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Review of the PIBRENTASVIR PATENT LANDSCAPE: A scoping report

March 2017

This report was prepared by Haining Ji (Pharmathen) with input from Karin Timmermans (UNITAID).

CONTENTS

ABBREVIATIONS

DAA	direct-acting antiviral
EPO	European Patent Office
HCV	hepatitis C virus
HIV	human immunodeficiency virus
NS	non-structural
PCT	Patent Cooperation Treaty
RNA	ribonucleic acid

I. INTRODUCTION

Hepatitis C is a major global health problem; some 130–150 million people worldwide are chronically infected with the hepatitis C virus (HCV). It is estimated that, worldwide, 2.9 million people are coinfected with HIV and HCV. Each year, approximately 700 000 people die of HCV-related liver disease, and evidence indicates that the HCV burden is increasing.[1, 2, 3] While the HCV epidemic is global in scope, the HCV burden varies considerably between countries.

The virus has six primary genotypes. Genotypes 1 and 3 are the most prevalent, accounting respectively for 46% and 30% of HCV cases worldwide. Together, genotypes 2, 4 and 6 represent around 23% of HCV cases, while genotype 5 accounts for less than 1%.[4]

Efforts to treat HCV have historically been hampered by suboptimal and inadequate treatments. However, the development of direct-acting antivirals (DAAs) has dramatically improved the prospects for HCV treatment and has altered the standard of care. Several new DAAs that do not require Pegylated interferon (PEG-interferon) have been launched since late 2013, and a number of other DAAs are in development.

These DAAs generate cure rates that approach or exceed 90%. Some combination regimens may have pan-genotypic efficacy, which would simplify treatment and monitoring. One compound of interest is AbbVie's investigational compound ABT-530, or pibrentasvir.

In view of its potential role in future treatment, this report explores the patent landscape of pibrentasvir.

1. Hepatitis C factsheet. Geneva: World Health Organization; July 2016 (http://www.who.int/mediacentre/factsheets/fs164/en/, accessed 29 January 2017).
2. Global health sector strategy on viral hepatitis 2016–2021. Geneva: World Health Organization; 2016.
3. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(117–71).
4. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2014;61(1):77–87.

II. METHODOLOGY

Relevant patents and patent applications were identified by searching patent and non-patent databases, namely: SciFinder, PatBase, TotalPatent and Google Patents. Searches were carried out using key words, semantic searches, International Patent Classification (IPC) searches, chemical structure searches and combinations thereof.

For each of the most relevant patents or applications, the equivalents were identified (INPADOC family) and the legal status of each of the equivalents was checked on the websites of the relevant patent offices. The countries listed in Annex 1 represent those for which INPADOC data are available.

The searches were carried out in December 2016. The analysis of the identified patents and patent applications was undertaken on the basis of the international phase and the European phase prosecution unless otherwise indicated.

Caveat: It is important to note that the patent status of a given product in a given country may change and that data may therefore become outdated. It is advisable always to check with the relevant national or regional patent office for the most up-to-date information on the status of a given patent or patent application.

This report was prepared by Haining Ji (Pharmathen) with input from Karin Timmermans (UNITAID). The patent searches were conducted by Haining Ji.

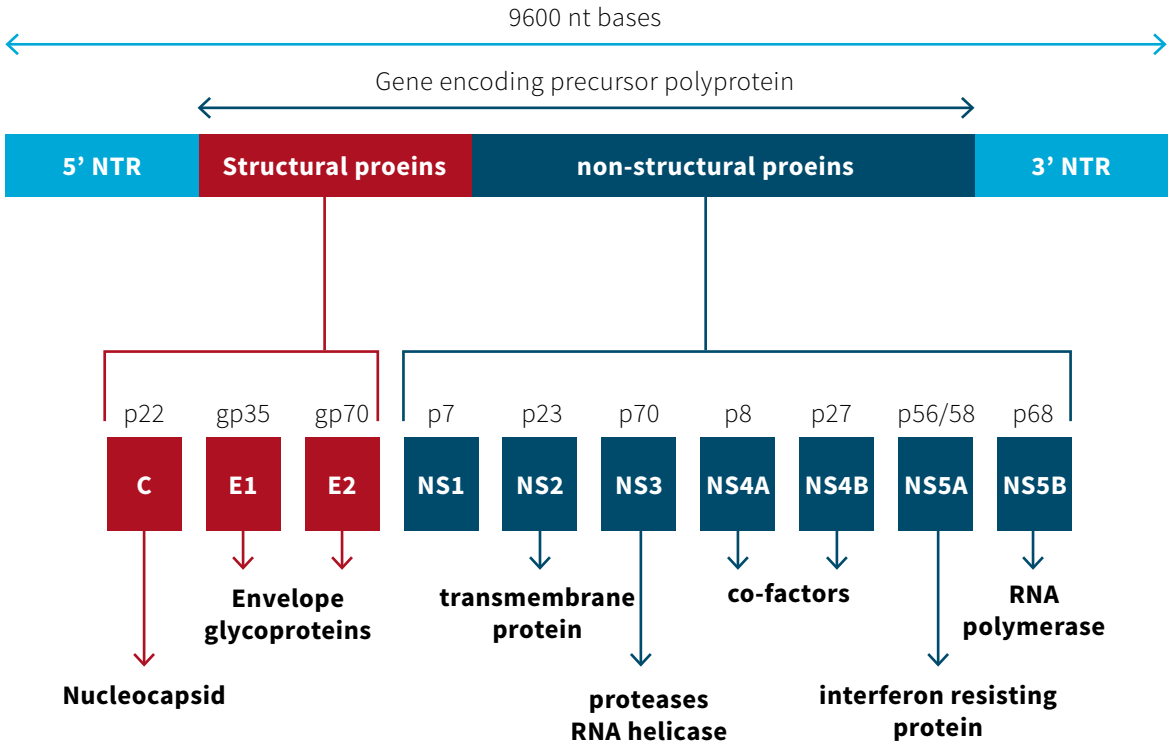
Peter Beyer and Pascale Boulet reviewed a draft version of this report, and provided valuable input and suggestions.

III. BACKGROUND

Hepatitis C virus

The hepatitis C virus is a small (55–65 nm), enveloped, positive-sense single-stranded RNA virus of the Flaviviridae family. The virus consists of three structural proteins (core, E1 and E2), the ion channel protein p7 and six non-structural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B) (see Figure 1). Each of these proteins plays a role in HCV entry, infection, replication or maturation and is therefore a potential target for medicines.

Figure 1. Hepatitis C virus RNA



Adapted from Graham Colm.

DDAAs block viral production by directly inhibiting one or more steps of the HCV replication cycle. DAAs can be divided into categories – notably NS3/NS4A serine protease inhibitors, NS5A complex inhibitors and NS5B RNA polymerase inhibitors (both nucleoside and non-nucleoside).

NS5A is a 447 amino acid, zinc-binding phosphoprotein that is believed to play a key role in HCV RNA replication. NS5A exists in two forms: a hypophosphorylated p56 and a hyperphosphorylated p58 based on electrophoric mobility. NS5A is essential to HCV genome replication.

Pibrentasvir is an NS5A inhibitor. In September 2016, the US Food and Drug Administration (FDA) granted breakthrough therapy designation to AbbVie's investigational, pan-genotypic fixed-dose combination glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection who failed previous therapy with DAAs in genotype 1.[5] In January 2017, the European Medicines Agency reportedly granted accelerated assessment for glecaprevir/pibrentasvir.[6]

5 Enanta Pharmaceuticals announces AbbVie's investigational HCV regimen receives U.S. FDA breakthrough therapy designation. Business Wire. 30 September 2016..

6 AbbVie. European Medicines Agency grants accelerated assessment, validates marketing authorization application for AbbVie's investigational regimen of glecaprevir/pibrentasvir (G/P) for the treatment of chronic hepatitis C in all major genotypes (GT1-6). PRNewswire. 24 January 2017.

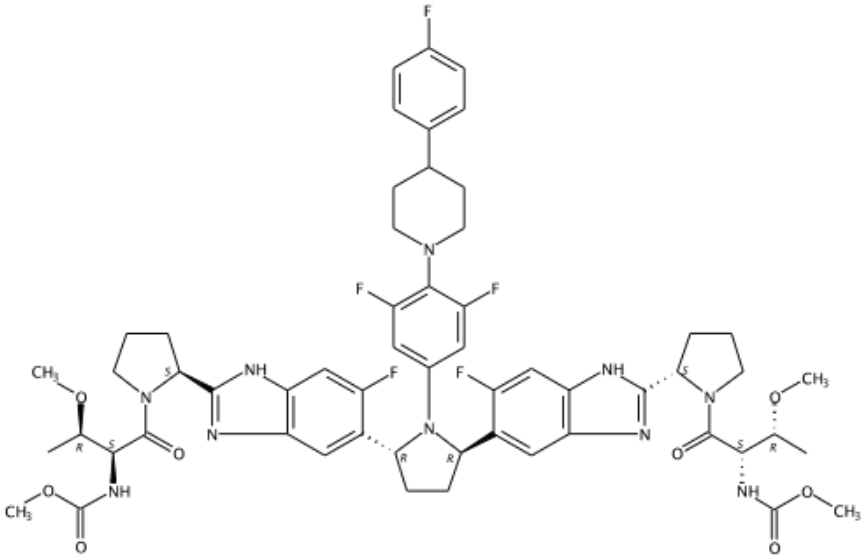
Pibrentasvir

Pibrentasvir (formerly known as ABT-530) is an HCV NS5A inhibitor with potent pangenotypic antiviral activity in vitro.

Pibrentasvir was found to have higher potency than most other NS5A inhibitors across all genotypes.[7]

The chemical structure of pibrentasvir is shown in Figure 2.

Figure 2. Structure of pibrentasvir



Chemical name:
methyl N-[(2S,3R)-1-[(2S)-2-[6-[(2R,5R)-1-[3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl] phenyl]-5-[6-fluoro-2-[(2S)-1-[(2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoyl] pyrrolidin-2-yl]-3H-benzimidazol-5-yl]pyrrolidin-2-yl]-5-fluoro-1H-benzimidazol-2-yl] pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl] carbamate;

dimethyl N,N'-(((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl) pyrrolidine-2,5-diyl)bis((6-fluoro-1H-benzimidazole-5,2-diyl)((2S)-pyrrolidine-2,1-diyl) ((2S,3R)-3-methoxy-1-oxobutane-1,2-diyl))) biscarbamate;

methyl {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl] pyrrolidin-2-yl}-1H-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl} carbamate.

Molecular formula:
$C_{57}H_{65}F_5N_{10}O_8$.

Molecular weight:
1113.2 g/mol.

CAS registry number:
1353900-92-1.

7 Alcorn K. AbbVie pangenotypic combination cures almost all hard-to-treat people with HCV genotype 3. InfoHep. 16 November 2016 (quoting studies presented at the 2016 AASLD).

IV. OVERVIEW OF PIBRENTASVIR PATENTS

Ten patents and/or patent applications related to pibrentasvir appear to be the most relevant. These patents/applications, and divisional patents/applications thereof, include the patents/applications covering the compound per se, various solid forms of the compound, formulations and combinations that include it, and methods of use in the treatment of HCV infection.

Patent 1 is the compound patent. It would be likely to block the production, import, marketing and use of generic versions of pibrentasvir in countries where it is in force.

Patent 2 is an equivalent document of Patent 1. It would potentially block generic market entry, depending on the actual claims granted in each jurisdiction.

Patent 3 relates to the use of pibrentasvir to treat HCV infection, where the HCV genotype has not been established.

Patents 4 to 7 relate to methods of treatment for HCV and comprise administration of at least two DAAs including glecaprevir and/or pibrentasvir.

Patents 8 and 9 relate to crystalline forms of pibrentasvir.

Patent 10 relates to combination therapy for HCV.

Non-sponsor patents

As of December 2016, there was competition for patents related to pibrentasvir. Patents that have been filed by other entities include:

- Glaxo (WO2016/075584): targeting a long-acting parenteral pharmaceutical composition comprising a compound of formula IIA or IIB with pibrentasvir (ABT-530).
- Medivir (WO2016/140615): targeting a combination of a compound of formula (IA) with pibrentasvir (ABT-530).

Table 1 gives a brief overview of the most relevant patents and/or applications. More detailed information is provided in section V and Annex 1.

Table 1. Overview of key patents on pibrentasvir

	PCT application number	Applicants	Filing date	Comments
PATENT 1	**WO2012/051361**	AbbVie	12 October 2011	Basic compound patent; claims pibrentasvir. Likely to constrain generic market entry where it is in force.
PATENT 2	**WO2012/116257**	AbbVie	24 February 2012	Equivalent document of Patent 1. Would potentially block generic market entry, depending on the actual claims granted in each jurisdiction.
PATENT 3	**WO2014/047039**	AbbVie	17 September 2013	Claims a method of treatment for HCV, which comprises administration of pibrentasvir or a salt thereof, where genotype is not established.
PATENT 4	**WO2014/152514**	AbbVie	14 March 2014	Claims an interferon- and ribavirin-free treatment for HCV, which comprises administration of glecaprevir and pibrentasvir.
PATENT 5	**WO2014/152635**	AbbVie	14 March 2014	Claims a method of treatment for HCV, which comprises administration of glecaprevir, pibrentasvir and ribavirin.
PATENT 6	**WO2015/153792**	AbbVie	01 April 2015	Claims a method of treatment for HCV, comprising administration of ribavirin and at least two of the DAAs selected from glecaprevir, pibrentasvir and sofosbuvir.
PATENT 7	**WO2015/153793**	AbbVie	01 April 2015	Claims an interferon- and ribavirin-free treatment for HCV, comprising administration of at least two of the DAAs selected from glecaprevir, pibrentasvir and sofosbuvir.
PATENT 8	**WO2015/171993**	AbbVie	08 May 2015	Claims crystalline forms of pibrentasvir.
PATENT 9	**WO2016/053869**	AbbVie	28 September 2015	Claims crystalline forms of pibrentasvir.
PATENT 10	**WO2016/134058**	AbbVie	17 February 2016	Combination therapy for HCV.

V. ANALYSIS OF PIBRENTASVIR PATENTS/APPLICATIONS

PATENT 1

Title: Antiviral compounds
WO 2012/051361 (AbbVie, filed 12 October 2011)

Summary

This is the basic compound patent covering pibrentasvir. It discloses and claims pibrentasvir as well as pharmaceutical compositions comprising it.

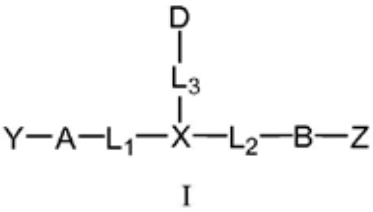
This patent would be likely to block generic market entry in the countries where it is in force.

Description

The PCT application relates to compounds that are useful as inhibitors of the HCV NS5A protein. It belongs to the same INPADOC patent family[8] as WO2010/144646, which is the primary patent of ombitasvir (another inhibitor of the HCV NS5A protein developed by AbbVie).

The first-generation HCV NS5A inhibitors such as daclatasvir are attractive because of their efficacy in inhibiting HCV replication in different HCV genotypes. This PCT application continues to investigate compounds that are effective in inhibiting the replication of the HCV NS5A protein and which can therefore be used in the treatment of HCV infections.

The inventors unexpectedly discovered that certain compounds represented by formula I exhibit drastically improved antiviral activities.



I

Example 3.52 corresponds to pibrentasvir.

Processes for making the disclosed compounds, compositions comprising such compounds, and methods of using such compounds to treat HCV infection are also disclosed.

General and specific schemes, procedures and examples are provided, describing the synthesis of the claimed

8 An INPADOC patent family includes all the documents directly (simple patent family) or indirectly (extended patent family) linked to one another via one priority document. Patent families directly linked via at least one priority document are equivalent documents and normally have an identical scope of protection. An INPADOC family may include many different documents which differ in terms of priority and scope of protection, such as this PCT application and WO2010/144646.

compounds as well as the intermediates used to prepare the compounds.

Claims

This PCT application has 22 claims, of which claims 1, 2, 11, 13, 14, 15, 17 and 21 are independent.

Pibrentasvir is specifically claimed in claim 15.

The application also claims pharmaceutical compositions comprising pibrentasvir or a pharmaceutically acceptable salt thereof (claim 16).

Observations

The PCT application was filed on 12 October 2011 and was published for the first time on 19 April 2012.

The International Searching Authority (EPO) found that the international application lacks unity within the meaning of rule 13 of the PCT. Two separate inventions have been identified:

- Invention I: Compounds of formula (I), wherein X is a carbocycle, pharmaceutical composition comprising these compounds and methods for their preparation; and
- Invention II: Compounds of formula (I), wherein X is a heterocycle, pharmaceutical composition comprising these compounds and methods for their preparation.

The applicant did not pay any additional searching fees; therefore only invention I has been searched during the international phase.

The PCT application entered the European phase as EP2627651A1 with amended claims. The examiners acknowledged that the new claims are novel but considered them as lacking an inventive step. EP2627651A1 application is closed (13 April 2015).

The applicant filed two divisional applications based on EP2627651A1, namely EP2692346A1 (which has been granted as EP2692346B1) and EP2692726A1. EP2692346B1 specifically claims the compound of pibrentasvir and a pharmaceutically acceptable salt thereof. EP2692726A1, which is currently pending, claims the prodrug of pibrentasvir.

The PCT application has also entered a number of other national phases (see Annex 1).

PATENT 2

Title: Antiviral compounds
WO 2012/116257 (AbbVie, filed 24 February 2012)

Summary

This PCT application covers pibrentasvir and pharmaceutically acceptable salts thereof.

This patent would potentially block generic market entry depending on the actual granted claims in each jurisdiction.

Description

This PCT application claims one of the priority documents of Patent 1 and is therefore an equivalent document to Patent 1. Equivalent documents normally have an identical priority number(s) and identical scope of protection.

The application focuses on certain compounds disclosed in Patent 1.

Claims

This PCT application specifically claims pibrentasvir and pharmaceutically acceptable salts thereof.

Observations

The PCT application was filed on 24 February 2012 and was published for the first time on 30 August 2012.

The international search has been performed by EPO. According to the international preliminary report on patentability, none of the claims as originally filed involve an inventive step in view of the documents cited in the international search report.

Pibrentasvir is specially claimed in the original PCT application. In countries where Patent 1 is granted, the claims covering pibrentasvir in Patent 2 should not be allowed. However, it is possible that these claims will be amended in a way that makes generic market entry challenging.

Furthermore, in countries that do not undertake substantive examination, or that have limited capacity for doing so, Patent 2 might be allowed and might become (another) compound patent.

PATENT 3

Title: Methods for treating hepatitis C
WO 2014/047039 (AbbVie, filed 17 September 2013)

Summary

This PCT application relates to pan-genotypic HCV inhibitors, in particular pibrentasvir, and methods of using the compound to treat HCV-infected patients who are not genotyped before the treatment.

Description

This PCT application is based on the surprising discovery that pibrentasvir is effective in inhibiting a wide array of HCV genotypes and variants, such as HCV genotypes 1, 2, 3, 4, 5 and 6. Therefore, the treatment can be initiated without establishing the specific HCV genotype.

The PCT application describes methods comprising administration of an effective amount of pibrentasvir to a patient with HCV infection, regardless of the specific HCV genotype(s). Optionally, pibrentasvir is co-administered with another anti-HCV agent.

Preferably, pibrentasvir is formulated in a solid composition comprising pibrentasvir in amorphous form, a pharmaceutically acceptable hydrophilic polymer and, optionally, a pharmaceutically acceptable surfactant.

The solid composition employed in the invention can be prepared by a variety of techniques such as melt-extrusion, spray-drying, co-precipitation, freeze-drying or other solvent evaporation techniques, with melt-extrusion and spray-drying being preferred. The solid dispersion produced by melt-extrusion, spray-drying or other techniques can be prepared into any suitable solid oral dosage form.

Each treatment regimen can be both interferon-free and ribavirin-free; however, if necessary, administration of interferon and/or ribavirin can be included. Each treatment regimen may also optionally include administration of one or more other anti-HCV agents.

The treatment duration is preferably no more than 24 weeks, or no more than 12 weeks.

Claims

This PCT application contains a total of 21 claims.

Claims 1–13 are directed to a method of treatment for HCV infection, comprising administration of an effective amount of pibrentasvir to a patient who is infected with HCV, where the genotype has not been established.

Claims 14–21 are directed to a method of treatment for HCV infection, comprising administration of an effective amount of pibrentasvir to a patient who is infected with HCV genotype 2, 3, 4, 5 or 6.

Observations

This PCT application was filed on 17 September 2013 and was published for the first time on 27 March 2014.

According to the international preliminary report on patentability, none of the claims as originally filed involves an inventive step in view of the documents cited in the international search report.

PATENT 4

Title: Combination of two antivirals for treating hepatitis C
WO 2014/152514 (AbbVie, filed 14 March 2014)

Summary

This PCT application relates to an interferon- and ribavirin-free treatment for HCV, comprising administration of at least two DAAs including glecaprevir and pibrentasvir.

Description

This PCT application is based on the unexpected finding that an interferon-free and ribavirin-free treatment using a combination of glecaprevir and pibrentasvir, for a duration of no more than 12 weeks, can achieve significant sustained virological response.

This PCT application describes a method of treatment for HCV infection, which comprises administration of at least two DAAs – including glecaprevir and pibrentasvir – wherein the administration of interferon and/or ribavirin to the subject is excluded during the treatment. Thus, the side-effects associated with interferon and/or ribavirin are avoided.

Optionally, the treatment may also include another anti-HCV agent. Each DAA can be administered at the same dosing frequency or at different ones, at around the same time or at different times. The treatment duration is preferably no more than 12 weeks, or no more than 8 weeks.

Claims

This PCT application contains a total of 24 claims, directed to a method of treatment for HCV infection, which comprises administration of at least two DAAs, including glecaprevir and pibrentasvir, wherein neither interferon nor ribavirin is administered during the treatment.

Observations

The PCT application was filed on 14 March 2014 and was published for the first time on 25 September 2014.

According to the international preliminary report on patentability, none of the claims as originally filed involve an inventive step in view of the documents cited in the international search report.

The PCT application entered the European phase as EP 2968301. A set of amended claims has been filed before examination. The new claims contain one independent claim which protects a combination of at least two DAAs comprising glecaprevir and pibrentasvir for use in a method for treatment of HCV infection, wherein neither interferon nor ribavirin are administered during the treatment. The new claims are currently intended to be granted.

PATENT 5

Title: Combination of direct-acting antiviral agents and ribavirin for treating HCV patients
WO 2014/152635 (AbbVie, filed 14 March 2014)

Summary

This PCT application relates to an interferon-free treatment for HCV infection, comprising administration of ribavirin and at least two DAAs including glecaprevir and pibrentasvir.

Description

This PCT application is based on the unexpected finding that an interferon-free treatment using a combination of ribavirin and at least two DAAs including glecaprevir and pibrentasvir, for a duration of no more than 12 weeks, can achieve significant sustained virological response.

This PCT application describes a method of treatment for HCV infection, which comprises administration of ribavirin, including its pro-drugs, and at least two DAAs including glecaprevir and pibrentasvir, without administration of interferon.

Optionally, the treatment may also include another anti-HCV agent (except interferon). Each DAA can be administered independently at the same or different dosing frequencies. The treatment duration is preferably no more than 12 weeks, or no more than 8 weeks.

Claims

The PCT application contains a total of 24 claims, directed to a method for treatment for HCV infection, which comprises administration of ribavirin and at least two DAAs, including glecaprevir and pibrentasvir, without administration of interferon.

Observations

The PCT application was filed on 14 March 2014 and was published for the first time on 25 September 2014. Both novelty and inventive step have been acknowledged in the preliminary examination.

PATENT 6

Title: Methods for treating HCV
WO 2015/153792 (AbbVie, filed 01 April 2015)

Summary

This PCT application relates to an interferon-free treatment for HCV infection, comprising administration of ribavirin and at least two of the DAAs selected from glecaprevir, pibrentasvir and sofosbuvir.

Description

This PCT application is based on the unexpected finding that a combination therapy of glecaprevir and pibrentasvir, in the absence of interferon and for duration of no more than 12 weeks, can achieve significant sustained virological response.

This PCT application describes a method for treating HCV infection, which comprises administration of at least two DAAs selected from glecaprevir, pibrentasvir and an HCV polymerase inhibitor. The method does not include administration of interferon. The HCV polymerase inhibitor is preferably sofosbuvir.

Each DAA can be administered independently at the same or different dosing frequencies. The treatment duration should preferably be no more than 12 weeks, or no more than 8 weeks.

Claims

This PCT application contains a total of 17 claims directed to a method for treating HCV infection, which comprises administration of ribavirin and at least two DAAs selected from glecaprevir, pibrentasvir and sofosbuvir, without administration of interferon.

Observations

The PCT application was filed on 13 February 2013 and was published for the first time on 08 October 2015.

According to the international preliminary report on patentability, none of the claims as originally filed involves an inventive step in view of the documents cited in the international search report.

PATENT 7

Title: Methods for treating HCV
WO 2015/153793 (AbbVie, filed 01 April 2015)

Summary

This PCT application relates to interferon- and ribavirin-free treatments for HCV infection, which comprise administration of at least two DAAs selected from glecaprevir, pibrentasvir and sofosbuvir.

Description

This PCT application is based on the unexpected finding that a combination therapy of glecaprevir and pibrentasvir, in the absence of interferon and ribavirin and for a duration of no more than 12 weeks, can achieve significant sustained virological response.

This PCT application describes a method of treating HCV infection, which comprises administering at least two DAAs selected from glecaprevir, pibrentasvir and a HCV polymerase inhibitor without administration of either interferon or ribavirin. The HCV polymerase inhibitor is preferably sofosbuvir.

Each DAA can be administered independently at the same or different dosing frequencies. The treatment duration should preferably be no more than 12 weeks, or no more than 8 weeks.

Claims

This PCT application contains a total of 17 claims, directed to a method for treating HCV infection, which comprises administration of at least two DAAs selected from glecaprevir, pibrentasvir and sofosbuvir, without administration of either interferon or ribavirin

Observations

The PCT application was filed on 13 February 2013 and was published for the first time on 08 October 2015.

According to the international preliminary report on patentability, none of the claims as originally filed involves an inventive step in view of the documents cited in the international search report.

PATENT 8

Title: Crystal forms
WO 2015/171993 (AbbVie, filed 08 May 2015)

Summary

This PCT application claims a number of crystalline forms of pibrentasvir, and pharmaceutical compositions comprising them.

Description

A number of crystalline forms of pibrentasvir are disclosed and PXRD data are provided.

Pharmaceutical compositions comprising a crystalline form of pibrentasvir and methods of preparing such compositions are also provided.

Claims

This PCT application contains a total of eight claims, directed to a number of different crystalline forms of pibrentasvir, relying on references to figures and tables in the description.

Compositions comprising a crystalline form of pibrentasvir and methods of preparing such compositions are also claimed.

Observations

The PCT application was filed on 08 May 2015 and was published for the first time on 12 November 2015.

According to the international preliminary report on patentability, none of the claims as originally filed involves an inventive step in view of the documents cited in the international search report.

PATENT 9

Title: Solid forms of antiviral compounds
WO 2016/053869 (AbbVie, filed 28 September 2015)

Summary

This PCT application claims crystalline forms and crystalline solvates of pibrentasvir, methods for preparing them and pharmaceutical compositions comprising them.

Description

This PCT application is based on the surprising discovery that pibrentasvir can be crystallized in a solvent system comprising n-butylamine and that such crystals can be used to seed saturated or supersaturated solution of pibrentasvir in other solvent systems in order to prepare other crystalline solvates of pibrentasvir. Further, crystalline pibrentasvir anhydrate can be obtained by drying a crystalline solvate of pibrentasvir.

Examples demonstrating the preparation of the crystalline patterns A to H are given.

This PCT application also relates to pharmaceutical compositions comprising a crystalline form of pibrentasvir.

This PCT application also relates to methods of treating HCV infection, wherein the said methods comprise administration of a crystalline form of pibrentasvir and, optionally, one or more other HCV inhibitors, with or without interferon.

Claims

This PCT application contains a total of 55 claims.

Claims 1–27 cover a crystalline form of pibrentasvir, in which claims 2–7 are directed to anhydrate (pattern C), claims 8–12 are directed to crystalline pibrentasvir anhydrate (pattern G), claims 16–21 are directed to crystalline pibrentasvir acetonitrile solvate or acetonitrile-di-n-butyl ether solvate (pattern F) and claims 22–27 are directed to crystalline methanol-diethylether pibrentasvir solvate (pattern B).

Claim 28 is directed to a pharmaceutical composition comprising an above-mentioned crystalline form.

Claims 29–50 cover a method for preparing a crystalline form of pibrentasvir solvate.

Claims 51–55 cover a method for preparing a crystalline form of pibrentasvir anhydrate.

Observations

The PCT application was filed on 28 September 2015 and was published for the first time on 07 April 2016.

According to the written opinion of the International Searching Authority, none of the claims as originally filed involves an inventive step in view of the documents cited in the international search report.

PATENT 10

Title: Combinations useful to treat hepatitis C virus
WO 2016/134058 (AbbVie, filed 05 June 2015)

Summary

This PCT application relates to a pharmaceutical composition comprising two or more therapeutic agents that are useful for treating HCV, including a nucleoside/nucleotide-based NS5B inhibitor (A-1 to A-6) and pibrentasvir (or ombitasvir). The composition may further contain glecaprevir.

Description

This PCT application describes methods for treating HCV using a combination of a therapeutic agent A selected from:

A-1: (2R)-isopropyl 2-(((((2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl) methoxy(phenoxy)phosphoryl)amino) propanoate,

A-2: (R)-isopropyl 2-(((S)-(((2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl)methoxy) (phenoxy)phosphoryl)amino)propanoate,

A-3: (R)-isopropyl 2-(((R)-(((2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl)methoxy) (phenoxy)phosphoryl)amino)propanoate,

A-4: ((2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl)methyl dihydrogen phosphate,

A-5: ((2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl)methyl trihydrogen phosphate,

A-6: (2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl)methyl trihydrogen phosphate

and a therapeutic agent B selected from (B-1) ombitasvir and (B-2) pibrentasvir. The method may further comprise a therapeutic agent selected from (C-1) paritaprevir and (C-2) glecaprevir.

Claims

This PCT application contains a total of 20 claims, of which claims 1, 2 and 11 are independent.

Claim 1 is directed to a pharmaceutical composition comprising a therapeutic agent A selected from compounds (A-1) to (A-3) and a therapeutic agent B selected from ombitasvir and pibrentasvir.

Claim 2 and its dependent claims are directed to a method for treating HCV using the combination comprising a therapeutic agent A selected from compounds (A-1) to (A-3) and a therapeutic agent B selected from ombitasvir and pibrentasvir. Dependent claim 9 is directed to the same method,

further comprising administration of a therapeutic agent C, selected from paritaprevir and glecaprevir.

Claim 11 and its dependent claims are directed to a method for treating HCV using the combination comprising a therapeutic agent A selected from compounds (A-1) to (A-6) and a therapeutic agent B selected from ombitasvir and pibrentasvir. Dependent claim 15 is directed to the same method, further comprising administration of a therapeutic agent C selected from paritaprevir and glecaprevir.

Observations

The PCT application was filed on 05 June 2015 and was published for the first time on 25 August 2016.

The examiner found that the chemical names of compounds A-1 to A-6 (on p14 of the PCT application) do not correspond to the structures in the claims (see the written opinion of the International Searching Authority).

The International Searching Authority (EPO) acknowledged novelty for all claims 1–20. However, none of the claims are acknowledged as involving an inventive step due to lack of data with respect to the antiviral effect of the compounds A-1 to A-6 or of combinations comprising the same.

ANNEX 1. PIBRENTASVIR PATENT SITUATION IN COUNTRIES

	Patent 1	Patent 2	Patent 3	Patent 4
Pub. No (Appl. No)	**WO2012/051361A1 (PCT/US2011/056045)**	**WO2012116257A1 (PCT/US2012/026456)**	**WO2014047039A1 (PCT/US2013/060103)**	**WO2014152514A1 (PCT/US2014/027423)**
Applicants	AbbVie	AbbVie	AbbVie	AbbVie
Filing date	12 October 2011	24 February 2012	17 September 2013	14 March 2014
Title	Antiviral compounds	Antiviral compounds	Methods for treating hepatitis C	Combination of two antivirals for treating hepatitis C
Subject matter	Basic compound patent, constraining for generic medicines where granted	Equivalent document of Patent 1.	Use of pibrentasvir	Combination of glecaprevir/pibrentasvir
Priority data	US13/100,827: 04 May 2011 US61/446,800: 25 February 2011 US12/964,027: 09 December 2010 US12/903,822: 13 October 2010	US61/446,800: 25 February 2011	US61/702,564: 18 September 2012	US61/783,376: 14 March 2013
Patent status				
Argentina	Status N/A AR083398A1	-	-	-
Australia	Granted AU2011316506B2 Pending AU2014203655BB	-	Pending AU2013318302A1	Granted AU2014239563B2 Pending AU2016202823A1
Bolivia	Status N/A SP-00314-2011	-	-	-
Brazil	-	-	-	-
Canada	Granted CA2807847C Pending CA2938547A	Pending CA2828495 A	Pending CA2884539A	Pending CA2942823A
Chile	Status N/A CL0970-2013	-	-	-
China	Granted CN103153988B Pending CN104193729A	Granted CN103596941B	Pending CN104797253A	Pending CN105073113A
China, Hong Kong SAR	Granted HK1188717	Pending HK1187053	Pending HK1209319	-
Colombia	Status N/A CO6761348	-	-	-
Costa Rica	Status N/A CR2013-0170	-	-	-
Dominican Republic	Status N/A DOP2013-0078	-	-	-
Ecuador	Status N/A ECSP2013-12622	-	-	-
Egypt	Status N/A PCT611/2013	-	-	-

The INPADOC patent family members for patents/applications 1 to 10 are listed in the tables below.

The equivalents were identified (INPADOC family) and, where possible, the legal status of each equivalent was checked on the websites of the relevant patent offices.

	Patent 5	Patent 6	Patent 7	Patent 8
Pub. No (Appl. No)	**WO2014152635A1 (PCT/US2014/027556)**	**WO2015153792A1 (PCT/US2015/023922)**	**WO2015153793A1 (PCT/US2015/023923)**	**WO2015171993A1 (PCT/US2015/029842)**
Applicants	AbbVie	AbbVie	AbbVie	AbbVie
Filing date	14 March 2014	01 April 2015	01 April 2015	08 May 2015
Title	Combination of direct-acting antiviral agents and ribavirin for treating HCV patients	Methods for treating HCV	Methods for treating HCV	Crystal forms
Subject matter	Combination of glecaprevir / pibrentasvir and ribavirin	Combination comprising ribavirin and at least two of the DAAs selected from glecaprevir, pibrentasvir and sofosbuvir	Combination comprising at least two of the DAAs selected from glecaprevir, pibrentasvir and sofosbuvir	Crystalline forms of pibrentasvir
Priority data	US61/783,437: 14 March 2013	US61/973,930: 02 April 2014 US61/989,953: 07 May 2014 US62/016,460: 24 June 2014	US61/973,929: 02 April 2014 US61/989,951: 07 May 2014 US62/016,459: 24 June 2014	US61/991,242: 09 May 2014
Patent status				
Argentina	-	-	-	-
Australia	Pending AU2014239322A	Pending AU2015240753A	Pending AU2015240754A	Pending AU2015255784A
Bolivia	-	-	-	-
Brazil	-	-	-	-
Canada	Pending CA2901818A	Pending CA2943054A	Pending CA2942823A	Pending CA2945205
Chile	-	-	-	-
China	Pending CN105007921A	-	-	-
China, Hong Kong SAR	Pending HK1213191	-	-	-
Colombia	-	-	-	-
Costa Rica	-	-	-	-
Dominican Republic	-	-	-	-
Ecuador	-	-	-	-
Egypt	-	-	-	-

	Patent 1	Patent 2	Patent 3	Patent 4
Eurasian Patent Office *	Granted EA024100 Pending EA201301158 Pending EA201390538	-	-	Pending EA201591702
European Patent Office **	Granted EP2692346B1 Pending EP2692726A1	Pending EP2678334A1	Pending EP2897611A1	Pending EP2968301A
Guatemala	Status N/A GT201300093	-	-	-
Gulf Cooperation Council ***	Status N/A GCC2011/19503	-	-	-
India	Pending 1310/DELNP/2013	-	-	-
Indonesia	Status N/A W00201301506	-	-	-
Israel	Granted IL225010 Pending IL238030	-	-	Pending IL240419
Japan	Granted JP5834085 Pending JP2015-212539	Rejected JP2014-510063	Pending JP2015-528511	Pending JP2016-513695
Malaysia	Pending PI2013700273	-	-	-
Mexico	Pending MX/a/2013/004150	Pending MX/a/2013/009763	Pending MX/a/2015/003501	Pending MX/a/2015/012538
Mongolia	Status N/A MN5013	-	-	-
New Zealand	Granted NZ606645 Pending NZ715562	-	Pending NZ630581	Granted NZ631155 Pending NZ719137
Pakistan	Status N/A PK752/2011	-	-	-
Panama		-	-	-
Paraguay	Status N/A PY43697/2011	-	-	-
Peru	Status N/A PE0038-2014 Status N/A PE0835-2014	-	-	-
Philippines	Pending PH/1/2013/500708	-	-	-
Republic of Korea	Granted KR101586215B Pending KR20140143152	-	-	Pending KR20150129032
Russian Federation	Granted EA024100 (designated)	-	Pending RU2015114543	Pending EA201591702
Singapore	Granted SG188951	-	Pending SG11201502095S	Pending SG11201507364S
South Africa	Pending ZA2013/02269 Pending ZA2013/06888	-	-	Pending ZA2015/05880
Thailand	Granted TH150551	-	-	-
Ukraine	Pending UA201305877	-	-	-
Uruguay	Status N/A UY33667 Status N/A UY35266	-	-	-
USA	Granted US8937150 Pending US20150087618	Granted US9394279 Abandoned US20120220562	Pending US2014080868	Pending US20140275099
Venezuela	-	-	-	-
Viet Nam	Status N/A VN15857	-	-	-

	Patent 5	Patent 6	Patent 7	Patent 8
Eurasian Patent Office*	Pending EA201591701A			
European Patent Office **	Pending EP2968302A	-	-	-
Guatemala	-	-	-	-
Gulf Cooperation Council ***	-	-	-	-
India	-	-	-	-
Indonesia	-	-	-	-
Israel	Pending IL240445	-	-	-
Japan	Pending JP2016-513703	-	-	-
Malaysia	-	-	-	-
Mexico	Pending MX/a/2015/012536	-	-	-
Mongolia		-	-	-
New Zealand	Pending NZ631789	-	-	-
Pakistan	-	-	-	-
Panama	-	-	-	-
Paraguay	-	-	-	-
Peru	-	-	-	-
Philippines	-	-	-	-
Republic of Korea	Pending KR20150129035	-	-	-
Russian Federation	Pending EA201591701A	-	-	-
Singapore	Pending SG11201507361Y	-	-	-
South Africa	Pending ZA2015/06031	-	-	-
Thailand	-	-	-	-
Ukraine	-	-	-	-
Uruguay	-	-	-	-
USA	Pending US2014274934A	Pending US2015283199A Pending US2016317603A	Pending US2015283198A Pending US2016317602A	Pending US2015322047A
Venezuela	-	-	-	-
Viet Nam	-	-	-	-

	Patent 9	Patent 10
Pub. No (Appl. No)	**WO2016053869A1 (PCT/US2015/052632)**	**WO2016134058A1 (PCT/US2016/018327)**
Applicants	AbbVie	AbbVie
Filing date	28 September 2015	17 February 2016
Title	Solid forms of antiviral compounds	Combinations useful to treat hepatitis C virus
Subject matter	Crystalline forms of pibrentasvir	Combination therapy of HCV (Note: the claims seem to contain faultily drawn formulae)
Priority data	US62/056,746: 29 September 2014	US62/117,764: 18 February 2015 US62/133,005: 13 March 2015

Patent status

Argentina	-	-
Australia	-	-
Bolivia	-	-
Brazil	-	-
Canada	-	-
Chile	-	-
China	-	-
China, Hong Kong SAR	-	-
Colombia	-	-
Costa Rica	-	-
Dominican Republic	-	-
Ecuador	-	-
Egypt	-	-
Eurasian Patent Office *	-	-
European Patent Office **	-	-
Guatemala	-	-
Gulf Cooperation Council ***	-	-

	Patent 9	Patent 10
India	-	-
Indonesia	-	-
Israel	-	-
Japan	-	-
Malaysia	-	-
Mexico	-	-
Mongolia	-	-
New Zealand	-	-
Pakistan	-	-
Panama	-	-
Paraguay	-	-
Peru	-	-
Philippines	-	-
Republic of Korea	-	-
Russian Federation	-	-
Singapore	-	-
South Africa	-	-
Thailand	-	-
Ukraine	-	-
Uruguay	-	-
USA	Pending US2016090373A	-
Venezuela	-	-
Viet Nam	-	-

Notes: Cells with "–" indicate that no patent or patent application has been found in the INPADOC database. This may mean that no patent application has been filed, that the patent application has not been found (e.g. in the case of clerical error), or the patent application had not been published at the time of the search. Information in this Annex should therefore always be checked at the relevant patent office.

* Eurasian Patent Organization (EAPO): Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyz Republic, Moldova, Russian Federation, Tajikistan, Turkmenistan.

** European Patent Office (EPO): designated contracting states: Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Macedonia (former Yugoslav Republic of Macedonia), Malta, Monaco, Netherlands, Norway, Poland, Portugal, Romania, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom; Extension states: Bosnia & Herzegovina, Montenegro. Validation states: Moldova, Morocco, Tunisia.

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