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Patent Analysis for Medicines and Biotherapeutics in Trials to Treat COVID-19

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SOUTH CENTRE

RESEARCH PAPER

120

PATENT ANALYSIS FOR MEDICINES AND BIOTHERAPEUTICS IN TRIALS TO TREAT COVID-19

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OCTOBER 2020

* This analysis was conducted by Ms. Srividya Ravi, consultant and Patent Agent in India.

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ABSTRACT

This report provides an analysis of patents covering medicines in trials to treat COVID-19. The aim of the report is to support national patent offices and interested parties in developing countries with information that can serve as guidance for the examination of the claims contained in relevant patents or patent applications.

The medicines considered for the patent analysis in this report are remdesivir, ruxolitinib and favipiravir, and the biotherapeutics tocilizumab, siltuximab and sarilumab.

Este informe proporciona un análisis de las patentes que cubren los medicamentos que se encuentran en ensayos clínicos para el tratamiento de COVID-19. El objetivo del informe es apoyar a las oficinas nacionales de patentes y demás partes interesadas de los países en desarrollo con información que pueda servir de orientación para el examen de las reivindicaciones contenidas en las patentes o solicitudes de patente pertinentes.

Los medicamentos considerados para el análisis de las patentes en este informe son remdesivir, ruxolitinib y favipiravir, y los bioterapéuticos tocilizumab, siltuximab y sarilumab.

Ce rapport fournit une analyse des brevets couvrant les médicaments en cours d'essai pour traiter le COVID-19. Le but du rapport est de fournir aux offices nationaux des brevets et d'autres parties intéressées dans les pays en développement des informations qui pourraient être utiles pour l'examen des revendications des brevets ou pour l'examen d'une demande de brevet.

Les médicaments considérés pour l'analyse des brevets dans ce rapport sont les médicaments remdesivir, ruxolitinib et favipiravir, et les produits biothérapeutiques tocilizumab, siltuximab et sarilumab.

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LIST OF ACRONYMS

CDR	complementary determining region
COVID-19	Infectious disease caused by the SARS-CoV-2 virus
EBV	Epstein Barr virus
EC50	Half maximal effective concentration
EPO	European Patent Office
EU	European Union
FDA	US Food and Drug Administration
FR	France
HCV	hepatitis C virus
HHV-8	human herpesvirus-8
HIV	human immunodeficiency virus
HPV	human papilloma virus
HTLV 1	human T-cell leukemia virus type 1
IC50	half maximal inhibitory concentration
IgG1	Immunoglobulin G1
IL-6	interleukin-6
IL-6R	Interleukin-6 receptor
iMCD	idiopathic multicentric Castleman's disease
IN	India
IPRP	International Preliminary Report on Patentability
ISR	International Search Report
IUPAC	International Union of Pure and Applied Chemistry
JAK	Janus kinases
K_D	Refers to the affinity of the antibody to the receptor
mM	millimolar
–NH2 group	compounds and functional groups that contain a basic nitrogen atom with a lone pair
nM	nanomolar
P	Phosphorus
PCT	Patent Cooperation Treaty
pM	picomolar

μM	micromolar
UNDP	United Nations Development Programme
US	United States
USPTO	United States Patent and Trademark Office
VZV	Varicella-zoster virus
WO	Prefix indicating a patent filling under the Patent Cooperation Treaty administered by WIPO
WIPO	World Intellectual Property Organization

INTRODUCTION

This report provides an analysis of patents covering medicines in trials to treat COVID-19. The aim of the report is to support national patent offices and interested parties in developing countries with information that can serve as guidance for the examination of the claims contained in relevant patents or patent applications.

The medicines considered for the patent analysis in this report are remdesivir, ruxolitinib and favipiravir, and the biotherapeutics tocilizumab, sarilumab and siltuximab.

The report examines the admissibility of the claims contained in patent applications or granted patents for a number of medicines under study in the light of rigorous patentability standards. The guiding criteria used to examine such admissibility are based on the "Guidelines for the examination of patent applications relating to pharmaceuticals", UNDP 2016 (hereinafter referred to as 'Guidelines').[2] The analysis addresses the technical aspects of the patent specifications and claims, described in a manner that is readable for a non-expert, including possible grounds for the amendment or rejection of the claimed invention.

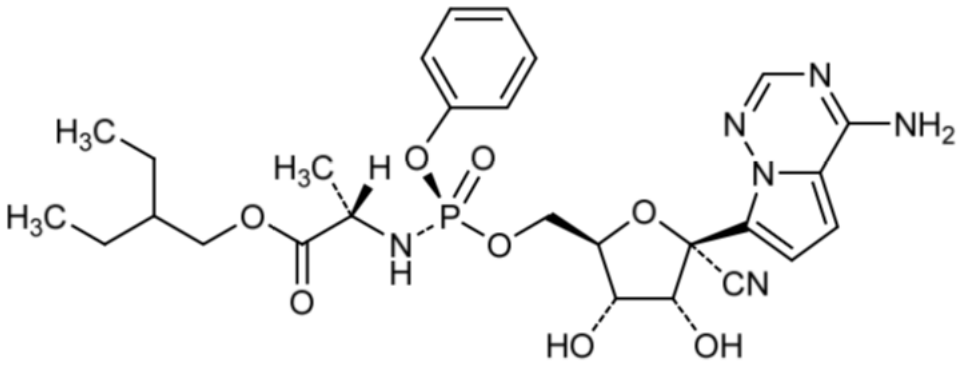
The methodology applied for preparing this report was as follows: the patent applications and the claims of the respective patents granted by the Indian Patent Office, the United States United States Patent and Trademark Office (USPTO) and by the European Patent Office (EPO) were studied, as well as the International Search Report (ISR) and Written Opinion of patent applications filed under the Patent Cooperation Treaty (PCT). The prosecution history of the patent applications at international stage (WO filing) and national phase (India, United States and Europe) were analyzed. A comparative analysis of claims in the various patent applications and eventually granted claims were also made. The patent specification and claims were critically examined for disclosure, enablement and other patentability requirements and a detailed claim analysis was conducted. The compliance to the basic tenets of patenting, and to the referred to Guidelines was evaluated. Accordingly, key findings were enlisted. If required, a brief prior art search was also conducted, and the identified documents studied.

[2] Available from https://www.undp.org/content/undp/en/home/librarypage/hiv-aids/guidelines-for-the-examination-of-patent-applications-relating-t.html.

REMDESIVIR

Background

Remdesivir is a broad spectrum anti-viral drug developed and patented by Gilead Sciences in nearly 70 countries. It is administered by parenteral route (injection) to relieve subjects of viral infections.



Molecular formula: $C_{27}H_{35}N_6O_8P$

IUPAC name: (2S)-2-{(2R,3S,4R,5R)-[5-(4-Aminopyrrolo[2,1-f] [1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]phenoxy-(S)-phosphorylamino}propionic acid 2-ethyl-butyl ester

Patents Studied

WO2009132135. Filed on 22 April 2009.

WO2012012776. Filed on 22 July 2011.

WO2016069826. Filed on 29 October 2015.

WO2017049060. Filed on 16 September 2019.

WO2009132135

WO2009132135 is a patent application that covers a broad Markush[3] structure and its pharmaceutically acceptable salts i.e. Compound of Formula I that can potentially protect millions of compounds. The patent specification has disclosed the synthesis of mere 44 compounds and the characterization data for only 13 compounds are included.

Several compounds and preferred substituents at various positions in the core ring are provided and claimed; however, Remdesivir is not explicitly disclosed in this application. It is

[3] A Markush claim is a particular kind of patent claim that lists alternative species or elements that can be selected as part of the claimed invention.

not one of the preferred embodiments of the compound of formula I, but remdesivir is broadly covered in the claims.

Some embodiments of the compounds are close to the chemical structure of remdesivir, but the exact compound is covered remotely, and not disclosed explicitly and particularly. Few Compounds that are very close to Remdesivir are those of e.g. 21 and 26, refer pages 135 and 137. Claim 18 claims particular compounds of Claim 1, around 36 compounds are disclosed, few have no P, few have more than one P, some do not have the group C≡N, remdesivir is not one of them.

Up to claim 18, the compound is claimed. Claim 19 includes a racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph or amorphous form.

Claims 20-22 is for a pharmaceutical composition alone or in combination with other therapeutic agents, including agents to treat Hepatitis C viruses (HCV) and interferons.

Claims 23-28 are method claims for inhibiting HCV polymerase and treating a viral infection caused by a virus of the Flaviviridae family including Dengue and Hepatitis C viruses amongst many other infections, alone or in combination with other agents.

Claim 29 pertains to a compound as in any one of claims 1 to 18 used in the manufacture of a medicament for treating a viral infection caused by a virus.

Regarding anti-viral activity, a general protocol has been provided. Also, protocols for cell-based EC50 and Cytotoxicity assay is provided, but no results are enlisted. The anti-viral study has been conducted on mouse model for dengue infection and a generic conclusion has been arrived at. There are no results for assay of even the few compounds (44) synthesized. There is also no result with regard to subject group and control group.

The IC50 for HCV by NS5b polymerase assay lists results as <100 μM, <10 μM and for compound 17 as < 1 μM. For the seven compounds for which EC50 results have been shared, one compound was < 1 μM, 2 were 1-10 μM and four were 10-100 μM. None of these seven compounds were Remdesivir.

Results of cytotoxicity tests are not disclosed.

To establish inventive step for EPO, following data was provided:

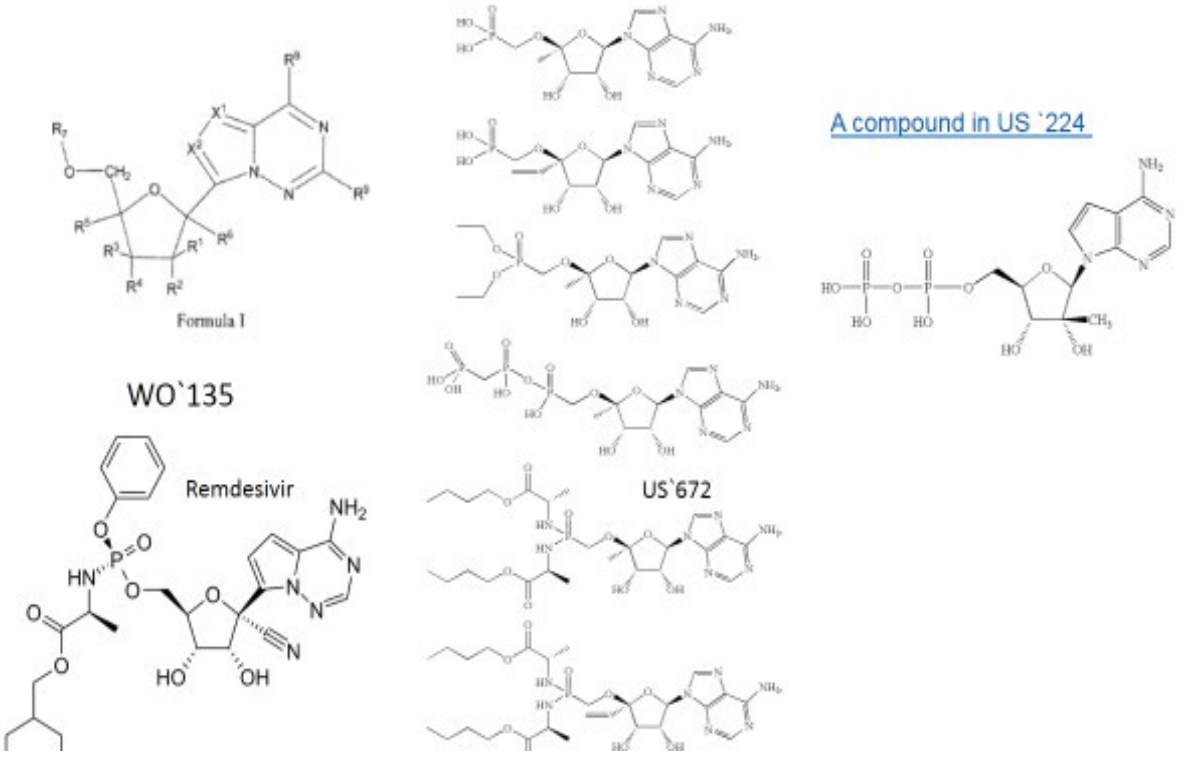
Moreover, in the following table exact values for the same compounds are given:

Compound No.	EC_{50} μM
2	24
3	33
4	>89
5	55
6	0.7
12	5.5
13	4.8

Since the Examining Division already acknowledged an inventive step in case exact data are provided, it is believed that no further comments with regard to an inventive step are required.

Activity specifically for seven compounds was provided and EPO processed a grant.

While the compounds disclosed may be novel, the compounds are a combination of two relevant prior arts, US 7842672 filed on 6 July 2007 by Gilead and US 7202224 filed on 31 July 2006 by Merck. Very closely related compounds are disclosed and they also possess anti-viral activity and are useful for treating various viral infections. US 7202224 claims a method of treating an infection caused by HCV, while US 7842672 is also used to treat viral infections, alone and in combination with other therapeutic agents.



Referring to the image above, compounds with nitrogen (N) and oxygen (O) containing rings and P=O and it being further substituted are known prior to the WO2009132135 patent for anti-viral activity itself. The Indian Patent Office has cited these two documents in its Examination report and accordingly claims were amended to move away from the citations. However, neither for the cited compounds nor for the invention's compound is activity studied in detail and disclosed.

Note: Referring to the image, as you view it, the right most panel lists the US 7202224 compound. The rings right most in the structure has three N and one –NH2 group. In the middle panel are compounds of another prior art, US 7842672. The rings contain four N and the –NH2 group. Remdesivir and its patent WO2009132135 (refer left most panel) also have the –NH2 group and rings of same structure, but with three N in different positions.

Referring to the P=O group on the left side of the different structures, all the molecules possess P=O group, but other groups are differently linked to P. The ring with O is common and the O group out of this ring linking to P=O directly or through one –CH is also common. Further groups on P however differ.

The two cited documents also refer to compounds with anti-viral activity and most parts of the structure that possibly play key roles in eliciting the said activity seem to be disclosed. So,

Remdesivir and compounds of formula I of WO2009132135 are bound to possess anti-viral activity and thus are obvious.

Summary of Observations

- The WO2009132135 patent claims a Markush structure which covers at least thousands if not millions of compounds.
- While remdesivir is covered by the Markush, it is not enabled and particularly disclosed in this application.
- The process and synthesis is provided for mere 44 compounds, and fewer compounds are characterized.
- None of the test results for anti-viral activity or toxicity studies are provided in detail. Just 8 compounds have been assessed for anti-viral activity.
- The compounds are highly obvious in light of two cited documents US 7842672 and US 7202224.

Key Findings

1. WO2009132135 lacks preferred embodiment description for remdesivir.
2. The compound is neither described, nor its process of synthesis described, nor is it characterized, nor is it evaluated for anti-viral activity.
3. The activity of remdesivir against Flaviviridae family of viruses is not demonstrated in this invention.
4. The patent demonstrates a few compounds to possess anti-viral activity and covers a huge number of possible anti-viral drug candidates.
5. Such possible compounds may be limited to the extent covered in prior arts, if they are demonstrated to show unexpectedly potent anti-viral activity, given that prior arts demonstrate similar compounds for the same activity.

WO2012012776

This is a narrower version of WO2009132135 and claims the compound of formula I or its salt or ester for use in treating a paramyxoviridae infection.

This is essentially a use claim, not allowed in many countries.

The scope is a little limited in terms of compounds covered in comparison to WO2009132135, however in terms of claim coverage, it is a use claim. Remdesivir is explicitly claimed with structure listed in claim 13 with its salts, also refer compound 9 on page 127- for synthesis and characterization. Pharmaceutical composition, combination with many drugs, administration by inhalation or nebulization (claims 17 and 18) and use against many viruses including parainfluenza, pneumonia, inhibition of Paramyxoviridae polymerase (claim 24) are all covered.

Examples for synthesis and characterization for 20 compounds provided. Organic, inorganic and amino acid addition salts are described, so are enantiomers and diastereomers.

Tablet formulations, eye formulations emulsions are all described with acceptable excipients. Other solid and liquid dosage forms are also described including emulsions, powders, and topical and inhaling formulations are covered. Nebulizing formulation and dry powder inhalation also disclosed. Parenteral, vaginal, rectal, and controlled release profiles also

disclosed. Combinations with a huge number of drugs is covered and metabolites of the drug are described.

Activity data for few compounds provided, just 5-10, however, remdesivir does not seem to be evaluated for activity against paramyxoviridae infection.

WO2016069826

The WO2016069826 patent application is titled “Methods for Treating Filoviridae Virus Infections”. It contains 24 claims. The first independent claim is a method of treating filovirideae infection in humans with compound of formula IV where option to only one substituent, R7, is retained and its salts and hydrates and esters are included. The options for R7 are very large and a huge number of compounds are possible. Particular substituents of remdesivir are claimed in claims 3 and 4. The diastereomers are listed in Claim 5 and 6 and claim 7 particularly covers remdesivir.

Claim 8 claims a carrier and excipient, 9 and 10 claim combination with few monoclonal antibodies, Ebola convalescent plasma, favipiravir and few more drugs. Claims 11-14 cover various viruses of the filoviridae type, and particularly Ebola is claimed.

Claim 16 is a compound claim and 17 compounds are listed. Claim 17 claims remdesivir in particular. Claim 18 claims compositions. Claims 19,20 and 21 claim a compound to treat filoviridae and claims 22-24 are use claims or Swiss claims.

The patent specification covers oral, parenteral, ophthalmic, rectal, veterinary, nasal buccal and sublingual formulations and for treatment ranging from 1-100 days. Combinations with various classes of drugs are also covered. The method of treatment is by inhibiting filovirideae polymerase, and assay for the same has been performed. Around 30 compounds and few salts and stereoisomers have been exemplified for synthetic procedure as well as characterized.

Biological assay: The protocols followed for the anti-viral assays and the evaluation of the compounds for their activity is provided. Few compounds were tested and the results for Remdesivir (ie Compound 32) and in comparison to its diastereomer (Compound 9) are provided. The activity is evaluated for Ebola, Nipah and Marburg viruses in particular.

Summary of observations

The Markush potentially covers hundreds of compounds. Just around 15 compounds and their salts and diastereomers are synthesized, and only few exhibit activity against the filoviridaea virus. Based on such data, a method claim is granted over the entire Markush strucuture.

The method of treating Filoviridae is novel, since prior arts disclose the use of same or similar compounds against other viruses. Having known that similar compounds can be used to treat viruses such as hepC, influenza, parmyxoviridae and so on, the challenge in using the particular diastereomer for treating filoviridae seems to be a matter of routine experimentation. If not, the onus is on the applicant to bring out the challenge in identifying remdesivir to treat filoviridae infections, in light of prior arts for various types of viruses.

Regarding the compound claims, the claim for remdesivir lacks novelty in view of the explicit disclosure in WO2012012776. The WO2012012776 patent application discloses a diastereomer that is different from the one claimed in the current case and also the one that

exhibits activity against filoviridae viruses. But referring to the guidelines, particularly pages 30-32, which states that enantiomers are inherently anticipated and obvious to try when evaluated for inventive step, the compound claims lack novelty and inventive step.

However, the equivalent patent is granted in several countries including US, EPO, India and so on. In India, a patent for selected compounds, including and specifically remdesivir has been granted in IN332280, since method of treatment and use claims are not allowed in India. The patent was voluntarily licensed by Gilead to several Indian pharmaceutical companies for combatting the COVID 19 pandemic. A post-grant opposition against the granted patent has been filed citing the WO2009132135 and WO2012012776 as affecting the novelty of the compound claims. A reply to the notice of the post grant opposition has been recently filed by Gilead and it states that the patent claims the diastereomer that is not explicitly disclosed in the prior arts, including WO2012012776 patent, and for a prior art to be affecting the novelty, it should disclose all elements of the invention. Further, the rebuttal to the opposition notice states that none of the prior arts suggest that this particular compound and the particular diastereomer can be efficacious against filoviridae viruses. No further update on the status of the opposition is available.

Similar arguments were also provided to overcome the comments in the FER and objections raised on the basis of Sec 3 (d) of the Indian Patent Act.

Key findings

- The application claims Remdesivir, and particularly a diastereomer, which is different from the one disclosed in WO2012012776.
- The D diastereomer claimed in the current case possesses activity against Ebola virus.
- Compounds claimed in this case lack novelty, are inherently anticipated and obvious to try.
- Opposition proceedings are ongoing in India and Argentina.

WO2017049060

Around 32 compounds synthesized, and a method of treating SARS, MERs and coronavirus is generally claimed. Very few compounds are assayed for activity, while Markush covers thousands of compounds. Remdesivir is disclosed, but its evaluation of activity is limited to corona viruses.

Coverage of patent in terms of claims is similar to WO2012012776.

Refer para 0405- Compounds 1, 9 (remdesivir) and 32 tested against Lassa and Junin viruses, (arena viruses) detailed test protocol is provided. The results of three compounds is tabulated, amongst those three compounds, activity of compound 1 was largely not determined. Compounds 9 (remdesivir) and 32 were studied for anti SARS and MERS activity (Corona viruses) and found to be active.

Further testing of compounds 1 and 32 for efficacy and toxicity was continued and also anti-viral activity in monkeys studied for compound 32. The symptoms were less pronounced in compound 32-treated monkeys, and viral RNA in the respiratory tract was significantly reduced in Compound 32-treated animals, refer para 0435, while para 0436 states virus was detected

in nose swabs and throat swabs at Day 1, 3, 5 and 6 post-infection There was no difference in viral load between vehicle-treated and Compound 32-treated animals.

Claims 1- 38 cover a method of treating Arenaviridae viruses (Junin and Lassa viruses), claims 39-74 are for a method of treating Coronaviridae viruses (MERS, SARS and few more) and claims to use of compounds to make a medicament for treating viruses, a compound to treat the viruses and a kit comprising dosage units of compounds or their stereoisomers, salt, ester, hydrate, solvate, mixture of stereoisomers or tautomers are covered.

Claims 25 and 61 particularly claim the enantiomers (i.e. four different substituents (groups attached)) with P being chiral.

Summary of Observations

- Both (WO2012012776 and WO2017049060) are method of use/treatment patents with very limited data to demonstrate activity against various viruses claimed.
- Compositions, various forms of the compound, kit with dosage forms, combination of drugs (with interferons and favipiravir) and Swiss-type claims are included in the claim set.
- Synthesis and characterization of remdesivir is provided.

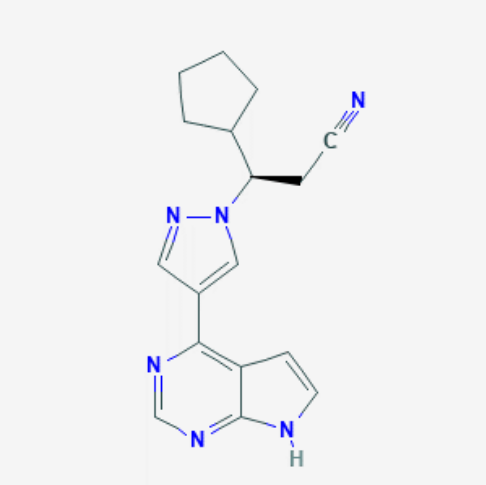
Key Findings

1. The coverage of the method claims is far broader than the disclosure.
2. Very poor enablement and disclosure of preferred embodiments.
3. On data for just three compounds, the use claim is extended over the entire Markush.
4. After having claimed activity over one group of viruses in WO2009132135 patent, the following patents just attempt to cover more family of viruses against which the compounds are supposed to be active.

RUXOLITINIB

Background

Ruxolitinib is a drug discovered by Incyte Corporation for the treatment of myelofibrosis. It is covered by a portfolio of around eight patents in over 40 countries.



Molecular formula: $C_{17}H_{18}N_6$
IUPAC Name
(3*R*)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propanenitrile

Patents Studied

WO2008157208. Filed on 12.06.2008.

WO2007070514. Filed on 12.12.2006.

WO2008157208

With 60 claims, the patent covers three salts of namely maleic acid, phosphoric acid and sulphuric acid salt of ruxolitinib, their process of synthesis, compositions and various methods of modulating JAK and methods of treating various diseases.

The specification has three examples covering the three salts, their synthesis and characterization. An in vitro JAK kinase assay is disclosed and concludes that the phosphoric acid salt and the corresponding free base compound had IC50 values of less than 50 nm for each of JAK1, JAK2 and JAK3. The efficacy of the other two salts is not established.

Claims 7, 8 and 9 cover composition comprising the salts suitable for topical and oral administration.

Claim 10 covers a method of modulating JAK activity and claim 12 covers method of treating diseases associated with JAK activity with compound of formula I. Several diseases are listed in subsequent claims, claim 20 lists a viral disease, and claim 21 states that said viral disease is Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus

(VZV) or Human Papilloma Virus (HPV). Claim 35 lists disease as inflammatory disease and claims 39 and 40 state it is inflammatory disease of upper and lower respiratory tract.

Summary of Observations

- IC50 values for base and one salt provided, that too not exact values.
- No efficacy data for two other salts.
- No test protocols and assay results for the various diseases being treated by the invention is provided.
- Method of treating various viral diseases (but not COVID-19) and inflammation of upper and lower respiratory tract are claimed.
- The three salts are synthesized, characterized and claimed.

Key Findings

1. The salts of Ruxolitinib disclosed in this patent are not novel, due to the implicit disclosure and claim 1 of WO2007070514. Page 35 of WO2007070514 patent covers salts and Ruxolitinib is disclosed as compound of example 67. Refer to page 14 of the Guidelines.
2. Maleic, phosphoric and sulphuric acids are well known acids to synthesize pharmaceutically acceptable salts, literature support for same can be provided. Refer to page 32 of the Guidelines.
3. No enhanced efficacy of salts can be established since WO2007070514 does not provide details.
4. No other property is demonstrated in the patent specification to show that the salts provide a distinct advantage over the base, making the salts highly obvious. Refer to page 14 and 32 of the Guidelines.
5. It is surprising that the ISA for this case made the following observation, see box below and opined all claims to be novel and inventive.

Re Item VI.

D3: WO 2007/070514 A (INCYTE CORP [US]; RODGERS JAMES D [US]; SHEPARD STACEY [US]; MADUSKUIE) 21 June 2007 (2007-06-21)

will not be considered at this stage, since it is not prepublished to the priority date of the present application and it is assumed that the priority has been validly claimed. However, it is noted that claims 1 of D3 encompasses the salts of the present application but there appears to be no specifically mentioned compound in D3 which falls under the scope of the subject matter as presently claimed.

WO2007070514

WO2007070514 has 88 claims. The claim 1 is a Markush structure with options that could conservatively cover thousands of compounds (could run into many more). The description of the options for the Markush covers over four pages and enumerates the multiple options for

substituents at every position of the compound i.e. the compound of formula I. The claim also covers pharmaceutically acceptable salts and prodrugs thereof. Claim 45 and particularly claim 46 disclose ruxolitinib (refer page 283 of WO2007070514).

To enable the Markush, over 700 compounds are synthesized and characterized with proton NMR data included in the examples. The examples elaborately cover the various options of the Markush enlisted in claim 1. However, limitation to the broad coverage sought can be made, since some substituents and options are not exercised in any compound.

The example 67 (refer to page 91-92 of WO2007070514) particularly discloses ruxolitinib, its synthesis and characterization. Both R and S enantiomers are disclosed and enabled. Claim 46 particularly claims ruxolitinib (refer page 283 of WO2007070514).

Claims 47 and 48 cover composition comprising compound of formula I suitable for topical administration.

Claim 49 covers method of modulating JAK activity and claim 55 covers method of treating diseases associated with JAK activity with compound of formula I. Several diseases are listed in subsequent claims, claim 63 lists a viral disease, and claim 64 states that said viral disease is Epstein Barr virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-zoster virus (VZV) or Human Papilloma Virus (HPV). Claim 78 lists disease as inflammatory disease and claims 81 and 82 state it is inflammatory disease of upper and lower respiratory tract.

Example A on page 268 of Annexure 1 provides the in vitro assay for JAK kinase, Example B lists cellular assays on the same page as above, Example C: *In vivo* anti-tumor efficacy and Example D: Murine Skin Contact Delayed Hypersensitivity Response Test on page 270 and Example E : *In vivo* anti-inflammatory activity on page 271 list detailed protocols for testing with criteria for evaluating the compounds, but in the entire specification the results of such tests are not provided. So, the activity of the compounds for the claims 49 onwards is not provided or supported in the specification

Summary of Observations

- Large number of examples are provided to support the Markush. They are synthesized and characterized. Partial satisfaction of the Guidelines advice of page 23 is accomplished.
- The preferred compound i.e. ruxolitinib is disclosed, synthesized, characterized and claimed.
- The results of the various assays enlisted to prove the efficacy of the compounds is not disclosed.
- Method of treating various viral diseases (but not COVID-19) and inflammation of upper and lower respiratory tract are claimed.

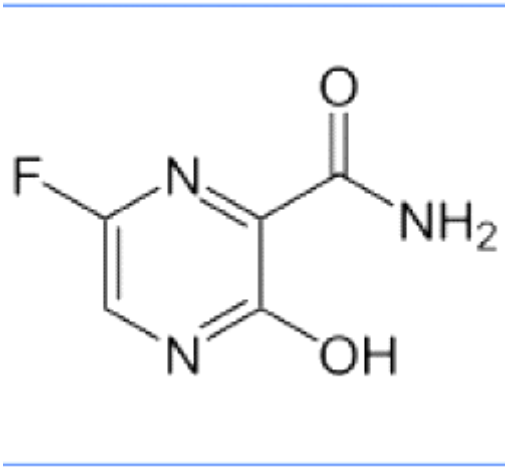
Key Finding

1. The compounds are disclosed and synthesized, but their utility or industrial application is not disclosed. Contravenes advice on page 17 of the Guidelines.

FAVIPIRAVIR

Background

Favipiravir is anti-viral drug developed and manufactured by Toyama Chemical (Fujifilm Group) and was approved for medical use to treat influenza in Japan in 2014. The drug became a generic in 2019, though follow-on patents are still in force.



Molecular formula: $C_5H_4FN_3O_2$
IUPAC name: 6-fluoro-3-oxo-3,4-dihydropyrazine-2-carboxamide.

Patents Studied

1. WO200010569. Filed on 18 August 1999.
2. WO2010104170. Filed on 12 March 2010.

WO0010569

The twenty year term of protection for patents stemming from WO0010569 and counted form its filing date has expired on 18.08.2019.

WO2010104170

WO2010104170 (its equivalent US 8513261 was referred for valid English translated document) with 18 claims covers a tablet and a granulated powder of favipiravir.

The WO0010569 patent states that “The nitrogen-containing heterocyclic carboxamide derivative represented by the general formula [1] of the present invention or a salt thereof can be used as a solution, a suspending agent, a powder, Pharmaceutical preparations such as granules, fine granules, tablets, capsules, syrups, elixirs, alcoholic beverages, lozenges, gargles and aerosols, orally and parenterally (injection, dermal, rectal) In the nasal cavity)”, refer column 10, line 51, WO2010104170.

And the WO2010104170 claims a tablet and a granulated powder. The tablet is a conventional tablet prepared by conventional methodologies and contains around 200 mg of compound of

formula A, which is favipiravir. The tablet does not overcome any specific challenges other than those posed by conventional tablet formulation development. The ingredients used and claimed in the tablet and granulated powder are known for several years before the filing date of the WO2010104170 patent and known specifically for the functions they are used in the patented formulations

Summary of Observations

- The tablet and granules are anticipated in the WO0010569 patent, but are not explicitly described with the other ingredients as stated by the EPO examiner (refer to the English translation of the ISR and IPRP).
- The disclosure in the patent is a routine experimentation carried out while developing a tablet formulation, and has no non-obvious features.
- The tablet formulation complies to the usually laid down parameters such as hardness and dissolution, and does not seem to overcome any novel challenges or unresolved problems in the art.
- Regarding the drug being 50-95% weight of tablet that is fairly common in many tablets.
- The reply provided by Applicant to EPO (against the citations in the ISR) lists the challenges in formulating a tablet, which are very well known in the art (refer para 2, page 2). The subsequent paras defend the invention in light of the citations, but there are very elementary text book level prior arts that describe the experiments listed in Tables 1 and 2 of the patent WO2010104170.

A standard text book used in graduation studies in pharmacy practice, lists the ingredients used, the techniques employed and the parameters tested.[4] A 200 mg dose is also very common in pharma formulation and does not pose any unique challenge. In fact, there are drugs with much higher doses in the market (e.g. paracetamol 500 mg).

Key Finding

1. Since there is no single prior art listing a tablet formulation of favipiravir with hydroxyl propyl cellulose and a binder, the claims may be opined novel, (also refer to comments above), however, the invention is highly obvious. Refer to the advice on page 36 of the Guidelines.

[4] Lachman, L., Lieberman, H., & Kanig, J. *The Theory And Practice of Industrial Pharmacy*, 3rd ed. (Philadelphia: Lea & Febiger, 1986).

TOCILIZUMAB

Background

Tocilizumab is a recombinant humanized monoclonal antibody of the Immunoglobulin G1 (IgG1) class, which is directed against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor.

Tocilizumab is recommended for the treatment of severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, and life-threatening cytokine release syndrome induced by chimeric antigen receptor T-cell therapy.

It was developed by Hoffmann–La Roche and Chugai and has been extensively patented in more than fifteen countries with a portfolio of over five patents.

Patents Studied

1. WO199611020. Filed on 7 June 1995.
2. WO2002080969. Filed on 2 April 2002.
3. WO2003068260. Filed on 14 February 2003.
4. WO2004096273. Filed on 28 April 2004.
5. WO2005061000. Filed on 17 December 2004.
6. WO2009084659. Filed on 26 December 2008.

Note

- The original applications have mostly been filed in Japanese, the corresponding US applications therefore have been used for the study.
- The Applicant Chugai has patented this monoclonal antibody, its formulations and various uses extensively and across several countries. Most of the six cases have very long prosecution history with the national patent offices.
- Many of the antibody related or methods related patent specifications contain common text matter, specifically with reference to making of the antibody and its details and characteristics and references.
- The Applicant has attempted to build a substantial portfolio around this antibody.

WO199611020

WO199611020 is expired, no national phase entry later than 1995 seen, so the said application has expired in all countries that it entered in national phase.

WO2002080969

WO2002080969 is an application containing 26 claims pertaining to a therapeutic agent for the treatment of chronic arthritis disease of childhood, where the therapeutic agent is an IL-6 antagonist.

This patent application suffers from various drawbacks:

- Lack of disclosure of what is the IL-6 antagonist. While the dependent claim specifically states that the antagonist is a monoclonal antibody, the specific features and aspects of the antibody is not described.
- Examples pertaining to preparation of antibody is disclosed, but specific features of the antibody which will make it act as the IL-6 antagonist are not disclosed.
- The Complementary determining regions (CDRs) and the specific antigen-antibody binding data is not provided. (Another assay protocol is provided to prove the antigen-antibody interaction, but Complementary determining region or CDR data has been requested by Patent Offices).
- To prove activity against chronic arthritis disease of childhood, one example of one 5-year-old male child treated for juvenile rheumatoid arthritis and one example of a 22-year-old female treated for Still's disease (claimed) is shown in the patent specification.
- The patent cannot be worked without undue experimentation and does not provide adequate written description.
- The US application 2004115197 has been abandoned for failure to respond to queries from Patent Office in 2007.
- There are several relevant prior arts indicating use of an IL-6 receptor antagonist for treatment of rheumatoid arthritis and so the invention lacks non-obvious features.
- Therefore, EPO rejected therapeutic agent as well as use (Swiss-type) claims.
- The case was appealed at the EPO by the Applicant and ultimately refused by the Office and the Appeals Board in 2017.

Key Finding

1. The patent is not in force in US and in countries who are members of the EU but may be allowed in some other countries, e.g. Australia. A corresponding application in the Indian Patent Office is not filed.

WO2003068260

WO2003068260 discloses a composition of an antibody to IL-6R (Interleukin-6 receptor).

The claim 1 of this application is as broad as: An antibody-containing solution formulation including a sugar as a stabilizer. The claim may include any antibody and such a claim does not even enjoy novelty and is completely unsupported by the specification for all the possible antibodies that could be covered by such a claim. Claim 14 however states that the antibody is an anti-IL-6 receptor antibody.

The patent also claims a method of stabilizing the formulation and method of inhibiting formation of multimers, which are formed when the formulation is subjected to freeze-thaw cycles.

The specific antibody is not adequately disclosed in terms of CDRs and other specific characterization data.

The excipients used are a sugar and a surfactant, which are very well-established ingredients in a pharmaceutical formulation. They are well known to stabilize antibody formulations also. The patent specification provides extensive studies with respect to interaction between the antibody and the excipients, establishing the best suited ones for the formulation. These are routine studies in formulation development of trial and error and is part of optimization of the formulation's ingredients. This does not involve an inventive activity, but an extensive exercise to eliminate the excipients that do not provide stability and choose the ones that do. Formulations have to be stable throughout the shelf-life or till expiry and is a regulatory requirement. The sugars and the surfactants that have been employed here are very well-known ingredients in the art, and have been widely used in formulation development.

The case has been allowed in US with the main claim being: refer US 8840884

1. A stable solution pharmaceutical formulation comprising a humanized anti-interleukin-6 receptor IgG1 antibody in an amount from 17.5 to 22.5 mg/ml, sucrose in an amount from 25 to 100 mg/ml, surfactant as a stabilizer, and phosphate buffer, wherein the pH of the formulation is from 6.5 to 7.0, wherein the sucrose inhibits dimerization of the antibody; and
2. Sixth claims is: A freeze/thaw stable solution pharmaceutical formulation comprising humanized anti-interleukin-6 receptor IgG1 antibody in an amount from 17.5 to 22.5 mg/ml, sucrose in an amount from 25 to 100 mg/ml, surfactant as a stabilizers, and sodium phosphate buffer, wherein the pH of the formulation is about 6.5, wherein the sucrose inhibits dimerization of the antibody.

Two more narrow claims of the formulation with specific quantities of sucrose and polysorbate (surfactant) and antibody has been allowed with specific pH (i.e. no ranges).

The patent family to which this patent application belongs is extensive, with grants in many countries and several divisionals and family members covering both a) varied formulations as well as b) method of stabilizing or inhibiting formation of impurities/dimers and so on. However, all have essentially the same ingredients i.e. a sugar and a surfactant and all are highly obvious. Narrowest embodiments are claimed and protected through the various granted patents.

The International Search Report opined that the claims lacked novelty and inventive step citing 17 documents, but eventually there are two US and three EP grants.

Key Findings

1. The formulation with a sugar (specifically sucrose) and surfactant is protected, though highly obvious. The claims are narrow and it may be possible to work around the claimed invention.
2. The family is very large and all members are covering various narrow aspects of stabilizing the formulation, though essentially using a sugar and a surfactant.

WO2004096273

The English translation filed at the Indian Patent Office has been used for reference.

The application was filed with 80 claims pertaining to a pharmaceutical composition, use claims and method claims.

The main claim reads as:

> A pharmaceutical composition for the treatment of IL-6 related diseases, comprising an interleukin 6 antagonist (IL-6 antagonist) and immunosuppressants.

Another claim reads as:

> A therapeutic agent for the administration at high doses, comprising an IL-6 antagonist.

Another independent claim reads as:

> A use of an interleukin-6 antagonist (IL-6 antagonist) and immunosuppressants for the production of a pharmaceutical composition for the treatment of IL-6 related diseases.

A fourth type of claim reads as:

> A method for the effect enhancement on the use of an IL-6 antagonist for the treatment of IL-6 related diseases, comprising administering immunosuppressants and an IL-6 antagonist to a patient requiring such *a* treatment.

The claims as filed are very broad, vague, indefinite and their metes and bounds are completely undefined.

The terms IL-6 related diseases, interleukin 6 antagonist (IL-6 antagonist) and immunosuppressants, administration at high doses and pharmaceutical composition for the treatment of IL-6 related diseases are all very broad, indefinite terms. IL-6 diseases can be any disease that involves interleukins in any manner and can be a huge list of possible diseases that can fall under the term IL-6 diseases and the patent specification has not provided adequate data or covered all these various possibilities. Similarly, IL-6 antagonist and immunosuppressant can mean a large number of possible candidates and this needs to be specified.

Thus, the IL-6 diseases, the IL-6 antagonist and the immunosuppressant are to be defined in claim 1 to overcome the above-mentioned objections.

Further, such claims as listed above lack novelty. There are several documents that will qualify as prior arts for such claims.

Also, even if the claim are made definite by specifying the IL-6 disease as rheumatoid arthritis, IL-6 antagonist as a monoclonal antibody and immune suppressant as Methotrexate, the composition should specify the concentrations of all the ingredients. Even then such compositions are generally covered in prior arts, though specific concentrations may not be disclosed or claimed in prior arts.

The huge amount of literature that can affect the novelty of the invention is evidenced by the citation of at least eight documents in the International Search Report and in the various Office Actions issued by the various national patent offices.

Further, the method claims are not patentable in some domains. e.g. EPO, India, and use claims are not allowed in some domains. Thus, the composition claims with amendments to make them definite have been pursued in EU (with use claims) and method claims have been pursued in US.

The status of the application in India is not updated, but appears to be abandoned, out of three EP filings, one was refused and oral proceedings has been withdrawn, second one has been withdrawn and in a third one with a narrow claim with dose of IL-6 antagonist specified in combination with Methotrexate is being pursued with an oral proceeding summoned.

USPTO has granted two narrow method claim patents.

Key Findings

1. The claims are too broad and indefinite.
2. As filed claims are not novel.
3. All cases have long prosecution history.
4. Compared to the as filed claims, the few grants have a narrower scope and few are method claims only.

WO2005061000

This patent pertains to an agent to prevent vasculitis, which is an IL-6R antibody. The patent specification (as in other applications by Chugai, except where stability of formulations is claimed) lacks disclosure with regard to antibody's features, CDRs, sequences and binding affinity.

The patent cannot be practiced without undue experimentation, since the claims include a preventive and/or a therapeutic agent for vasculitis, the use of interleukin-6 (IL-6) antagonist for the manufacture of a preventive and/or therapeutic agent for vasculitis (Swiss claim) and a method of preventing and/or treating vasculitis comprising administering an interleukin-6 (IL-6) antagonist to a subject in need thereof. To support the agent's activity in vasculitis, two patients were studied, one a 19-year-old female and second a 42-year-old male and activity and method are concluded on this basis.

The case has been filed in many countries, granted in a few, refused in a few, and there are no updates in a few. In US method claims are granted in 8617550. (use and agent claims -not allowed) There appears to be no divisional application. This case was filed in India, 3057/DELNP/2006, and was objected in the Examination report for following reasons: Method and use claims-not patentable under Sec 3(i) and new use under Sec 3(d) and agent claims being obvious in view of cited prior arts. The reply to the Examination report has not been filed within time limits, (deemed to be abandoned) but there is no update on the status of the case.

EPO had granted this patent for agent and use claims, EP1707215. Further, the EPO granted patent has been withdrawn on 13 February 2020, since the patent was revoked. The patent was objected on the grounds of lack of novelty and inventive step and insufficiency of disclosure. From the two patients treated and exemplified in the patent specification, it is difficult to conclude that the agent claimed therein can treat any type of vasculitis as claimed.

Key Findings

1. Only method claims are allowed in US.
2. Therapeutic/preventive agent for vasculitis is a rejected claim in US.
3. The patent stands revoked in EPO.

WO2009084659

The patent claims are very broad stating a stable antibody-containing liquid formulation, characterized by comprising arginine and methionine (from translated document submitted to Indian Patent Office). 20 claims are on file, while US application contained only two claims. Another independent claim on this file is a method of inhibiting deamidation of molecules of an antibody in a liquid formulation containing the antibody, comprising adding arginine to the liquid formulation.

One of the most relevant prior arts is Chugai's earlier filing, refer WO 200213860, wherein the histidine buffer and use of surfactant as stabilizer as well as addition of arginine is claimed. There are more prior art documents, making the invention highly obvious.

US 8568720 and EP2238985 are granted with a single example as allowed claims. The EP2238985 and IN respective patent were granted with far broader scope of claims. While in IN there was no opposition, Glaxo opposed in EPO and after a prolonged proceeding the claims are limited to almost what is granted in the US. In the US too the prosecution was very long. The allowed claims are listed herein:

1. A stable liquid formulation suitable for subcutaneous administration comprising 180 mg/mL humanized anti-IL-6 receptor IgG1 antibody, 100 mM arginine, 10 to 50 mM methionine, further comprising 0.005 to 3% polysorbate 80 and 20 mM histidine buffer, said formulation having a pH of 6.
2. The stable liquid formulation of claim 1 wherein the antibody comprises the humanized anti-IL-6 receptor IgG1 antibody MRA.

Granted claim 1 covers a particular concentration of the antibody and with a particular buffer and arginine concentration. So, in terms of coverage or scope, the claims are very limited and narrow.

Key Findings

1. Scope of patent very narrow.
2. Few embodiments lacked novelty and were highly obvious.
3. They pertained to formulations with obvious pharmaceutically acceptable excipients with obvious effects.
4. The patent was opposed in EPO and scope of claims restricted.

SILTUXIMAB

Background

Siltuximab is a chimeric (made from mouse and human proteins) monoclonal antibody patented by Centocor Inc. Siltuximab targets the IL-6 receptor (Interleukin) and inhibits its activity. It has been investigated for activity against many cancers, but is approved by FDA for the treatment of patients with idiopathic multicentric Castleman's disease (iMCD), who do not have human immunodeficiency virus (HIV) or human herpesvirus-8 (HHV-8). The antibody has been patented in over 15 countries globally, in addition to a few European countries.

Patent Studied

1. WO2004039826. Filed on 26.10.2002

WO2004039826

The WO application discloses at least one novel chimeric, humanized or CDR-grafted anti-IL-6 antibodies derived from the murine CLB-8 antibody, including isolated nucleic acids that encode at least one such anti-IL-6 antibody, vectors, host cells, transgenic animals or plants, methods of making and using thereof, including therapeutic compositions, methods and devices.

A murine IL-6 monoclonal antibody (referred to as CLB-8) is known with high affinity to IL-6 receptor, however its complementary directing regions or antigen binding regions are not known. Murine antibodies are immunogenic in humans and decrease their therapeutic value. Thus, for an improved pharmaceutical profile and increased affinity, a new monoclonal antibody was required, which is the chimeric siltuximab.

The WO application claims multiple inventions, there are nearly 15 inventions covered in this application:

> The monoclonal antibody, an isolated antibody coding nucleic acid, an antibody vector, a host cell comprising the nucleic acid, a method of producing the antibody, an IL-6 antibody composition, a method of treating an immune disorder, a method of modulating a cancerous disorder, a medical device comprising the IL-6 antibody, a formulation comprising the antibody, a method of preparing the formulation, a method of treatment, an article of manufacture and a transgenic animal or plant expressing the antibody.

The claims pertaining to the antibody i.e. claims 1-9 are supported in the description and through the examples. The antibody encoding nucleic acid, the antibody vector and a host cell comprising the nucleic acid are also described in the WO specification.

The antibody and its method of manufacture is described and exemplified in the WO specification, however, the other inventions particularly, the pharmaceutical compositions and formulations are not disclosed by way of even a single example. Same applies to the claim on the medical device and for the huge number of diseases against which the antibody is expected to possess activity. The claims pertaining to compositions, formulations and device cannot be worked without undue experimentation.

There is no evidence in the patent specification that the antibody indeed exerts its effect against the huge number of disease and disorders listed and claimed, refer claims 23-26, especially claim 26.

Referring to claim 35, a very long list of agents that are to be administered with or after administering the antibody, the specification has no examples of such compositions or the effect of such combinations and their effects. Referring to page 61 of the specification where agents co-administered are listed, anti-viral agents is listed and so is hydroxychloroquine sulphate.

Claims 54-58 claims a transgenic animal or plant for producing the antibody and expressing the antibody is claimed.

Summary of Observations

- Multiple inventions are covered in a single patent application, so at national phase there may be several divisional patents to be watched for.
- The claim to the antibody appear to be novel and inventive.
- Claims to compositions, methods of use, treatment and formulations, combinations and device are poorly supported and not enabled.
- The list of diseases that can be potentially treated and the list of agents that the antibody can be combined with seem too long, with no specific supporting data to back such claims.

Key Finding

1. While the main claim to the anti-IL-6 receptor chimeric antibody is supported and is novel and inventive, the other inventions are not enabled in the patent specification and the claims are too broad and unsupported.

SARILUMAB

Background

Sarilumab is a fully human monoclonal antibody patented by Regeneron Pharmaceuticals for the treatment of rheumatoid arthritis that targets the IL-6 receptor (Interleukin).. The antibody has been patented in over 15 countries globally, in addition to a few European countries.

Patents Studied

1. WO2007143168. Filed on 1 June 2007.

2. WO2011085185. Filed on 7 January 2011.

WO2007143168

The WO2007143168 patent has claimed very broadly for an antibody or an antigen binding fragment that binds to IL-6receptor. The claims of the WO patent i.e. claim 1 as such has not been granted in the US, India or Europe. The as filed WO patent lacks support in the written description and enablement for the broad claim 1. The claim refers to an antibody or antigen-binding fragment, which specifically binds to human interleukin-6 receptor (hIL-6R) with a K_D of about 500 pM or less and 300 pM or less, measured by plasmon resonance. K_D refers to the affinity of the antibody to the receptor.

Essentially, the claim 1 could refer to any antibody or antigen-binding fragment that possesses the specified K_D values, with no other characteristics defined. This could lead to a huge number of possibilities and therefore this claim is not even searchable. For e.g. Tocilizumab is also an antibody that binds to hIL-6R with K_D less than 600 pM, and the first patent filing of Tocilizumab or FR 2694767 would be a novelty destroying prior art for the WO2007143168 patent.

The antibody Sarilumab contains two heavy chains and two light chains of polypeptides linked by disulphide bonds. Each heavy and light chains have a variable and a constant region. The light chain comprises one domain and the heavy chain constant region comprises three domains. The variable region in the heavy and light chains are subdivided into regions of hyper variability known as complementary determining regions (CDR) interspersed with more conservative regions known as framework regions. Each variable heavy and light chains is composed of three CDRs and four framework regions arranged from amino terminus to carboxy terminus arranged in the order, FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

The antigen binding capacity of the antibody depends on all the three CDRs on each of the light and heavy chains and defining merely one of them on each of the heavy and light chains will not aid the person skilled in the art to arrive at the antibody with the affinity claimed. In antigen-antibody interaction, it is well known that it is the interplay of the six specific CDRs to obtain the claimed affinity and specificity. Since this is not defined in clams 1 and 2 of the filed WO claims they are opined not inventive. The other claims are still not adequately specifying the requisite six CDRs, however claim 7 claims the antibody with the required six CDRs, though all pairs are not enabled enough in the patent specification.

The other claims cover a nucleotide coding for the antibody, a host for the nucleotide, a host-vector system, a method producing antibody, uses of the antibody a pharmaceutical composition comprising the antibody.

Paragraphs 0016 and 0042 of the specification disclose a pharmaceutical composition comprising the antibody with a pharmaceutically acceptable carrier. But an injection is not covered.

Summary of Observations

- Large number of CDRs are claimed, but not supported in the specification.
- Only few CDRs are well supported in the description and only those particular three heavy and three light chain CDRs can give the required $K_{D.}$
- Pharmaceutical compositions are broadly described and claimed.
- Use of the antibody for several IL-6 mediated diseases are claimed, including inflammatory diseases are described, but viral infections are not covered or claimed.

Key Findings

1. The FR 2694767 patent can be a novelty destroying prior art for claim 1 of the WO2007143168.
2. The EPO granted patent has the broadest claim coverage, while the corresponding US and IN patents are narrower specifying the CDRs of the heavy and light chains in claim 1, of specifically embodied CDRs only.
3. The scope of claims 1 and 2 of the WO patent application is too broad and lacks support in detailed description and examples and is not workable without undue experimentation.
4. The granted US and IN claims are enabled, supported and described and are novel and inventive.

WO2011085158

This application claims formulation of Sarilumab with a sugar, an amino acid and optionally a non-ionic surfactant as pharmaceutically acceptable carriers.

A formulation is anticipated in the WO2007143168 patent, but not particularly an injectable. The novelty of the claims lie in the new antibody. The carriers employed are those well known in the art, even before the WO2007143168 patent.

The WO2011085158 claims a pharmaceutical formulation comprising:

i) A human antibody that specifically binds to hIL-6R
ii) Histidine and
iii) A carbohydrate

The carbohydrate is claimed to be Sucrose.

The formulation may optionally comprise a nonionic surfactant selected from polysorbate 20, polysorbate 80 or polyoxyethylene sorbitan monooleate.

Further Arginine is also claimed to be added to the formulation, refer claim 15.

The ingredients are very common for use in formulating antibodies to be delivered as an injection.

The use of a sugar, particularly sucrose and Histidine as a buffer to stabilize the formulation and decrease freeze-thaw is very well established before the filing date of this application. Addition of Arginine is known to further stabilize the antibody injectable formulations.

Literature exists to establish the excipients to be added to antibody formulations and the inventors have used very well established and well-known ingredients. They have standardized the ranges of their concentrations, but that is routine experimentation in formulation development.

The ingredients are known to impart stability to the antibody formulations, and exactly the same is proved in the patent application. Nothing non-obvious there, expected results have been obtained.

That “the stability of sarilumab is a problem in the art” is not stated anywhere in the patent. Stability of formulation is one of its basic criteria and this patent provides a stable formulation using pharmaceutically acceptable ingredients well established in the art.

Summary of Observations

- The formulation uses ingredients well-known in the art as excipients.
- Each of Histidine, Arginine, Sucrose and a non-ionic surfactant are well known through prior arts to be used for stabilizing an injectable antibody formulation and this invention claims the same ingredients.
- The Complementary determining regions claimed in this patent are different from the ones claimed in the WO2007143168 patent.
- The patent covers the use of this formulation for treatment of viral diseases, refer page 17-18. The formulations are useful for treatment, prevention and/or amelioration of any disease or disorder associated with IL-6 receptor. Examples include viral infection, e.g. HIV, EBV infection.

Key Findings

The formulation patent WO2011085158 is highly obvious, with no evidence of inventive activity.

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