-interferonribavirin-produces-high-rates-of-hcv-suppression, May 2016)

[8] August 2014 (http://www.firstwordpharma.com/node/1231982#axzz3CFzwqvbI, May 2016)

[9] 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).

MOLECULAR STRUCTURE



SUMMARY

Patent searches revealed eight Sponsor patents, referred to as Patent 1 - 9 in the following analysis section and in the Annex (Patent 6 was removed from the list, see below). For Patent 1, the data was provided by the Sponsor Bristol-Myers Squibb.

Patent 1 is the primary patent, claiming the base compound. Patents 2-5 and 7-9 are secondary patents, claiming formulation, methods of use, processes, product derivatives, or methods for identifying NS5A-targeting compounds. An additional three patents on combinations were identified during the search (see page 15-16). They have not been included in the Annex or in the list of relevant patents as they cover combinations that are not currently used. All patents were filed and remain in the name of the Sponsor entity Bristol-Myers Squibb.

The patent filing that may be problematic to the launch of generic patents after the expiry of product patent (Patent 1) is Patent 4. Generic products will have to consider the expiry of patents 6 and 7 in the paritaprevir/ombitasvir/dasabuvir report, as well as their combinations. These patents by AbbVie cover combinations of at least two DAAs for treating HCV, where the treatment is either interferon-free or interferon- and ribavirin-free. These patents, together with Patent 4, should be monitored.

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 daclatasvir. This patent is may constrain the launch of generic products where it is granted and enforceable.

Patent 2 covers a process to make daclatasvir. Thus, if granted, competitors will be required to design around the patent and use other production processes.

Patent 3 claims specific derivatives of daclatasvir. Seeking subsequent patents on the derivatives of existing drugs is a common strategy of companies (i.e., obtaining multiple patents that cover various aspects of the same product). This patent covers intermediate compounds that can potentially be used in the manufacturing of daclatasvir.

Patent 4 claims new crystalline forms of substituted imidazole compounds, their composition and use in the treatment of HCV infection.

Patents 5, 7 and 8 claim daclatasvir for use in combination therapy with HCV protease inhibitors. Co-administration of certain drugs can have a synergistic effect on the treatment of disease and therefore provides an advantage over a single-agent therapy.

Patent 6 (WO2012009394A2) is a method patent for the screening of NS5A-targeting compounds to inhibit HCV replication. While included in the initial report, this patent was removed in the updated version as it is considered less/not relevant for generic entry.

Patent 9 relates to a process for preparation of a useful intermediate of daclatasvir.

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 DAAs for treating HCV, where the treatment does is interferon-

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

LICENSE AGREEMENTS

Bristol-Myers Squibb and the Medicines Patent Pool have signed sub-licensing agreements with 4 Indian generic manufacturers who under these agreements can produce and sell generic daclatasvir in combinations with other compounds to treat HCV in 112 low- and middle-income countries. The sub-license agreement covers patent 1, 2, 4 and 9 in the report.[10]

DACLATASVIR PATENT SITUATION

PATENT 1

This patent is listed in the US Orange Book with patent numbers US8329159, US8642025 and US8900566.

Patent application WO2008021927A2 is a primary patent disclosing the base compound of daclatasvir. The patent claims a general structural formula of the base compound along with various substituents. This patent, if granted, blocks competitors from making the product. Also disclosed with the compound are its salts, pharmaceutical compositions and combinations containing the compounds and methods for using these compounds in HCV treatment.

As per the WIPO ISR, the patent application is novel and not obvious when compared to the closest prior art retrieved through the search. The application relates to biphenyl-imidazole compounds, which either inhibit HCV replication or directly act on the NS5A protein. According to the report, the novelty of the present invention resides in the saturated N-containing rings depicted in the claimed structure.

Prosecution at the USTPO

There are four patents granted in the United States: US8303944B2, US8329159B2, US8574563B2 and US8642025B2. US8303944B2 is a continuation-in-part of US8329159B2. It relates to substituted imidazole compounds and their salts. US8574563B2 is a divisional of US8303944B2 and continuation-in-part of US8329159B2. It relates to imidazole substituted biphenyl derivatives or their salts for the treatment of HCV infection. US8642025B2 is a continuation application of US8329159B2. It relates to biphenyl-imidazole compounds, which inhibit HCV replication or inhibit the NS5A protein.

[10] The text of the license agreement can be found here; November 2015 (http://www.medicinespatentpool.org/current-licences/, May 2016)

Patent application WO2009020825A1 is a process patent. The patent claims a process for the preparation of antiviral compounds or a pharmaceutically acceptable salt, and specifically describes a reaction and deprotection process of diacetylbiphenyl. The process is stated to allow for efficient large-scale synthesis of the antiviral compounds. The claims are broad and cover a set of compounds specifically synthesized by the claimed process. Thus, the application of the process is limited to these specific compounds.

As per the WIPO ISR, the patent application is novel and not obvious in comparison to the closest prior art retrieved through the search.

PATENT 3

Patent application WO2008021928A2 claims specific daclatasvir derivatives and their salts. The compounds include a core structure consisting of six directly linked functional groups. The claims are very broad, covering a Markush structure of the antiviral agents.

As per the WIPO ISR, the patent application is novel and not obvious in comparison to the closest prior art retrieved through the search. Though the prior art discloses similar compounds, the novelty lies in the core structure consisting of six directly linked core functional groups claimed. Claim 15 as filed under the Patent Cooperation Treaty potentially covers intermediate compounds may be used to manufacture daclatasvir.

PATENT 4

This patent is listed in the US Orange Book with patent number US8629171.

Patent application WO2009020828A1 claims new crystalline forms of substituted imidazole compounds, their composition and use in HCV treatment, and includes coverage of the therapeutically-effective dose of crystalline compounds administered to patients. The claimed crystalline forms are subject to limitations regarding cell structure dimensions, temperature, and other structural parameters. Polymorphisms have been observed for daclatasvir dihydrochloride. The thermodynamically most stable polymorph, designated as N-2, is used in the reference product. The European Medicines Assessment Report discloses that there also exists an alternative N-1 form. If this form proves to be stable, it may be an option generic companies can pursue to circumvent this patent.

As per the WIPO ISR, the patent application is novel and not obvious when compared to the closest prior art retrieved through the search.

PATENT 5

Patent application WO2011046811A1 is a formulation patent, disclosing a combination of daclatasvir and a HCV NS3 protease inhibitor (asunaprevir). The application claims the compositions as described, which exhibit synergistic activity in HCV treatment. Further claimed is the administration of the compositions in combination with an additional anti-HCV agent, preferably interferon or ribavirin.

As the composition claims a combination of two known compounds without claiming any substituents, the scope of the claims is limited to the combination of the claimed compounds. Daclatasvir is currently sold as a single product used in combination with other

anti-HCV medicines, notably sofosbuvir. Nevertheless, this patent should be monitored in case the targeted combination is added to the indications approved for daclatasvir.

As per the WIPO ISR, the patent application is novel but lacks an inventive step. Lack of inventive step refers to the synergetic combination claimed in the present invention. The ISR deems this synergetic effect as obvious based on existing prior art.

PATENT 7

Patent application WO2012018829A1 is another formulation patent, claiming a formulation comprising one or two HCV polymerase inhibitors and a pharmaceutically acceptable carrier. The composition shows synergistic activity, effectively inhibiting HCV, maximizing efficacy, and potentially eradicating HCV. Combinations contain a HCV NS5A inhibitor (e.g. daclatasvir), a HCV NS3 inhibitor (e.g. asunaprevir) and a HCV NS5B inhibitor (e.g. beclabuvir). As the claimed composition pertains to a combination of one or two compounds without reference to their substituents, the scope of the claims is limited to the claimed compounds. Though as mentioned earlier in this report, daclatasvir is currently sold as a single product used in combination with other anti-HCV medicines, notably sofosbuvir, for which this patent is not relevant, this patent should be monitored in case the targeted combination is added to the indications approved for daclatasvir.

PATENT 8

Patent application WO2013106520A1 is another formulation patent. The claimed formulation comprises a combination of an NS5A-targeting compound (daclatasvir) and a NS5A synergist. As these synergists target the structural protein NS5A, they can confer inhibition should the efficacy of daclatasvir diminish due to mutations.

The compounds are called synergistic as each is considerably less active against daclatasvir-resistant viruses when administered alone as opposed to in combination with daclatasvir. The synergistic compounds claimed in this patent and patents 10-12 are slightly different and cover a wide range of molecules under Markush structures. The broad Markush claims indicate that specific data on the effectiveness of the compounds remains elusive. Thus, these synergists will not likely gain approval soon. As stated previously, daclatasvir is currently sold as a single product used in combination with other anti-HCV medicines, notably sofosbuvir for which this patent is not relevant. This patent should be monitored in case combinations with the described NS5A synergists are added to the indications approved for daclatasvir.

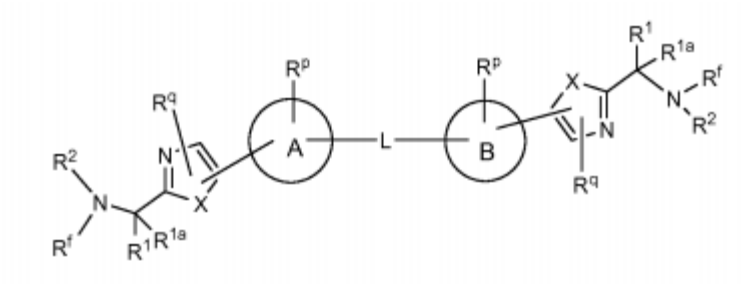


Figure 1: Markush base structure of compounds covered under patent 8

As per the WIPO ISR, the patent application lacks novelty and is obvious in comparison to closest prior art retrieved through the search, including patent and non-patent publications which disclose combinations of compounds that can inhibit HCV.

PATENT 9

Patent application WO2011059850 claims a process for the preparation of an intermediate of daclatasvir. Claim 13 is directed at a process for preparing an intermediate that is can be used to manufacture daclatasvir.

Additional combination patents:

The search revealed three additional patent applications covering combinations comprising an NS5A-targeting compound (daclatasvir) and an NS5A synergist in the same manner as Patent 8. As these patents do not cover any combinations that are currently marketed, they have not been included in this report. They may become relevant for future combinations of daclatasvir with the described NS5A synergists.

Patent application: WO2015005901 (Patent 10)

No name given for the synergistic compounds.

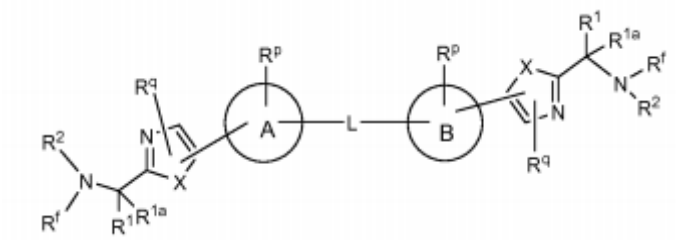


Figure 2: Markush base structure of compounds covered under patent 10

Patent application WO2015009744 (Patent 11)

BIPHENYL DERIVATIVES

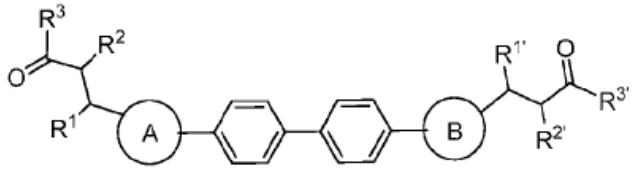


Figure 3: Markush base structure of compounds covered under patent 11

Patent application WO2015026454 (Patent 12)

TRICYCLOHEXADECAHEXAENE DERIVATIVES

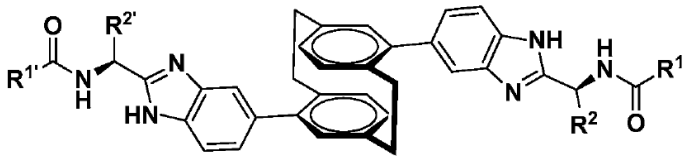


Figure 4: Markush base structure of compounds covered under patent 12

ANNEX - DACLATASVIR PATENT SITUATION

	Patent 1[11]	Patent 2	Patent 3	Patent 4	Patent 5	Patent 7	Patent 8	Patent 9
Subject Matter	Patent application WO2008021927 covers the base compound of daclatasvir.	Patent application WO2009020825 covers a process for synthesizing daclatasvir for the treatment of HCV.	Patent application WO2008021928 covers a novel HCV inhibitor or its salts useful for the treatment of HCV infection.	Patent application WO2009020828 covers crystalline forms of daclatasvir.	Patent application WO2011046811 covers a formulation comprising a combination of daclatasvir and asunaprevir.	Patent application WO2012018829 covers a formulation comprising one or two HCV polymerase inhibitors.	Patent application WO2013106520 covers a formulation comprising a combination which provides synergistic anti-HCV activity.	Patent application WO2011059850 covers a process related to the preparation of daclatasvir.
Applicant	Bristol-Myers Squibb Co.	Bristol-Myers Squibb Co.	Bristol-Myers Squibb Co.	Bristol-Myers Squibb Co.	Bristol-Myers Squibb Co.	Bristol-Myers Squibb Co.	Bristol-Myers Squibb Co.	Bristol-Myers Squibb Co.
Int'l Patent Publication Number	WO2008021927	WO2009020825	WO2008021928	WO2009020828	WO2011046811	WO2012018829	WO2013106520	WO2011059850
Priority Number	US2006836996P	US2007954595P	US2006836999P	US2007954592P	US2009250648P	US2010371399P	US2012586558P	US20090260115P US20100378806P US20100915605
Expected expiry[1]	8 Aug 2027	30 Jul 2028	8 Aug 2027	30 Jul 2028	7 Oct 2030	1 Aug 2031	9 Jan 2033	2 Nov 2030
PATENT STATUS								
ARIPO (AP)[2]	Not filed	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]

[11] For Patent 1, the original data was kindly complemented by the Sponsor Bristol-Myers Squibb. The data was updated since, see section on Methodology.

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Argentina (AR)	Pending AR63684A1	Pending AR67896A1	Not filed[7]	Pending AR070016A1	N/A	N/A	Pending AR089711A1	Pending AR078968
Australia (AU)	Granted AU2007286222B2	Granted AU2008284097B2	Granted AU2007286223B2	Granted AU2008284100B2	Granted AU2010307144B2	Granted AU2011285890B2	N/A	Pending AU2010319764
Brazil (BR)	Pending PI0716483.1	Pending[9] BRPI0815611.5	Pending BRPI0716220	Pending BRPI0815142.3	Pending[9] BR112012008533.6	N/A	Pending[9] BR112014017266.8	Pending BR112012011134.5
Canada (CA)	Granted CA2660520	Granted CA2695711	Pending CA2660628A1	Granted CA2695729	Pending CA2777560A1	Pending CA2807589A1	Pending CA2863268	Pending CA2780790
Chile (CL)	Granted CL49393	Not filed[7]	Not filed[7]	Granted CL51056	Pending CL2012/0919	No application identified	No application identified	Not filed[8]
China (CN)	Granted CN101558059B Pending CN104447707A	Granted CN101778841B	Pending CN101528232A	Granted CN101778840B	Pending CN102655873A	Granted CN103153280B	Pending CN104302290A	Granted CN102686565B
China, Hong Kong SAR (HK)	Granted HK1126486 Pending HK1201535A	Granted HK1137454	Granted HK1125576A1	Granted HK1144089A1	Pending HK1172237A0	Pending HK1180211A0	N/A	Pending HK1168358
Colombia (CO)	Granted CO615	Granted CO6251317A2	Granted[9] CO09012755	Rejected CO10-011972	Granted CO6430507	N/A	N/A	Granted CO6541557A2
Costa Rica (CR)	Not filed	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]
Ecuador (EC)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]

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Egypt (EG)	Technically rejected EG2009020174	Not filed[7]	Pending EG2009020175	Pending EG2010020177	Not filed	Not filed	Not filed	Not filed
Ethiopia (ET)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]
EAPO (EA)[3]	Granted EA15756B1	Granted EA17173B1	Granted EA17348B1	Granted EA018152B1	Granted EA020527B1	Granted EA201390155B1	Pending EA201491361	Granted EA021194B1
EPO (EP)[4]	Granted EP2049522 Withdrawn EP2385048A1 Pending EP2784075A	Granted EP2178863B1	Granted EP2049116B1	Granted EP2183244B1	Pending EP2488192A1	Pending EP2600835A1	Pending EP2802326	Pending EP2499115A1
GCC[5]	Pending GC8874	Granted[9] GC2517	Not filed[7]	Pending GC11478	N/A	N/A	Pending[9] GC23325	Not filed[8]
Georgia (GE)	Not filed	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]
India (IN)	Pending IN200900853P1 853/DELNP/2009	Pending IN201000854P1 854/DELNP/2010	Pending IN200900753P1 753/DELNP/2009	Pending IN201000806P1 806/DELNP/2010	Pending IN201203372P1 3372/CHENP/2012	N/A	Pending 4845/CHENP/2014	Pending 3999/CHENP/2012
Indonesia (ID)	Not filed	Not filed[7]	Not filed[7]	Not filed[7]	Pending[9] W00201201835	N/A	N/A	Not filed[8]

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Iran (Islamic Republic of) (IR)	Not filed	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]
Israel (IL)	Granted IL196813A	Granted IL203685	Granted IL196815A	Granted IL203684	Pending IL219123	Pending IL224369	N/A	Pending IL219517
Japan (JP)	Granted JP05235882B2 Pending JP2013151535A Granted JP5769749 Pending JP2015105694	Granted JP05324574B2 Pending JP2013231072A Rejected 2013-149167	Granted[9] JP5306203	Granted JP05244179B2	Pending JP2013507439A	Pending JP2013535487A	Pending JP2015-503617	Pending JP2012538854A Granted JP2014246170B2
Jordan (JO)	Not filed	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]
Lebanon (LB)	Granted LB7962	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]
Malaysia (MY)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	Pending MYPI2012001583	N/A	N/A	Not filed[8]
Mexico (MX)	Granted MX287005	Granted MX290356B	Granted[9] MX283096	Granted[9] MX307552B	Pending[9] MX2012003835A	Status: N/A MX2013001170A	Status: N/A MX2014008227	Granted MX326534 Pending MX2013/011736
Morocco (MA)	Not filed[7]	Not filed[7]	Not filed	Not filed[7]	Not filed	Not filed	Not filed	Not filed[8]
New Zealand (NZ)	Granted NZ574805A	Not filed[7]	Granted NZ574769A	Granted NZ583148A	Granted NZ599284A	N/A	N/A	Not filed[8]

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Nigeria (NG)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]
OAPI[6]	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]
Pakistan (PK)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]
Peru (PE)	Granted PE006425	Not filed[7]	Not filed[7]	Granted PE6534	Pending[9] PE14322012A1	N/A	N/A	Not filed[8]
Philippines (PH)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	Pending PH12012500571A1	N/A	N/A	Not filed[8]
Republic of Korea (KR)	Granted KR101450352 Granted KR101475189	Granted KR101528542B1	Granted[9] KR1438851	Granted KR101508022B1	Pending KR2012088743A	Pending KR2014002611A	N/A	Granted KR20127014893
Russian Federation (RU)	Granted RU015756	Granted RU17173	Granted[9] RU017348	Granted RU18152	N/A	N/A	N/A	Granted RU21194
Singapore (SG)	Granted SG150106	Not filed[7]	Granted SG150105B	Granted SG159059B	Pending SG179814A1	Pending SG2014008346	N/A	Not filed[8]
South Africa (ZA)	Granted ZA200900962A	Not filed[7]	Granted ZA200900935	Granted ZA201000843A	Granted ZA201203451A	N/A	N/A	Not filed[8]
Thailand (TH)	Pending TH0701003997	Not filed[7]	Not filed[7]	Pending TH0801004156	Pending TH1201001642	N/A	N/A	Not filed[8]

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Tunisia (TN)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]
Ukraine (UA)	Not filed	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	N/A	Not filed[8]
The United States (US)	Abandoned US20100158862A1 Abandoned US20110268697A1 Granted US8303944B2 Granted US8329159B2 Granted US8574563B2 Granted US8642025 Granted US8846023 Granted US8900566 Pending US2015011754	Granted US7728027B2	Granted US7659270B2	Granted US8629171B2	Pending US20130259832A1 Granted US8415374B2	Pending US20120196794A1	Pending US20130183269A1	Granted US9006455
Uruguay (UY)	Not filed	Not filed[7]	Not filed[7]	Not filed[7]	N/A	N/A	Pending[9] UY34570A	Not filed[8]
Venezuela (VE)	Pending VE20071726	Not filed[7]	Not filed[7]	Pending VE20081614	N/A	N/A	Pending[9] VE888/2013	Not filed[8]

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Vietnam (VN)	Not filed[7]	Not filed[7]	Not filed[7]	Not filed	Status: N/A VN31028A	N/A	N/A	Not filed[8]

[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] No family member for this patent is listed in the licence agreement from the Medicines Patent Pool; November 2015 (http://www.medicinespatentpool.org/current-licences/, May, 2016.)

[9] 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 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.

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.

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