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Analysis of Strategy for Extending Patent Protection of Rucaparib

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Abstract

As a knowledge-intensive and promising strategic emerging industry, the biomedical industry has high entry thresholds, large R&D investment, long cycle, high risk and high return. In all technical fields, the biomedical industry has the highest dependence on intellectual property rights, and the protection of pharmaceutical intellectual property rights by domestic and foreign biomedical enterprises also runs through the whole process of drug research and development. Extending the patent protection period of drugs as well as forming and strengthening patent fortresses requires a patent network that surrounds drugs to maximize the value of intellectual property protection, which is also the focus of every pharmaceutical company with patent rights. By analyzing the patent portfolio of Clovis Oncology Company in the United States on Rucaparib and the patent portfolio of other companies or applicants on Rucaparib, we can have a clearer understanding of the strategy of extending the patent protection period of a new drug product.

Keywords

Patent Portfolio, Patent Analysis, Rucaparib, New Drug Research and Development, Patent Protection

1. Brief Introduction of Rucaparib

Rucaparib was first prepared and patented by the University of Newcastle in England in 2000. Rucaparib was approved by the U.S. Food and Drug Administration (FDA) in April 2015 as a breakthrough therapy for ovarian cancer and was launched in the United States on December 19, 2016, under the trade name Rubraca, in tablet forms including 200 mg and 300 mg as monotherapy for patients with refractory advanced ovarian cancer [1].

2. Strategies for Patent Portfolios

After completing the basic research of Rucaparib, pharmaceutical enterprises began to apply for basic patents, such as patents for general compounds and patents for specific compounds. Subsequently, the applicant began to apply for peripheral patents, such as patents for preparations, indications, preparation methods, crystal form, etc., to further strengthen and expand the protection of basic compounds. The protection period can be effectively extended through the portfolios of basic patents and subsequent peripheral patents. Specifically as shown in Figure 1.

US6495541 is the basic core patent of Rucaparib, which can be considered as the first stage of patent portfolio of Rucaparib. The patent was filed on January 10, 2000 and expired on January 10, 2020. The claims of patent request protection of a compound and a composition comprising that compound. Example IIII discloses the synthesis, ^{1}H-NMR and mass spectrometry of 8-fluoro-2-(4-methylaminometh-ylphenyl)-1,3,4,5-tetrahydro-azaheterocyclic heptene [5,4,3-CD] indole-6-one. Rucaparib is used in this patent as a powerful poly (ADP-ribosyl) transferase (PARP) inhibitor and as a compound for treating cancer and improving the curative effects of stroke, head trauma, and neurodegenerative diseases.

After the filing of the compound base core patent, the applicant immediately put forward six patents for indications, which can be regarded as the second stage of patent portfolio of Rucaparib.

In chronological order, the first two indications patents are US7351701 and US7531530 filed on July 23, 2004. US7351701 requests to protect the application of three specific compounds in preparing medicines for treating BRCA1 and/or BRCA2 expression deficient cancer cells (*i.e.* specific breast cancer). Figure 6 in the description of US7351701 shows the plasma and tumor concentrations of the compound of formula I and its pharmacokinetics on peripheral blood lymphocytes (pbl PARP) and SW620 xenograft (tumor PARP) in mice at different times

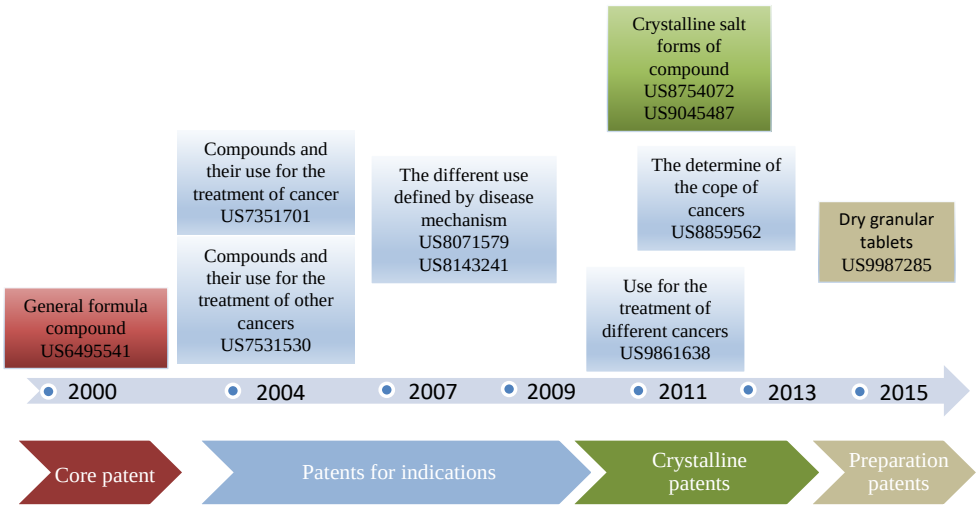

Figure 1. Strategy for extending patent protection of Rucaparib.

after intraperitoneal administration of phosphate of the compound of formula I. The phosphate of the compound of formula I increases the solubility of the product. However, when administered to animals (including humans), plasma phosphatase breaks the phosphate of formula I (formula I-phosphate) into the parent compound, namely formula I. US7531530 also requests to protect the use of three specific compounds in the treatment of cancer. The general scope of cancer is different, including different cancers with genetic defects, such as lung cancer, gastric cancer, breast cancer, ovarian cancer and cervical cancer.

On August 12, 2007, the applicant filed two patents for indications, namely US8071579 and US8143241. Both US8071579 and US8143241 claim the use of transferase (PARP) inhibitors for treating BRCA1 and/or BRCA2 expression deficient cancer cells, and the dependent claims mainly provide a further overview of the disease mechanism, and the difference in protection scope between the two patents mainly lies in the difference defined by the disease mechanism.

Then, on February 10, 2011, the applicant filed an indication patent US9861638, and the technical solution for which protection was sought mainly for different cancers.

The most recent indication patent is US8859562, filed on August 4, 2011, which expired on August 4, 2031. The granted patent has only one claim that further qualifies the cancer, specifically, the use of poly ADP-ribose polymerase-1 inhibitors for the production of drugs for the treatment of homologous recombinant defective cancer cells. The cancer cells are defective in genes selected from XRCC2, XRCC3 and BRCA2.

New crystalline salt forms of compound 1 have been discovered, and they may be more suitable for batch preparation and processing than other forms. For example, although phosphate of compound 1 is particularly suitable for intravenous dosage forms, it is less suitable for solid dosage forms due to its sensitivity to hydration. Based on this, the applicant began the third stage of patent portfolio on crystal form. On February 10, 2011, the applicant filed two crystal invention patent applications US8754072 and US9045487. The two applications relate to maleate and camphorsulfonate forms (e.g., maleate polymorphism B and S-camphorsulfonate polymorphic form A) as physically stable forms less readily hydrated than other salt forms of compound 1, which makes them particularly suitable for the preparation of solid dosage forms.

On August 17, 2015, the applicant applied for invention patent US9987285 relating to formulation research, which can be considered the fourth stage of patent portfolio of Rucaparib. The patent relates to tablets as well as dry granular tablets. According to the description of the patent, camphorsulfonate formulations show better tensile strength values at much lower compressive forces than maleates (suitable for tablet compression). In fact, the maleate preparation did not achieve the target tensile strength of 2 MPa even at 250 MPa. In addition, the asymptotic appearance of a curve of >200 MPa indicates that an acceptable tensile strength tablet may not be achieved at all, even at extreme values of compressive force. In other words, the tabletability of maleate is about 2 - 2.5 times

lower than that of camphorsulfonate and falls below the acceptable threshold for tableting. Thus, compared to camphorsulfonate, significantly lower load maleate formulations are required for dry granulation tablets. Since all camphorsulfonate formulations with 60% - 100% loading exhibit an achievable tensile strength of at least 2.0 MPa under moderate compressive stress, the following general conclusion can be drawn: they are all acceptable from a tabletability perspective. Conversely, none of the 60% - 100% maleate preparations achieve a tensile strength of 2.0 MPa. The data shown in paragraph 23 - 25 of the description are CTC properties of 4 formulations analyzed with camphorsulfonate. Similarly, the data shown in paragraph 26 - 28 of the description are the CTC properties of 3 formulations that can be used for maleate analysis. Pure maleates cannot be modified for analysis, as intact compacts cannot be formed at 90% and 100% API preparations. The resulting CTC properties indicate that the camphorsulfonates evaluated are far more modifiable for dry granulation and tablet compression methods. In addition, maleate compressibility is inferior to camphorsulfonate, making it necessary to reduce the maleate drug load from the target of 70% to an estimated 50% to obtain tablets of sufficient strength for downstream coating, packaging, and/or shipping processes. Finally, it is worth noting that the CTC characteristics of camphorsulfonate API load at 60% - 100% are not highly sensitive to API loading. Thus, compressibility will not be limiting for very high loading (high dose: tablet size ratio) tablets. Instead, the upper limit may be other quality or processing properties (such as disintegration, dissolution, powder flow, or sticking), which enables tablet strength greater than 300 mg of rucaparib camphorsulfonate. That is, by providing compounds in different salt forms, tablets which meet the strength requirements are obtained.

3. Patent Application of Other Applicants

According to chronological order, the first patent application for Rucaparib was filed by Shanghai Dongfang Hospital on January 19, 2016. The patent CN106975079 for Rucaparib combination claimed protection for a pharmaceutical composition comprising: an active ingredient USP13 inhibitor, an active ingredient PARP inhibitor, and a pharmaceutically acceptable carrier. Among them, the weight ratio of USP13 inhibitor and PARP inhibitor can be 1:100 to 100:1; USP13 inhibitor can be selected from the following group: compounds, antibodies, nucleic acid molecules or combinations thereof. Its active ingredients have significant synergistic effect in anti-tumor, and the combination can significantly reduce the homologous recombination repair efficiency of tumor cells, enhance the therapeutic effect of PARP inhibitors, and more effectively inhibit tumor growth.

Shijiazhuang Jiuzheng Biotechnology Co., Ltd. applied for a patent application involving Rucaparib intermediates on July 24, 2016, which disclosed a preparation method for key intermediates of anti-ovarian cancer drug Rucaparib. The present invention avoids nitrification reaction, reduces the risks in the production process and the possibility of damaging the environment. The raw materials

are readily available and the price is low, which effectively reduces the production cost. It effectively shortens the reaction route, saves time and effort, and greatly improves the reaction efficiency.

Then there is a patent application for pharmaceutical preparations, CN108201534 filed by Suzhou Surong Biopharmaceutical Co., Ltd. on December 16, 2016. The present application relates to an oral sustained and controlled release pharmaceutical composition containing Rucaparib and its use. The oral sustained and controlled release pharmaceutical composition comprises a dissolution-improved form of Rucaparib and matrix polymer for the adjustment of the release rate. The dissolution-improved form of Rucaparib is preferably a solid dispersion of Rucaparib. The matrix polymer for the adjustment of the release rate is preferably selected from one or more combinations of hydroxypropyl cellulose, sodium alginate, hypromellose and carbomer. Regulating precisely the absorption rate and absorption time of Rucaparib in the gastrointestinal tract has improved Rucaparib drug load, oral absorption, bioavailability, blood drug concentration control, enzyme inhibition level control, improved drug absorption efficiency, reduced adverse reactions of patients, and improved patient compliance.

In 2017, there were mainly 5 patent applications involving Rucaparib. On January 25, 2017, Qingdao Chenda Biotechnology Co., Ltd. filed four patent applications involving Rucaparib intermediates. CN106748958 specifically relates to the preparation method of methyl6-fluoro-3-[(E)-2-nitrovinyl]-1H-indole-4-car-boxylate of Rucaparib intermediate. The materials of the present invention are cheap and easy to obtain, the reaction route is refined, the selectivity of the reaction is high, and the yield is high. CN106749282 discloses process for preparing an intermediate of Rucaparib, a medicine for treating ovarin cancer. The process provided by the present invention can produce the target compound with high yield and high purity. The conditions are mild, the steps are fewer, the reaction time is short, and it is more suitable for industrial production. CN106831792 specifically relates to a preparation method of PARP inhibitor Rucaparib intermediate (8-fluoro-1,3,4,5-tetrahydro-azalazeno [5,4,3-cd] indol-6-one). The materials of the present invention are cheap and easy to obtain, the reaction route is refined, and the yield of the three-step reaction can reach more than 75%, which greatly reduces the cost of Rucaparib intermediate and is conducive to the industrial production of Rucaparib. CN106831793 discloses a synthesis process for Rucaparib intermediates. The synthesis process of Rucaparib intermediates provided by the present invention has fewer reaction steps, low production cost, and short reaction time of the synthesis process. Its high production efficiency is more suitable for industrial production. The intermediate prepared by the process of the present invention has high yield and high purity.

On November 30, 2017, Jiangsu Hengrui Pharmaceutical Co., Ltd. filed a patent application involving Rucaparib combination drug, CN108778336, disclosing the use of combination of VEGFR inhibitor and PARP inhibitor in the preparation of medicament for treating gastric cancer.

In 2018, there were mainly 6 invention patent applications involving Rucaparib. Nanjing Qike Pharmaceutical Co., Ltd. applied for a patent application involving Rucaparib on January 8, 2018, disclosing a preparation method of Rucaparib key intermediates. The preparation method of Rucaparib key intermediates of the present invention has reasonable route design, cheap and easy availability of raw materials, green environmental protection, and easy and effective control of reaction conditions.

On March 7, 2018, Cheng Chunxiao personally filed two patent applications involving Rucaparib intermediates. The application CN108409626 disclosed the preparation method of key intermediates of the anti-ovarian cancer drug Rucaparib, involving the preparation of pharmaceutical intermediates. The patent can avoid nitrification reaction of nitrosulfur mixed acid and discharge of waste water and waste gas, which is safe and environmentally friendly. The raw materials are easy to obtain and the price is low, which improves the reaction yield and is convenient for industrial production. The other application CN108752353 avoids the nitrification reaction of nitrate-sulfur mixed acid, avoids the discharge of waste water and waste gas, and ensures safe production, safety and environmental protection; Raw materials are readily available, low price, low cost, convenient for industrial production; The reaction yield is greatly improved, the reaction route is optimized, the product purification steps are simplified, and it is conducive to industrial production.

Li Li personally filed a patent application involving Rucaparib pharmaceutical preparations on June 27, 2018. CN108743557 disclosed a soft capsule of Rucaparib phosphate and its preparation method. The soft capsule of Rucaparib phosphate includes a rubber skin and the contents wrapped in the rubber skin. The rubber skin includes gelatin, glycerin, purified water, preservatives, and colorants. The contents include Rucaparib phosphate, polyethylene glycol 200, antioxidants, etc. The antioxidant consists of sodium thiosulfate and disodium edetate. The patent provides for a soft gel capsule of Rucaparib phosphate with fast onset of action and high bioavailability. The finished product has good stability. The capsule shell will not lose moisture during the storage process and make the capsule shell hard and cracked. The pH of the contents has not changed significantly for 24 months. The increment of relevant substances in long-term storage products is small, only increased by 0.09%, and the shelf life is long, which can be as long as 24 months.

On August 1, 2018, Ningbo Jinwei Biotechnology Co., Ltd. filed a patent application involving a new crystal form of rucaparib. CN109111454 disclosed a rucaparib S-camphor-sulfonate (compound name: 8-fluoro-2-{4-[(methylamino) methyl[phenyl}-1,3,4,5-tetrahydro-6H-azazo[5,4,3-cd[indole-6-one S-camphor-sulfonate; Rucaparib Camsylate). The present invention provides a new crystalline rucaparib S-camphor-sulfonate (compound name: 8-fluoro-2-{4-[(methylamino) methyl[phenyl}-1,3,4,5-tetrahydro-6H-azazo[5,4,3-cd[indole-6-one S-camphor-sulfonate) with good stability, excellent solubility, dissolution performance, and druggable properties. The production process of the new crystal form has the

characteristics of mild conditions, simple operation and good reproducibility, and is suitable for industrial production.

On September 26, 2018, Li Min personally filed a patent application involving the Rucaparib pharmaceutical preparation. CN108853030 discloses a pharmaceutical preparation and preparation method for the treatment of malignant tumors, the pharmaceutical preparation is Rucaparib phosphate granules. The Rucaparib phosphate granules is made of Rucaparib phosphate as raw material, and a specific amount of fillers, flavor correctants, adhesives, lubricants, co-solvents, antioxidants and other substances prepared by pretreatment, premixing, granulation, drying, whole granule, total mixing, packaging and other steps. The patent provides a Rucaparib phosphate granule with fast absorption, rapid onset, high bioavailability, easy to carry and take. Its solubility is good, 10 seconds can be all dissolved. The placement process will not absorb moisture and agglomerate, with good stability, small increase of impurities in the storage process, stable and uniform content. The labeling content of the placement process is between 100% - 101%. The microbiological inspection is qualified and the shelf life of the product is long, up to 24 months.

Chongqing Beisheng Pharmaceutical Technology Co., Ltd. submitted a patent application involving rucaparib on December 26, 2018, specifically involving a purification method of N-(2.2-diethoxyethyl) phthalimide. The purification process of the present invention is simple and mild, which can effectively improve the purity of N-(2.2-diethoxyethyl) phthalimide to more than 99%, ensuring the synthesis quality of Rucaparib.

4. Summary

Compound patents are the most important core patents. Compound patents include general formula compounds, pharmaceutically acceptable salts, active metabolites, prodrugs, chiral drugs/optical isomers, intermediates, derivatives, pharmaceutical impurities, biological drugs, etc. The compound patents are often the top priority of everyone's attention. The most important compound patent is the general formula compound. In the process of compound design and screening, the patent portfolio of the general formula compound can be carried out after finding lead compounds, modifying their structure, synthesizing a series of compounds with active or industrial utility and determining several required candidate compounds through research. The patent portfolio can be also carried out through a narrower, more firmly defined, more active compound patent protection or even patent protection for specific compounds. The core patent of the compound is characterized by high technical content, wide scope of claim protection, and strong concealment of the real target compound. Once a generic compound patent is granted, it is an absolute protection for chemical substances or drug-active molecules (APIs), which are difficult to circumvent, and the claims against APIs are generally difficult to invalidate by patents.

Crystal form is the most common form of drug protection. Usually, after the

development of the base compound, the applicant will apply for a crystal form patent one after another (such as US8754072, US9045487), extending and strengthening the protection of the base compound. Drugs with the same chemical structure can obtain different crystals due to different crystallization conditions. The phenomenon of drug polymorphism is also one of the important factors affecting the quality and clinical efficacy of drugs [2]. Good crystal forms of drugs often have new effects, such as improving the thermodynamic stability of APIs, facilitating formulation molding, improving formulation stability and solubility, increasing bioavailability, improving efficacy, and so on [3]. Through the protection of new crystal forms, the patent protection period can be effectively extended.

It is of great significance to develop different indications and expand their scope of application (such as US7351701, US7531530, US8071579, etc.), further broaden the indication range of products, expand the consumers of drug, and effectively consolidate the original market position while developing new potential markets [3].

Preparation is the specific application form of drugs. On the basis of comprehensive consideration of various properties of compounds, the most reasonable product dosage form (such as ordinary dosage form of tablets, capsules, granules, injection, etc.), preparation process (such as dry granulation, wet granulation, powder direct tableting) and workshop production process improvement have been developed [2]. Drugs are usually first marketed in standard tablet, capsule or injectable form (such as US9987285). The improvement of the dosage form of existing drugs from ordinary dosage forms to high-end dosage forms (such as sustained and controlled release preparations, subcutaneous implants, nano-suspensions, etc.), and then the secondary development of the process for new dosage forms, can effectively expand the scope of use of existing drugs and extend the patent protection period [4].

By extending the patent protection period, pharmaceutical enterprises can effectively prevent or delay other competitors from entering the market, and maximize the market monopoly period of listed drugs.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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