DRUG PATENT AND EXCLUSIVITY STUDY

uspto UNITED STATES PATENT AND TRADEMARK OFFICE

For questions or inquiries, please send an email to **USPTO-FDAcollaboration@uspto.gov**.

CONTENTS

EXECUTIVE SUMMARY

On January 31, 2022, and April 1, 2022, Senator Thom Tillis wrote to the United States Patent and Trademark Office (USPTO) and the FDA, emphasizing the importance of policymaking based on accurate and transparent data and requesting that the agencies conduct an independent assessment and analysis of certain sources and data that are being relied upon by those advocating for patent-based solutions to drug pricing. These letters are included in Appendix 1.

This study was undertaken to respond to Senator Tillis's letters.

The purpose of the study is to provide a baseline approach that researchers and policy makers can use in future analysis for examining the number of years from the time a New Drug Application (NDA) is first approved until the first launch of a generic. Using publicly available USPTO and FDA data, the report applies this approach to case studies of 25 NDAs.

As to the sources referenced in Senator Tillis's letters, the USPTO did not specifically assess their data or analysis. Rather, the USPTO, with the assistance of the FDA, conducted an analysis of a representative sample of 25 New Drug Applications (NDAs) (representing 13 distinct active ingredients) listed in the FDA's Orange Book[1] between 2005-2018[2] that were also considered by these data sources using available public data points (e.g., patent numbers and exclusivities listed in the Orange Book, patent filing and issue dates, and drug application approval dates). The representative samples were selected based on one of several factors, including top grossing products by revenue in 2017, most prescribed branded products in 2017, and other factors as set forth in more detail below in the discussion of the methodology. Specifically, the USPTO mapped the scope and duration of patent protections and FD&C Act exclusivities associated with this representative sample of drugs. Importantly, the study identifies the launch date, if any, of the first generic version of the drug product, which had occurred as of September 18, 2023. The FDA provided data to the USPTO as needed to conduct this study and analysis.

This study is one of many ways in which the USPTO and the FDA have recently collaborated. The Biden Administration is committed to promoting access to affordable medicine as set forth in President Biden's Executive Order on "Promoting Competition in the American

---

[1] For more information, see https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface (Orange Book Preface) and visit https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book (Approved Drug Products with Therapeutic Equivalence Evaluations | Orange Book | FDA).

[2] As explained in further detail in the methodology section, this study is limited to patents listed in FDA's Orange Book between 2005-2018 to match the time period covered in the data sources identified in Senator Tillis's letters. Patents and exclusivities listed in the Orange Book during this period are included in the study even if they were removed from the Orange Book during the 2005 to 2018 period, or afterwards.

Economy" (Executive Order).[3] In response to the Executive Order, the USPTO and the FDA have been working together to help ensure that the patent system continues to play its critical role in incentivizing and protecting the investments essential for bringing life-saving and life-altering drugs to market, while not unnecessarily delaying getting generic, biosimilar, and more affordable versions of those drugs into the hands of Americans who need them. The USPTO is working to ensure that patent rights are robust and reliable, and comply with the requirements for patentability. Among these initiatives, the USPTO and the FDA have engaged in collaborative efforts to ensure that patent examiners are able to utilize all publicly available FDA information. The work between the agencies is detailed on our USPTO - FDA Collaboration Initiatives webpage.[4]

As described in greater detail in the methodology section, this study examines patent, exclusivity, and drug approval data found in USPTO databases, the archives of Orange Book data,[5] and FDA public databases for drug products approved in 25 New Drug Applications (NDAs) (representing 13 distinct active ingredients) listed in the Orange Book between 2005 and 2018. Specifically, the study identifies the NDA number and the first marketing approval date for the first product(s) approved in each selected NDA. The USPTO independently determined the patent filing and issue dates and the patent expiration date for every Orange Book-listed patent associated with drug products approved under the NDA, based in part on review of terminal disclaimers filed in the listed patents for each drug product.[6] In consultation with FDA, USPTO also identified exclusivity data listed in the Orange Book for each NDA drug product approved on that date, and, as applicable, the date of market launch for a first generic product approved for such drug in an Abbreviated New Drug Application (ANDA).[7]

---

[3] Executive Order on Promoting Competition in the American Economy, Exec. Order No. 14036, 86 Fed. Reg. 36,987 (2021). The Executive Order instructs the Secretary of Health and Human Services to continue to promote generic drug and biosimilar competition to lower the prices of and improve access to prescription drugs and biologics. Additionally, the Order instructs the Secretary to communicate with the USPTO to ensure that the patent system, while incentivizing innovation, does not also unjustifiably delay generic drug and biosimilar competition.

[4] See https://www.uspto.gov/initiatives/fda-collaboration.

[5] For certain years of Orange Book data not available on the FDA website, the following archives of the Orange Book were used: https://www.thefdalawblog.com/orange-book-archives/.

[6] This study was limited to issued patents and did not consider pending patent applications because patent applications are not listed in the Orange Book. The study reviewed patent litigation for patents related to each NDA, as discussed in detail below.

[7] The date of launch of any authorized generics are not included in this study because they are not approved in an ANDA. The term "authorized generic" drug refers to a version of the drug approved under the NDA and most

As a general matter, mapping the scope and duration of patent protections and FD&C Act exclusivities associated with a particular FDA-approved drug product can be complex and may inform but not fully reflect the time it took (or can be expected to take) for a generic version of that product to come to market. In some cases, the timing of the entry of generic products is not fully reflected by a computation of patents and exclusivities, and competition could be affected by other factors. The study is intended to demonstrate a baseline approach for examining the duration of "market exclusivity" (which, for the purposes of this study, includes both patent protection and the FD&C Act exclusivities (hereafter patents and exclusivities)) from the date the first drug product(s) is approved in an NDA until generic competition for that first product enters the market. The study illustrates that, in some cases, quantifying raw numbers of patents and exclusivities, determining the duration[8] of certain patents and exclusivities for individual products approved in an NDA, and, where applicable, the possible effect of such patents and exclusivities on the market launch of a generic product can be a complex endeavor.

To reduce the complexity in the graphical depiction of the study results, the baseline study focuses on the first approved product in an NDA and does not capture patent and exclusivity data for all products in an NDA (e.g., strengths approved after the first date of NDA approval). Further, in light of the limited number of products studied, the study does not conduct a statistical analysis of the drug products in this study compared to all drug products included in the Orange Book during the same period.[9]

The study is not intended to provide a complete patent landscape for each product or provide a complete description of the universe of patents that could be asserted. For example, the analysis does not include patents that cannot be listed in the Orange Book, such as patents directed only to processes for making the drug product and patents claiming only metabolites

---

commonly used to describe an approved brand name drug that is marketed without the brand name on its label. Other than the absence of the brand name on its label, an authorized generic is the exact same drug product as the branded product. An authorized generic may be marketed by the brand name drug company, or another company with the brand company's permission. Authorized generics are usually marketed at a lower cost than the brand name drug. See https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/fda-list-authorized-generic-drugs.

[8] In this context, patent duration is the period from patent grant to anticipated patent (or patent term extension) expiration. The period from the earliest effective filing date to patent grant, and any period of disclaimed term are also depicted. In this context, the duration of an exclusivity period is from the beginning of the exclusivity period to the expiration of the exclusivity.

[9] Such a study has been done by other authors. See, e.g., C. Chien, et al., "Distinguishing and Predicting Drug Patents," Nature Biotechnology (March 2023), available at: https://www.nature.com/articles/s41587-023-01703-0 ("Each drug in the Orange Book was associated, on average, with 5.4 patents and 2.7 patent families. However, there was wide variability among studied drugs: 50% of drugs were covered by three or fewer patents, while fewer than 2% were covered by more than 20 patents").

or intermediates.[10] Non-Orange Book-listed patents that cover the approved drug product or a process for making the approved drug product do not affect when the FDA can approve an ANDA filed by a generic competitor though they may impact the cost and complexity of developing a competing product. A full accounting of the entire universe of patents that may be reasonably asserted against an ANDA applicant is outside the scope of this study.

The study examines the timing of entry of generic competition for the drug products studied, if applicable, and does not assess whether drugs approved in other NDAs, were available during the period studied to be used as alternatives to the products reviewed in this report. For example, it does not evaluate the availability of different therapeutic agents used for the same condition (e.g., meperidine hydrochloride vs. morphine sulfate for the treatment of pain).

A range of 1 to 27 Orange Book-listed patents are associated with each of the 25 NDAs examined. The claims of a patent covering a drug product define its scope and provide the contours of the patent owner's property rights with respect to that product. Not every patent listed in the Orange Book has the same scope,[11] and therefore the impact of each listed patent on the timing of approval and launch of a generic drug product can vary. Among the studied drug products with a higher number of Orange Book-listed patents, there are examples of some without generic competition yet (e.g., IMBRUVICA[12]) and others with generic approval and launch while one or more listed patents for the product remained in force (see, e.g., LIPITOR). Generic launch may occur before all of the patents listed in the Orange Book expire for a number of reasons, including e.g., the unexpired patents are not infringed by manufacture, use, or sale of the generic drug, or the patent owner and generic applicant have agreed to a generic launch date before the expiration date of all listed patents as part of a litigation settlement. For at least some of the drug products studied, a generic launch occurred before all of the Orange Book-listed patents associated with that drug product expired. For these products, the study provides data on the actual years of market exclusivity enjoyed by the NDA applicant prior to the generic launch date. For the drug products in the study with

---

[10] See Section 505(b)(1)(A)(viii) of the FD&C Act, which states that an applicant "shall submit to the Secretary as part of the application . . . the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted [. . .] and that (I) claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent; or (II) claims a method of using such drug for which approval is sought or has been granted in the application."

[11] Only certain kinds of patents are listed in the Orange Book (i.e., drug product patents, drug substance patents, and patents claiming an approved method of using the drug). The report generally describes the scope of each listed patent, but does not conduct a detailed assessment of claim scope.

[12] IMBRUVICA was first approved in 2013.

identified launch of generic competition, the market exclusivity ranged from about 3 to about 16 years.

This study does not contain sufficient data for generalized findings concerning all Orange Book listed patents and the timing of marketing of all generic drugs.[13]

The study explores whether continued innovation of a marketed drug, which results in follow-on patents, such as patents granted for a change to a patented drug product or a method of use after the issuance of an earlier patent, resulted in extended market exclusivity for the product beyond the expiration of the earlier patent(s). The USPTO grants patents on patent applications only after an examination to ensure that the claimed invention meets the statutory requirements for patentability.[14] Such patents can be the result of follow-on innovation that results from shifting dynamics in the market. For example, companies may file patent applications for changes to drugs that they intend to evaluate as a means to address patient compliance or side effect issues, to improve administration of the drug (e.g., via new dosage forms or routes of administration), or to expand the use of the active ingredient for treatment of additional diseases and conditions. Some improvements, if patented, may be economically significant yet have lower research and development costs than the original invention.[15]

Within the 25 NDAs analyzed, this study identifies several examples of such follow-on patents, including for once-daily dosage forms of a drug (LYRICA), new indications (or methods of treatment) of a drug (IMBRUVICA), or changes to inactive agents or devices for delivering medicines (VENTOLIN). This report explores each of these examples in greater detail below in the discussion of the products studied. In some of these examples, the data indicates that a generic competitor drug was approved and launched, while later patents directed to follow-on innovation and listed in the Orange Book were still in force. For example, a generic competitor launched a competing product to LIPITOR, before all the patents expired.

---

[13] For a broader discussion of factors affecting entry of generic competition, including non-IP barriers, see "Cost of Generic Drug Development and Approval," submitted to HHS by Eastern Research Group, Inc., Contract No. HHSP233201500055I, Dec. 31, 2021 (ERG Report).

[14] These requirements are addressed later in the report. At a high level, any claimed invention, as presented in a patent application, must be useful and eligible for patenting (35 U.S.C. § 101); novel and non-obvious over the prior art (35 U.S.C. §§ 102 and 103); and adequately described and disclosed so that another person skilled in that art can make and use the claimed invention (35 U.S.C. § 112). As noted above, patent applicants with applications that claim an invention that is not patentably distinct from the invention claimed in a commonly-owned patent are statutorily permitted to obtain patent protection if the other criteria for patenting are met, but will be required to file a terminal disclaimer to ensure that the patents remain commonly owned and have the same expiration date so that the invention that is not patentably distinct cannot extend the duration of exclusivity.

[15] The innovation cycle in general is described in Appendix 2.

In other cases, later patents may have claims directed only to specific aspects of the NDA holder's drug product, and may not block a generic from launching a competing product once the earlier patents have expired. However, this study is limited to patent and FD&C Act exclusivity data listed in the Orange Book and is not designed to capture other data that may be indicative of potentially anticompetitive behavior that can result in generic market entry having little effect on the price or market share of a brand name product.

In addition, the study identifies at least one instance where prior to market entry of a generic, FDA approved NDAs by other sponsors with different formulations of the same active ingredient (see, e.g., zolpidem tartrate). In this instance the drugs in the NDAs by other sponsors were not therapeutically equivalent to the drugs in the first approved NDA and the study is not designed to assess whether the availability of these alternative products impacted prescribing behavior or the pricing.

As noted above, this study demonstrates a baseline approach for examining the duration of protection associated with Orange Book-listed patents and exclusivities for at least the first drug product approved in an NDA. Other approaches may be used to assess relevant patents that were not listed in the Orange Book during a specific period. Additional information is also necessary to assess the practical state of competition for a patented product. For example, this study does not examine whether the availability of alternative products with the same active ingredient could discourage generic competition for the patented product. Likewise, although the study identifies generic launch dates when applicable, the study does not examine the effect of generic launch on drug price or market share of the patented product.[16]

[16] As the study does not examine the effect of generic launch on price, the study also does not examine whether generic launches, particularly those following settlement of litigation, represent unfettered competition. See, e.g., ERG Report, supra note 13, at pp. 53-60 (discussing settlements of ANDA litigation).

BACKGROUND

"A fair, open, and competitive marketplace has long been a cornerstone of the American economy."[17] The U.S. intellectual property system, rooted in the U.S. Constitution, provides property rights to inventors in the form of patent protection. The patent system promotes innovation and open competition by granting rights to patent owners to exclude others from making, using, offering to sell, selling and importing the patented invention into the United States for a limited time in exchange for publicly disclosing the invention. These public disclosures serve as the foundation upon which further research and innovation is made.

Patents also embody and incentivize investment in research, development, and clinical trials by innovator pharmaceutical and biotech companies. Innovator companies bear the expense and risk of developing life-saving drug[18] products and, under the U.S. statutory framework, are granted patents protecting those inventions for a limited period of time. In addition, upon marketing approval, innovators can also be eligible for a period of exclusivity under the U.S. statutory framework, for example, a Federal Food, Drug and Cosmetic Act (FD&C Act) exclusivity[19] before lower cost generic competitors can be approved or licensed. Patent protection and exclusivities are intended to promote a balance between the desires for new drug innovation and a greater public access to drugs that results from competition and use of new innovations. For instance, the prospect of patent protection and exclusivity can motivate innovators to invest in the development of novel products and new treatment options for patients. By its nature, the generic industry relies on innovator companies taking substantial

---

[17] Executive Order on Promoting Competition in the American Economy, Exec. Order No. 14036, 86 Fed. Reg. 36,987 (2021).

[18] This report generally uses the term "drug" to mean human drug products approved under section 505 of the FD&C Act. Biological products, including biosimilar biological products, are outside the scope of this study.

"Drug" is defined in the Federal Food, Drug, and Cosmetic Act (FD&C Act) as: (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). Section 201(g)(1) of the FD&C Act (21 U.S.C. § 321(g)(1)).

[19] Exclusivity refers to certain delays and time-limited prohibitions on acceptance or approval of applications for competitor drugs available under the FD&C Act. Exclusivity generally attaches upon approval of a drug product if the statutory requirements are met. See Appendix 3 for information on exclusivity provisions of the FD&C Act.

initial risks during such development, which must occur before lower cost versions of innovator products can be brought to market. The innovation system of the U.S. strives to strike the appropriate balance between encouraging meaningful innovation in drug development and providing access to more affordable medicines for patients.

In the United States, new drugs generally cannot be legally marketed for human use without FDA approval.[20] Applicants seeking to market a novel new drug must file a New Drug Application (NDA)[21] with the FDA and provide enough information to permit the FDA to determine whether the drug is safe and effective for its intended use (i.e., that the benefits of the drug outweigh the risks for its intended use). A single NDA may include more than one strength and each strength is considered a different drug product. Take, for example, an NDA that initially includes a tablet approved in a 5 mg strength and later is approved in a 10 mg strength. While approved in the same NDA, these drugs are considered different drug products and there can also be differences in the patents applicable to the two drug products.

A generic drug product is one that is required to be the same as an innovator drug product in active ingredient, dosage form, strength, route of administration, quality, performance characteristics,[22] labeling, and intended use. Applicants seeking to market a generic drug must file an Abbreviated New Drug Application (ANDA) to demonstrate that their product performs in the same manner as the innovator drug, among other required demonstrations.[23] An ANDA relies on FDA's finding that the previously approved drug product, referred to as the Reference Listed Drug (RLD), is safe and effective.

Another kind of follow-on application is a 505(b)(2) application, which is an NDA that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference or use. The previously approved drug product upon which the 505(b)(2) application relies is referred to as the listed drug. In the example above, the 5 mg and 10 mg drug products are the distinct RLDs/listed drugs that could be relied upon in an ANDA or 505(b)(2) application.

---

[20] See 21 U.S.C. §§ 355(a) and (b).

[21] NDAs are filed under Section 505(b) of the FD&C Act; 21 U.S.C. § 355(b).

[22] As explained in the preface to the Orange Book, a determination of therapeutic equivalence is made when an Abbreviated New Drug Application (ANDA) is approved. "FDA classifies as therapeutically equivalent those drug products that... contain identical amounts of the identical active drug ingredient in the identical dosage form and route of administration.... The concept of therapeutic equivalence applies only to drug products containing the identical active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., meperidine hydrochloride vs. morphine sulfate for the treatment of pain)."

[23] ANDAs are submitted under Section 505(j) of the FD&C Act; 21 U.S.C. § 355(j).

An NDA applicant must identify each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent, or claims a method of using such drug for which approval is sought or has been granted in the application. The NDA applicant must submit this information to the FDA as part of the NDA, and following approval of the NDA. The Patent and Exclusivity Information Addendum of the Orange Book compiles the submitted patent information in an annual edition and monthly supplements updating the information therein.[24] This information is also available in association with each product listing in the electronic version of the publication, which is updated each business day. The Orange Book compilation also identifies certain innovator and generic drugs that qualify for exclusivities under the FD&C Act.[25] The Orange Book thus illustrates the interplay of patents and exclusivities. In addition, the Orange Book, which can be searched by active ingredient, contains therapeutic equivalence evaluations for approved multisource prescription drugs, which can be used by healthcare providers and others to identify products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and which can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Drug products that contain the same active ingredient but differ in dosage form, strength or route of administration are not considered therapeutically equivalent with each other.

The timing of filing and approval of an ANDA or a "505(b)(2) application"[26] is determined, in part, by any exclusivities that exist for the drug. For example, five-year New Chemical Entity (NCE) exclusivity governs the earliest time that an ANDA or 505(b)(2) referencing the listed NCE drug may be submitted to the FDA and filed,[27] and orphan-drug exclusivity precludes for

---

[24] This study relied on electronic images of paper copies of the Orange Book. If the information printed in paper copies of the Orange Book is incorrect, for example, the wrong patent expiration date is printed, a later version of the Orange Book will contain a correction.

[25] A 505(b) application may qualify for a variety of FDA statutory exclusivities, as detailed in Appendix 3. An ANDA applicant may qualify for certain other statutory exclusivities under the FD&C Act, including a 180-day period of market exclusivity for the "first applicant" to file a substantially complete ANDA that challenges an Orange Book-listed patent by filing a "paragraph IV" certification. See, e.g., 505(j)(5)(B)(iv) of the FD&C Act (21 U.S.C. § 355(j)(5)(B)(iv)).

[26] The reference to 505(b)(2) is a reference to a section of the Federal Food, Drug and Cosmetic Act, which is codified as 21 U.S.C. § 355(b)(2).

[27] If the listed drug relied upon by such an ANDA or 505(b)(2) drug application containing a paragraph IV certification has five-year NCE exclusivity, the ANDA or 505(b)(2) application can be submitted after the

a seven-year period the approval of an ANDA or 505(b) application for the same drug for the same use or indication within the orphan designated disease or condition.

An applicant seeking to market a drug that is the subject of an ANDA or 505(b)(2) application is required to address any patent(s) listed in the Orange Book for the listed drug relied upon in the application.[28] If the applicant indicates that there are unexpired Orange Book-listed patents on the listed drug, and the applicant does not choose to challenge the patents, the FDA can approve the ANDA or 505(b)(2) application once the patents expire. If the applicant indicates that there are unexpired patents and asserts that each of the patents are either invalid, unenforceable, or will not be infringed by the generic or 505(b)(2) drug (often referred to as a "paragraph IV certification"), the applicant must provide notice of that paragraph IV certification to the NDA holder and patent owner, who can then initiate a patent infringement action against the ANDA or 505(b)(2) applicant. If such an action is initiated within 45 days of receiving notice of the paragraph IV certification, the approval of the ANDA or 505(b)(2) application generally will be stayed for 30 months from the date of receipt of the notice, allowing time for the patent holder and applicant to litigate the patent dispute.

Although this report identifies generic drug launch dates for certain drug products where applicable, it does not investigate the effect of generic launch on drug pricing or market share for the products listed in this report. Drug pricing is outside the scope of this report and requires further study that goes beyond the USPTO's expertise. In addition to pricing being outside of the scope of this report, market share is also outside of the scope of this report.[29] Additional information about key concepts related to patents and exclusivities is available in Appendix 3.

METHODOLOGY

To contribute to the policy discussion on the development of innovative medicines and generic drugs, the USPTO, in consultation with the FDA, conducted an independent assessment and analysis of patent and Orange Book data. To conduct this study, the USPTO reviewed patent and exclusivity information for 25 NDAs that included 13 active ingredients (or combinations of active ingredients).

---

expiration of four years from the date of approval of the listed drug, and the applicant is not required to wait until the five-year NCE exclusivity has expired to submit the ANDA or 505(b)(2).

[28] See 21 U.S.C. §§ 355(b)(2)(A)-(B) and 355(j)(2)(A)(vii)-(viii).

[29] See, e.g., ERG Report, *supra* note 13, for a thorough discussion barriers and incentives to generic competition and market share.

The selection criteria were designed to incorporate a sample of the same products reviewed in the data sources mentioned in Senator Tillis's letters. For example, all NDAs studied were included in the Orange Book at some point between 2005 and 2018, the years covered by the University of California College of the Law, San Francisco Evergreen Drug Patent Database (UC Database).[30]

In addition, the study includes some of the top grossing products by revenue in 2017, which was the year covered by an I-MAK report mentioned in Senator Tillis's letters.[31] These top grossing products include: apixaban (ELIQUIS), lenalidomide (REVLIMID), pregabalin (LYRICA), and rivaroxaban (XARELTO).[32] Further, the study includes ibrutinib (IMBRUVICA) and bictegravir sodium (BIKTARVY), which were referenced in more recent I-MAK reports.[33] The study also includes some of the most prescribed branded products in 2017 (the most prescribed data consulted was presented by drug trade name (trademark), not active ingredient): atorvastatin (LIPITOR), amlodipine besylate (e.g., NORVASC), and albuterol sulfate (VENTOLIN HFA).[34] In order to include a fixed dose combination drug, lopinavir/ritonavir (KALETRA) is included in the study. Zolpidem tartrate (e.g., AMBIEN) is included because it was a drug widely available during the period studied, with an active ingredient that was marketed by more than one manufacturer in drug products approved in separate NDAs. Finally, in order to study examples of Orange Book-listed patents directed to new innovation of well-known active ingredients, the study includes an aspirin-containing product (VAZALORE).

---

[30] This Database is one of the data sources mentioned in the letters discussed above. The Database can be accessed here: https://www.uclawsf.edu/2022/02/02/evergreen-drug-patent-database-center-for-innovation/ (Evergreen Drug Patent Database - Center for Innovation - UC Law San Francisco (Formerly UC Hastings) (uclawsf.edu)) and https://sites.uclawsf.edu/evergreensearch/ (Evergreen Drug Patent Database - UC College of the Law (uclawsf.edu)).

[31] I-MAK has produced additional information regarding drug products since the reports addressed in Senator Tillis's letter. This includes the I-MAK Drug Patent Book, which according to its website, provides patent information for several drugs including four drugs in this study: BIKTARVY, ELIQUIS, IMBRUVICA, and REVLIMID. This is available at https://drugpatentbook.i-mak.org/. This information has not been analyzed as part of this report.

[32] The Top 15 Best-Selling Drugs of 2017, Genetic Engineering & Biotechnology News, which is available at https://www.genengnews.com/a-lists/the-top-15-best-selling-drugs-of-2017/ and I-MAK report.

[33] See Imbruvica's Patent Wall, which is available at https://www.i-mak.org/imbruvica/, and Overpatented, Overpriced (2022), which is available at: https://www.i-mak.org/wp-content/uploads/2022/09/Overpatented-Overpriced-2022-FINAL.pdf.

[34] New 2017 Data and Statistics for Pharmaceutical Products (acs.org), Table 4, which is available at https://pubs.acs.org/doi/10.1021/acschemneuro.8b00320, citing Good Rx Guide.

To manage the scope of work, in general, the study does not examine in each instance all NDAs listed in the Orange Book during the study period that contained the same active ingredient. For example, as noted above, one product containing albuterol sulfate (VENTOLIN HFA) is included in the study while NDAs for other products containing the active ingredient albuterol sulfate that were also listed in the Orange Book between 2005 and 2018 are not included in the study. Similarly, two products with the active ingredient amlodipine besylate are included in the study, but other amlodipine besylate containing products which appeared in the Orange Book between 2005 and 2018 are not included in the study. For one active ingredient, zolpidem tartrate, at least one product for each of 5 NDAs listed in the Orange Book between 2005 and 2018 is included, because the NDAs had different sponsors or different formulations or routes of administration and their inclusion in the study seemed appropriate to examine the innovation process for an active ingredient.

Once the drugs to be included in the study were selected, the USPTO identified the NDA numbers for the drugs that were included in the Orange Book in the 2005 to 2018 time period, and set out to gather the patent and exclusivity data associated with these NDAs published in the Orange Book during the relevant time period. To collect data for the years 2005 to 2015, the USPTO relied upon a database that compiled all Orange Book Data from 2005 to 2015, and checked the Orange Book archives when necessary. For the years 2016, 2017, and 2018, the USPTO reviewed the Annual editions, as well as monthly supplements in the Orange Book archives.

For each patent listed in the Orange Book, the USPTO determined the patent filing and issue dates from the USPTO database of patents. Although the Orange Book lists the expiration date submitted to the FDA by the NDA sponsor for each patent, for this study the USPTO independently determined the projected patent expiration date, using the previously calculated patent term adjustment[35] or patent term extension,[36] and the effect of any terminal disclaimer.[37] In addition, the NDA approval dates, exclusivities, and exclusivity expiration dates were determined from the Orange Book. Generic launch dates were determined from a

---

[35] Patent term adjustment is granted for delays in the processing of a patent application. See 35 U.S.C. § 154(b). The length of any patent term adjustment may be different from that printed on the face of the patent. The USPTO reviewed the file history of the patent to determine the correct length. This independent analysis resulted in some expiration dates that were different (both earlier and later) from expiration dates included in the Orange Book.

[36] Patent term extension is based upon regulatory review of certain products by the FDA or U.S. Department of Agriculture. 35 U.S.C. § 156.

[37] A terminal disclaimer may shorten the term of a patent to expire the same date as another patent, and requires the two patents to remain commonly owned. See 35 U.S.C. § 253 and 37 CFR 1.321. In reviewing any terminal disclaimers of patents included in the study, the USPTO reviewed the file histories of the patents, including those that were only available in paper.

variety of sources, including any date shown as the "date of first commercial marketing by FTF" on the Paragraph IV Certifications List available on the FDA's website[38], and company press releases. This information was compiled in spreadsheets for each NDA, and charted. The USPTO also created tables for each NDA to show patent and FD&C Act exclusivity information in a different format. These tables are found in Appendix 4.

An active ingredient may be the subject of multiple NDAs, and multiple drug products can be approved in a single NDA. Where the trade name of a drug was associated with more than one NDA during the time period studied, all NDAs with that trade name were included in the study. However, individual drug products approved in an NDA may include products with different strengths, each separately listed in the Orange Book. In the study, some strengths approved in an NDA through a supplement at a later date had fewer patents and exclusivities, because certain patents or exclusivities were not applicable to the later-approved strength(s) or they were approved after some patents or exclusivities had expired. Similarly, subsequently approved strengths could have had additional patents or exclusivities.[39] Although the subsequent approval of additional strengths in an NDA is acknowledged in this report, the charts only depict the baseline of the first approved products.

The study includes only granted patents and does not include pending or abandoned patent applications. Abandoned applications do not result in granted patents, and thus, do not pose a barrier to competition. The study also does not discuss pending patent applications, because they are not listable in the Orange Book and may never become patents, and if no patent is granted, there is no enforceable right. As a result, the total of all abandoned and pending applications is not a meaningful metric.

Finally, the study includes only those patents listed in the Orange Book and is limited to the FDA drugs approved for human use, as opposed to, for example, veterinary use. Whether a patent is listed in the Orange Book is an important distinction because only patents listed in the Orange Book can affect the timing of FDA approval of a generic drug. Patents that are not listed in the Orange Book do not impact the timing of FDA approval of a generic drug application. These non-Orange Book-listed patents have the same exclusive effect as any other patent in any other non-pharmaceutical industry. In other words, as with any company operating in a competitive marketplace, non-Orange Book-listed patents must be evaluated to assess risk from infringement considerations; however, these patents would not present a regulatory barrier to approval of a competitor drug. Patents that were listed in the Orange

---

[38] This list is available here: https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/patent-certifications-and-suitability-petitions#List.

[39] Although our study focused on the first approved drug product associated with each NDA, later-approved drug products associated with these NDAs did not result in additional patents listed in the Orange Book during the period of study.

Book during the 2005 to 2018 period were included in the study even if they were removed from the Orange Book during the 2005 to 2018 period or afterwards.

DISCUSSION

Detailed information for each studied drug product follows with each drug listed in alphabetical order by the active ingredient. The detailed information includes bar charts used to illustrate first date of NDA approval, patents, and exclusivities under the FD&C Act that were listed in the Orange Book between 2005 and 2018 for each studied drug product, and the date of launch of a generic for such product, if applicable.

Figure 2, shown below, is an example bar chart, including a key. In Figure 2 and the bar charts depicting this data, patent-based market exclusivity beginning at the time of the FDA drug product approval is shown in green. Orange hash marks indicate a reduction of patent term due to terminal disclaimer, if applicable. The bar charts also show (1) the earliest priority date for each patent, shown in light gray, (2) the period during which a patent application was pending, shown in light red, and (3) the period after which a patent was granted but prior to the FDA drug product approval, shown in yellow. During these three periods prior to the FDA product approval, the patent owner cannot market a drug product despite the running of the 20-year patent term.[40] Patent term extension, which compensates patent holders for marketing time lost while developing the product and awaiting FDA approval, is shown in lavender, if applicable. Patent term adjustment, which compensates patent holders for delay at the USPTO, is shown in turquoise, if applicable. Stand-alone exclusivities under the FD&C Act are shown as dark-blue hashed lines, if applicable. Pediatric exclusivities (PED), which extend existing exclusivities and prohibitions on approval based on listed patents by six months, are shown with gold hashed lines, if applicable. The bar charts indicate the NDA approval date with a green dotted line and the generic launch date is shown in purple, when one was identified. Some products in this study do not yet have generic competition, but others had generic versions launch years before all the Orange Book-listed patents for the product expired. The charts do not include the date of generic (ANDA) approval because not all approved generic products are launched. Instead, the charts use generic launch to indicate the marketing of a generic. The study does not evaluate whether such competition was limited by the terms of a settlement with the NDA holder.

Use code information is submitted to the FDA by the NDA holder for each patent that claims an approved method of using the drug product that is the subject of the NDA, and a

---

[40] Generally speaking, the enforceable term of the patent begins on the day a patent issues and ends 20 years from the earliest non-provisional priority date relied on by the patent. See 35 U.S.C. § 154(a)(2). Patents issuing from applications filed prior to June 8, 1995, are subject to a patent term that ends 17 years from the date of issuance.

corresponding code is published by the FDA in the Orange Book. Use code information is the NDA holder's interpretation of the scope of the patent as it relates to the approved method of using the drug.[41] Although the Orange Book publishes use codes and the corresponding information, the figures and charts do not list use codes because they are not themselves an intellectual property right or a FD&C Act exclusivity (e.g., a form of protection).

Similarly, pediatric exclusivities extend by six months existing exclusivities and prohibitions on approval based on listed patents, and are not a stand-alone form of protection from the exclusivity or patent to which they are added.[42] These findings are addressed in more detail for each drug product in Appendix 4.

Figure 2, shown below is provided here as an example of how the information is displayed. A larger version of the Figure is reproduced below in the discussion of atorvastatin calcium (LIPITOR).

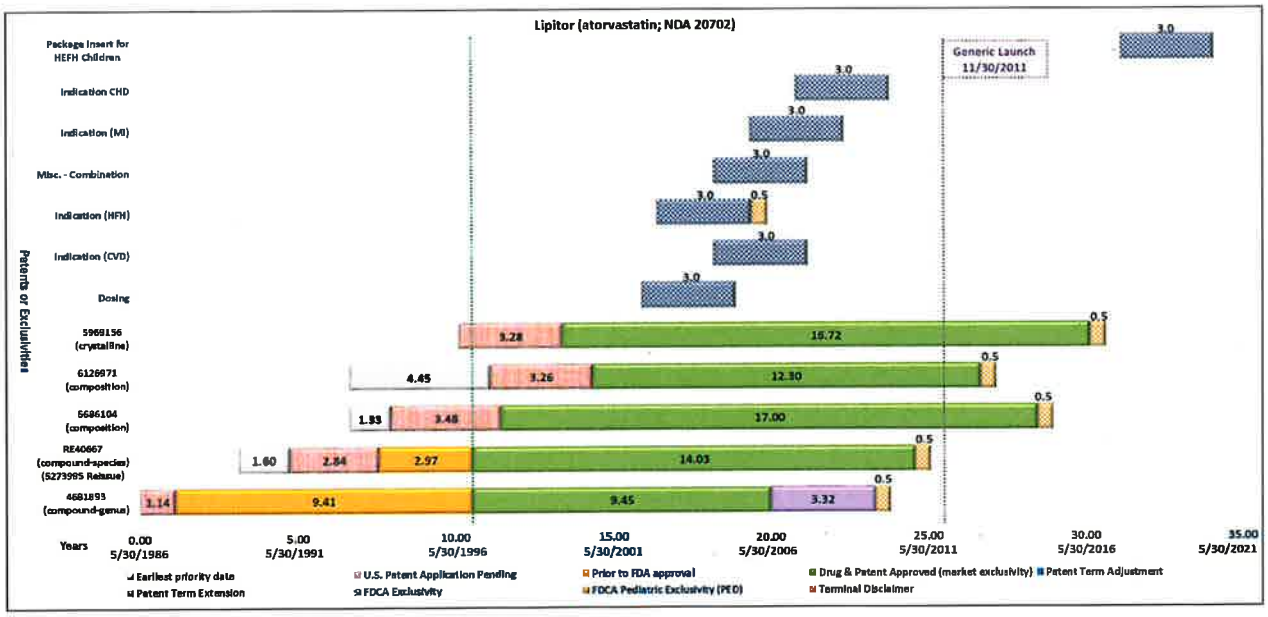


Figure 2.

---

[41] See 21 CFR 314.53(c)(2)(ii)(P)(3). FDA Form 3542 and 3542a are used to provide patent information to FDA. Section 4.2b of Form 3542 and 4.2a of Form 3542a include a space to provide the "specific approved method of use claimed by the patent that the FDA should include as the 'Use Code" in the Orange Book, using no more than 250 total characters including spaces." If there is more than one specific approved method of use, then more than one use code would be established. The forms are available through FDA's website here: https://www.fda.gov/about-fda/reports-manuals-forms/forms. Instructions for completing such forms are provided here: https://www.fda.gov/media/102047/download and https://www.fda.gov/media/69894/download.

[42] See "Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A)" on FDA's website here: https://www.fda.gov/drugs/development-resources/qualifying-pediatric-exclusivity-under-section-505a-federal-food-drug-and-cosmetic-act-frequently.

Key:

- Earliest priority date
- U.S. Patent Application Pending
- Prior to FDA approval
- Drug & Patent Approved (market exclusivity)
- Patent Term Adjustment (not applicable to this example)
- Patent Term Extension
- FDCA Exclusivity
- FDCA Pediatric Exclusivity (PED)
- Terminal Disclaimer (not applicable to this example)

1. albuterol sulfate (VENTOLIN HFA)

Albuterol sulfate is used as a bronchodilator to treat asthma. The active ingredient has been used in a variety of dosage forms including tablets, capsules, oral solutions, inhalation solutions, powders, and aerosols, and with a variety of different dosing devices. Albuterol sulfate illustrates the potential for innovation and differentiation associated with a single active ingredient. The study includes VENTOLIN HFA as an example of a drug product containing albuterol sulfate, because VENTOLIN HFA was identified as one of the top 10 "most popular prescribed medications" in 2017,[43] and illustrates the importance of device innovation in new drug products.

As shown in the bar chart of Figure 4 below, VENTOLIN HFA was approved on April 19, 2001. There is no generic version of VENTOLIN HFA at this time. However, a number of albuterol sulfate products, including generic products, were approved for treating asthma well before 2005.

As shown in Figure 3 below, the UC Database, which compiles the NDAs listed in the Orange Book between 2005 and 2018, lists six different NDAs that are products containing albuterol sulfate as the only active ingredient. This does not mean that the products are all therapeutic equivalents or for the same patient population. These NDAs are: ACCUNEB, PROVENTIL HFA, VENTOLIN HFA VOLMAX, PROAIR HFA, and PROAIR RESPICLICK. Many of these NDAs relate to different dosing/delivery devices, but they all have the same active ingredient, and they all have an approved indication for bronchospasm associated with asthma. Notably, VENTOLIN HFA (EQ 0.09MG BASE/INH) is not therapeutically equivalent to any listed product. ACCUNEB (EQ 0.021% BASE), PROVENTIL HFA (EQ 0.09MG BASE/INH), and PROAIR HFA, for example, do have therapeutic equivalents. Products are considered by the FDA to be therapeutic equivalents, if, among other things, they "contain identical amounts of

---

[43] New 2017 Data and Statistics for Pharmaceutical Products (see *supra* note 34); available at: https://pubs.acs.org/doi/10.1021/acschemneuro.8b00320.

the identical active drug ingredient in the identical dosage form and route of administration."[44] This concept should not be confused with whether there are other products that can be used to treat the same disease or condition. For example, generic albuterol HFA, VENTOLIN HFA and a number of other drugs can all be used to treat asthma, although the dosage and patient population may vary.

During the 2005 to 2018 time period, and before 2005, other products (including generics, not all of which are inhalation products) containing albuterol sulfate were approved. A discussion of the albuterol sulfate product landscape, including what the product was approved to treat and for what patient population, is beyond the scope of this study.

NDA #	Ingredient(s)	Company	Product Name	Approval Date	First Cliff Expiration Date	Latest Prot Date	Additional Prot Time
19604	Albuterol Sulfate	MURO	Volmax*	12/23/92	10/11/05	10/11/05	0 years 4 months
20503	Albuterol Sulfate	3M DRUG DELIVERY	Proventil-HFA*	8/15/96	12/23/17	12/23/17	8 years 1 months
20949	Albuterol Sulfate	MYLAN SPECIALITY LP	Accuneb*	4/30/01	12/28/21	12/28/21	0 years 0 months
205636	Albuterol Sulfate	TEVA BRANDED PHARM	Proair Respiclick	3/31/15	3/12/18	8/28/35	17 years 8 months
20983	Albuterol Sulfate	GLAXOSMITHKLINE	Ventolin HFA*	4/19/01	12/23/17	8/26/26	12 years 0 months
21457	Albuterol Sulfate	TEVA BRANDED PHARM	Proair HFA*	10/29/04	10/29/07	5/18/31	23 years 7 months

Figure 3. A truncated view of Albuterol Sulfate (Single Drug Product) entries from UC Database

VENTOLIN HFA (NDA 20983) contains the active ingredient albuterol sulfate (0.09 milligram (mg)/inhale) and a hydrofluoroalkane (HFA) propellant.

As shown in the bar chart of Figure 4 and in Table 1 of Appendix 4, the study identifies 20 patents listed in the Orange Book during the 2005 to 2018 time period,[45] as well as a 6-month

[44] Orange Book Preface; see generally 21 CFR 314.3(b).

[45] As explained in the methodology section, the study identifies patents and exclusivities listed in the Orange Book during the 2005 to 2018 period, even if they expired or were removed from the Orange Book during that period or after 2018.

pediatric exclusivity[46] that is attached to each of the patents.[47] The patents are generally directed to metered dose inhalers, many addressing problems arising from the change from chlorofluorocarbon (CFC) propellants to non-ozone damaging HFA propellants due to the Montreal Protocol on Substances that Deplete the Ozone Layer.[48] Transitioning from CFC to HFA propellants involved significant investment in research and development leading to one of the Orange Book-listed patents.[49] The new HFA propellants degraded the previous polymer stoppers requiring new innovation to solve this problem. First, the polymer used for the stoppers had to be replaced with a new polymer. The change in polymer created a need to redesign the inhaler valves. A family of patents all expiring at the same time are directed to the new valve designs. The new HFA propellants also caused drug deposition and stability problems, which required changes to the aerosol container, also patented. Other patents cover specific features of the dispenser, including actuating and indicating mechanisms.[50] Notably, each patent is limited to a specific innovation. There is no generic version of VENTOLIN HFA at this time.[51]

Examining the patent and exclusivity information associated with one product in isolation, does not necessarily indicate whether any other products with the active ingredient albuterol sulfate were approved before the period of protection associated with VENTOLIN HFA has expired. As shown in the UC Database listings included in Figure 3 above, there are a number of approved NDAs containing albuterol sulfate. Furthermore, databases of Orange Book-patent and exclusivity data for any specific time period may not include all albuterol sulfate products, such as those approved well before the specific time period studied, and usually would not include generic products. A number of albuterol sulfate products, including generic products, were approved for treating asthma well before 2005. However, generic CFC

---

[46] See Appendix 3 below for a detailed listing of Exclusivities under the FD&C Act.

[47] U.S. Patent No. 6,743,413 was filed prior to June 8, 1995, and was subject to a patent term of 17 years from the date of issuance.

[48] September 16, 1987, S. Treaty Doc. No. 10, 100th Cong., 1st sess., 26 I.L.M. 1541 (1987).

[49] See S.W. Stein and C.G. Thiel, "The History of Therapeutic Aerosols: A Chronological Review," 30(1) J. Aerosol. Med. Pulm. Drug Deliv. 20–41 (2017).

[50] Federal Trade Commission (FTC) submitted a patent listing dispute to FDA asserting that U.S. Patent No. 7,500,444 was improperly listed in the Orange Book.

[51] On January 15, 2019, the NDA holder for Ventolin HFA launched an authorized generic. The term "authorized generic" drug is most commonly used to describe an approved brand name drug that is marketed under the brand name drug's NDA but without the brand name on its label. (See FDA List of Authorized Generic Drugs | FDA, which is available online at: https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/fda-list-authorized-generic-drugs). Since it is otherwise the exact same drug product as the branded product this launch is not represented on the chart below.

albuterol inhalers were withdrawn from the U.S. market by December 31, 2008.[52]

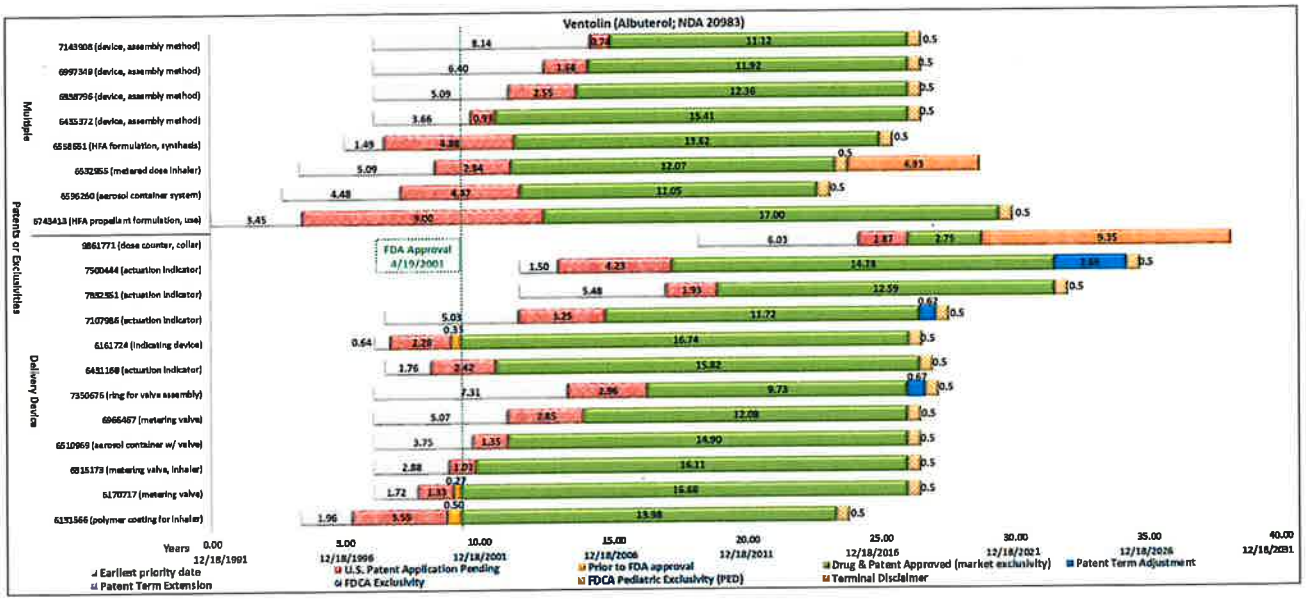


Figure 4. Bar chart of VENTOLIN (NDA 20983) (Orange Book entries 2005-2018)

[52] A. B. Jena, O. Ho; D. P. Goldman; *et al.*, "The Impact of the US Food and Drug Administration Chlorofluorocarbon Ban on Out-of-pocket Costs and Use of Albuterol Inhalers Among Individuals with Asthma," JAMA Internal Medicine (2015), 175(7), which is available online at: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2293081.

2. amlodipine besylate (NORVASC and orally disintegrating tablet (ODT))

Amlodipine besylate is a calcium channel blocker that works to treat chest pain and other conditions of coronary artery disease by widening blood vessels. Other calcium channel blockers include amlodipine benzoate, amlodipine maleate, diltiazem, verapamil, nifedipine, and nimodipine. In addition to calcium channel blockers, other treatments for chest pain include anticoagulant medicines, antiplatelet medicines, beta blockers, nitrates, and statins.[53] Amlodipine besylate is often used in combination with other anti-hypertensive drugs as discussed below. Amlodipine besylate was chosen for the study because it is the active ingredient in NORVASC, which was one of the top 10 most commonly prescribed drugs in 2017.[54]

As shown in Figure 5 below, a search of the UC Database for amlodipine besylate results in two NDAs in which amlodipine besylate is the sole active ingredient: NDA 19787 (NORVASC), filed by Pfizer, and NDA 22026 (amlodipine besylate ODT), filed by Synthon Pharmaceuticals. The active ingredient amlodipine besylate is also available in anti-hypertensive fixed dose combination drug products that include other active ingredients. Although these combination products are not included in this report, they demonstrate that the NORVASC patents and exclusivities discussed below did not prevent the approval of NDAs for all products which contained amlodipine besylate. This table also helps to demonstrate the complexity of the analysis of patents and protections in this space.

---

[53] See Angina (Chest Pain) - Treatment | NHLBI, NIH, which is available on the National Institutes of Health (NIH) website at https://www.nhlbi.nih.gov/health/angina/treatment.

[54] See *supra* note 34.

NDA #	Ingredient(s)	Company	Product Name	Approval Date	First Cliff Expiration Date	Latest Prot Date	Additional Prot Time	Months of Additional Prot Time
19787	Amlodipine Besylate	PFIZER	Norvasc*	7/31/92	9/25/07	9/28/08	2 years 2 months	26
22026	Amlodipine Besylate	SYNTHON PHARMS	Amlodipine Besylate	9/27/07	11/20/22	11/20/22	0 years 0 months	0
21540	Amlodipine Besylate; Atorvastatin Calcium	PFIZER	Caduet*	1/30/04	8/11/18	8/11/18	12 years 1 months	145
20364	Amlodipine Besylate; Benazepril Hydrochloride	NOVARTIS	Lotrel*	3/3/95	12/19/17	12/19/17	12 years 6 months	150
210045	Amlodipine Besylate; Celecoxib	COEPTIS	Consensi	5/31/18	5/31/21	2/28/30	8 years 9 months	105
200175	Amlodipine Besylate; Hydrochlorothiazide; Olmesartan Medoxomil	DAIICHI SANKYO	Tribenzor	7/23/10	7/23/13	10/25/16	3 years 3 months	39
205003	Amlodipine Besylate; Perindopril Arginine	ADHERA	Prestalia	1/21/15	10/5/29	10/5/29	11 years 9 months	141
22401	Amlodipine Besylate; Telmisartan	BOEHRINGER INGELHEIM	Twynsta	10/16/09	1/7/14	1/7/14	1 years 3 months	15

Figure 5. A truncated view of UC Database entries with active ingredient amlodipine besylate

To more fully understand the landscape of anti-hypertensive products that contain amlodipine besylate, a detailed review of other approved drug products that contain this active ingredient would be required to obtain more complete comprehension, including about therapeutic alternatives.

a) NORVASC

NORVASC (Pfizer NDA 19787) contains the active ingredient amlodipine besylate in a tablet formulation with drug products in 2.5, 5.0, and 10.0 mg strengths. As shown in the bar chart of Figure 6 and Table 2 of Appendix 4, the study identifies two patents listed in the Orange Book during the 2005 to 2018 time period. The exclusivities include three-year new clinical investigation (NCI) exclusivities for a new patient population (NPP) and for a new indication of use in patients with angiographically documented coronary artery disease (I-472).

As shown in the bar chart of Figure 6 below, NORVASC was approved on July 31, 1992. Generic versions of amlodipine besylate (2.5 mg, 5.0 mg, 10.0 mg) (ANDA 076418) were launched on March 23, 2007, after U.S. Patent No. 4,879,303 was found invalid.[55] Thus, the NDA applicant enjoyed less than 15 years of market exclusivity (the period from the date of FDA approval until the generic launched).

As shown in Figure 6 below and Table 2 of Appendix 4, one patent covers a genus of compounds, including amlodipine, and methods of treating or preventing hypertension. The other patent covers amlodipine besylate and pharmaceutical formulations containing amlodipine besylate, including tablets, capsules, and solutions. Figure 6 depicts all three strengths.[56]

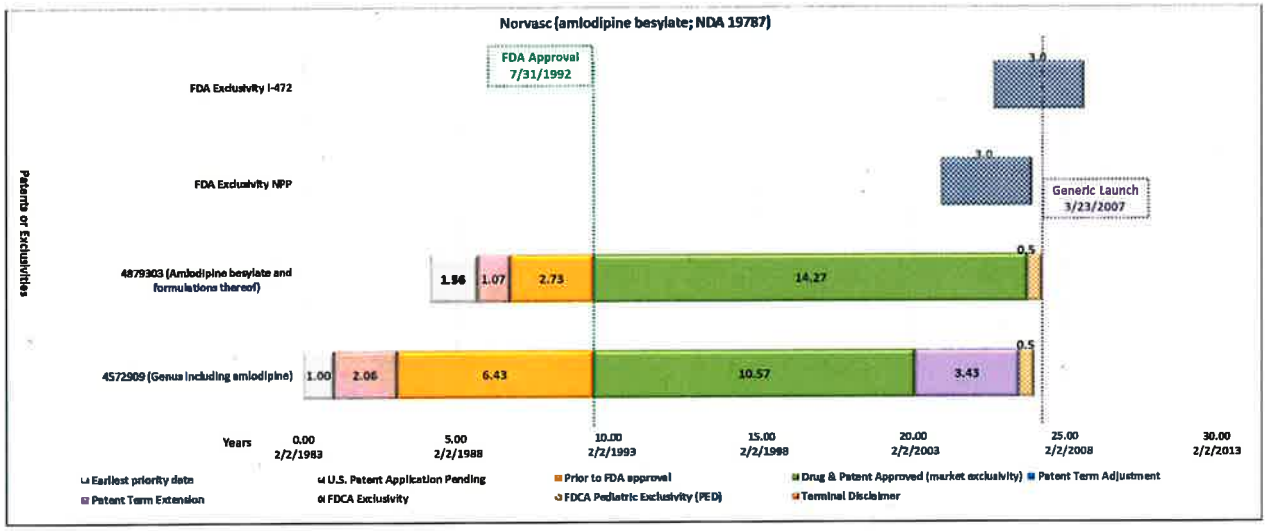


Figure 6. Bar chart of Norvasc (NDA 19787) (2.5, 5.0, 10.0 mg) (Orange Book entries 2005-2018)

---

[55] *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007).

[56] U.S. Patent Nos. 4,572,909 and 4,879,303 were each filed prior to June 8, 1995, and were subject to a patent term of 17 years from the date of issuance.

b) amlodipine besylate ODT (Tablet, Orally Disintegrating)

Synthon Pharmaceuticals submitted an NDA (NDA 22026) for products distinct from NORVASC, containing the active ingredient amlodipine besylate in 2.5 mg, 5 mg, and 10 mg strengths. This NDA was submitted pursuant to section 505(b)(2) of the FD&C Act.[57] Synthon obtained a patent on a specific formulation that incorporated the previously known amlodipine besylate active agent. Synthon Pharmaceutical's amlodipine besylate products are ODTs, distinct from Pfizer's NORVASC amlodipine besylate conventional tablet.[58]

As shown in the bar chart of Figure 7 below, Synthon Pharmaceuticals NDA for amlodipine besylate ODT was approved on September 27, 2007. The product was discontinued and there is no generic available.

As shown in Figure 7 below and Table 3 of Appendix 4, the study identifies one patent listed in the Orange Book for each product covered by NDA 22026 (2.5 mg, 5 mg, 10 mg) during the 2005 to 2018 time period. As shown in the bar chart below, the patent covers the active ingredient crystalline amlodipine besylate monohydrate and formulations containing the active ingredient.

Synthon's amlodipine besylate product is currently discontinued, and the FDA has approved no other amlodipine-containing orally disintegrating tablet. As shown in the bar chart for NORVASC above, Synthon's patent on an orally disintegrating tablet was not a listed patent for NORVASC and was not applicable to the approval of a generic version of NORVASC, because the two products have different formulations of the active ingredient, amlodipine besylate.

---

[57] 21 U.S.C. ch. 9 § 301 *et seq.*

[58] See Synthon, Teva to Market Generic Norvasc | FDAnews, which is available online at: https://www.fdanews.com/articles/95584-synthon-teva-to-market-generic-norvasc.

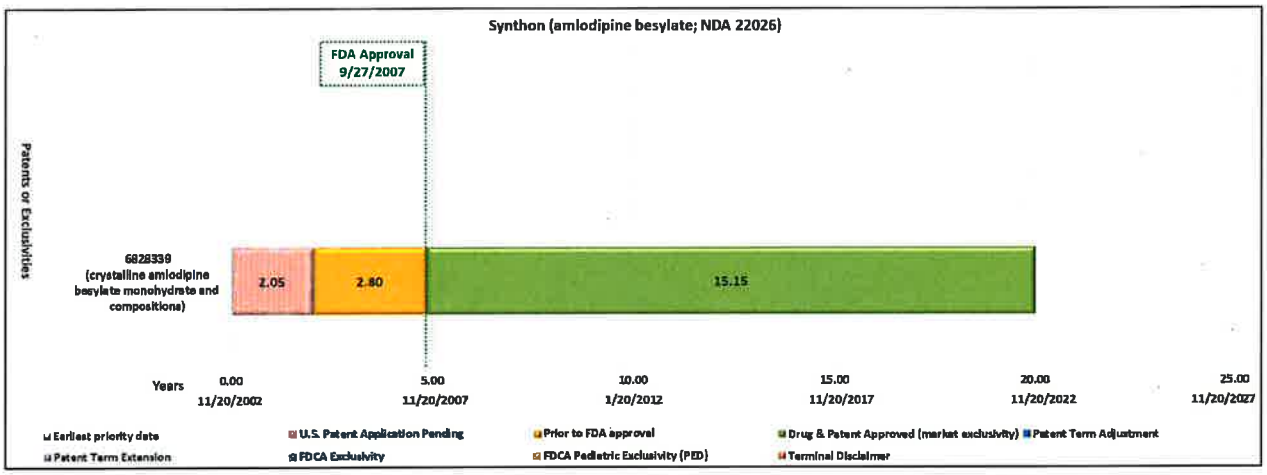


Figure 7. Bar chart of Amlodipine Besylate ODT (NDA 22026) (2.5, 5.0, 10.0 mg) (Orange Book entries 2005-2018)

3. apixaban (ELIQUIS)

ELIQUIS (NDA 202155) relates to drug products containing the active ingredient apixaban in a tablet composition. Apixaban is in the drug class Factor Xa inhibitors (a type of anticoagulant) and is used to lower the risk of stroke and to prevent deep vein thrombosis (DVT). Factor Xa inhibitors work by blocking the activity of clotting factor Xa. ELIQUIS is used to treat nonvalvular atrial fibrillation and blood clots. The study includes ELIQUIS because it was one of the twelve top grossing drugs of 2017.

As shown in the bar chart of Figure 8 below, ELIQUIS was approved on December 28, 2012. No apixaban generic is available. Two ELIQUIS patents were challenged and found infringed and not invalid in district court.[59]

As shown in Figure 8 below and Table 4 of Appendix 4, the USPTO identified three patents listed in the Orange Book between 2005 and 2018 for the first ELIQUIS product (2.5 mg). The USPTO also identified exclusivities, including one, five-year NCE exclusivity for the apixaban compound, and four, three-year new clinical indication ("NCI") exclusivities.

The first expiring patent covers a family of drug compounds, including apixaban generally. The second expiring patent also covers a variety of drug compounds and covers apixaban specifically. The third expiring patent covers specific pharmaceutical formulations containing crystalline apixaban particles with improved drug exposure.

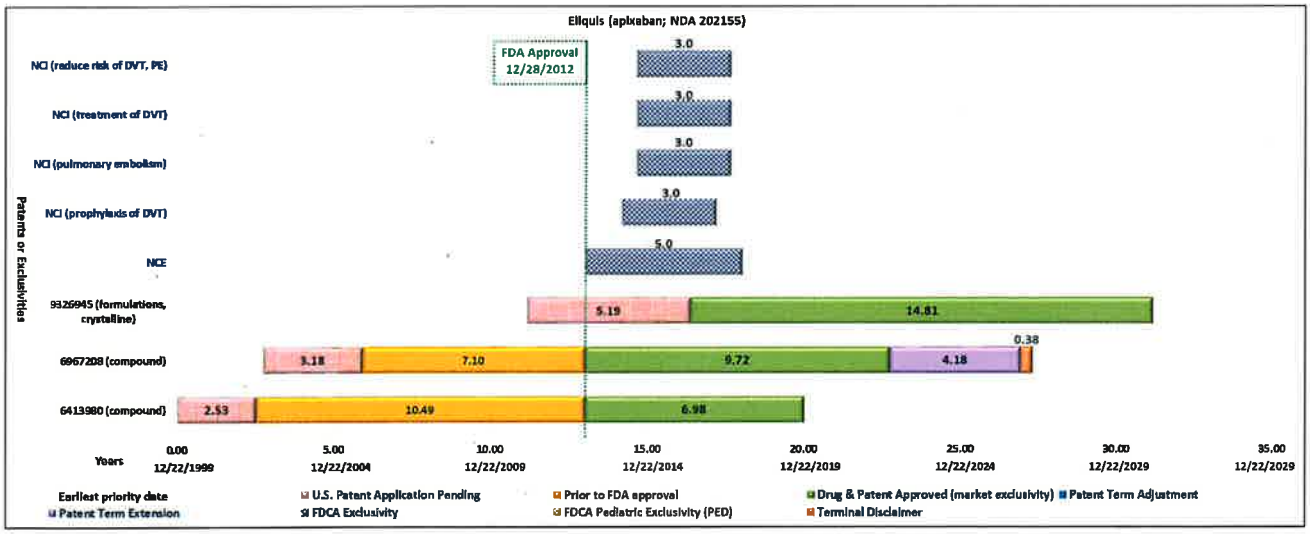


Figure 8. Bar chart of ELIQUIS (NDA 202155) (2.5 mg) (Orange Book entries 2005-2018)

[59] See *Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.*, 477 F. Supp. 3d 306 (D. Del. 2020), aff'd sub nom. *Bristol-Myers Squibb Co. v. Sigmapharm Lab'ys, LLC*, 858 F. App'x 359 (Fed. Cir. 2021).

4. aspirin (VAZALORE)

Aspirin is in the non-steroidal anti-inflammatory drugs (NSAIDs) drug class. Aspirin or acetylsalicylic acid was first produced in a laboratory in 1853 and is widely used today.[60] Aspirin works by reducing substances in the body that cause pain, fever and inflammation, and is used to treat pain and reduce fever or inflammation.[61] Other well-known and widely available NSAIDs include ibuprofen (e.g., MOTRIN) and naproxen (e.g., ALEVE).

As shown in the bar chart of Figure 9 below, the FDA approved the NDA for VAZALORE on January 14, 2013. To date, no generics of VAZALORE are available.

VAZALORE is a non-prescription drug that contains aspirin in combination with other inactive ingredients in a specific formulation designed to minimize release of the active ingredient within the stomach, thereby reducing the risk of stomach ulcers in patients who show such sensitivity when taking aspirin. The study includes VAZALORE (NDA 203697) because it is an example of the continued innovation that occurs on previously approved and well-known drugs (e.g., aspirin). The study is limited to the first approved strength in this NDA of 325 mg.

As shown in the bar chart of Figure 9 below and Table 5 of Appendix 4, the USPTO identified five patents for VAZALORE listed in the Orange Book between 2005 and 2018. The USPTO did not identify any exclusivities.

The Orange Book listing (2005–2018) for this product includes five patents that fall into two families. The first set of patents, expiring on December 19, 2021, cover pharmaceutical formulations containing aspirin combined with specific amounts of monocarboxylic acid and phospholipids as well as methods of administering the formulation to patients. The second set, expiring on September 29, 2032, covers formulations containing aspirin in sunflower oil with soy lecithin components, methods of manufacturing the formulations, and methods of treating patients by administering the formulations.

Although no generics of VAZALORE are available, the active ingredient (aspirin) continued to be widely available over the counter throughout the duration of the relevant patents.

---

[60] The Prescription Drug Product list contained in the Orange Book lists many products containing aspirin. In addition, a search of the FDA label search page (https://labels.fda.gov) yields over 2000 entries for products containing aspirin.

[61] *Aspirin Uses, Dosage, Side Effects & Interactions* - Drugs.com.

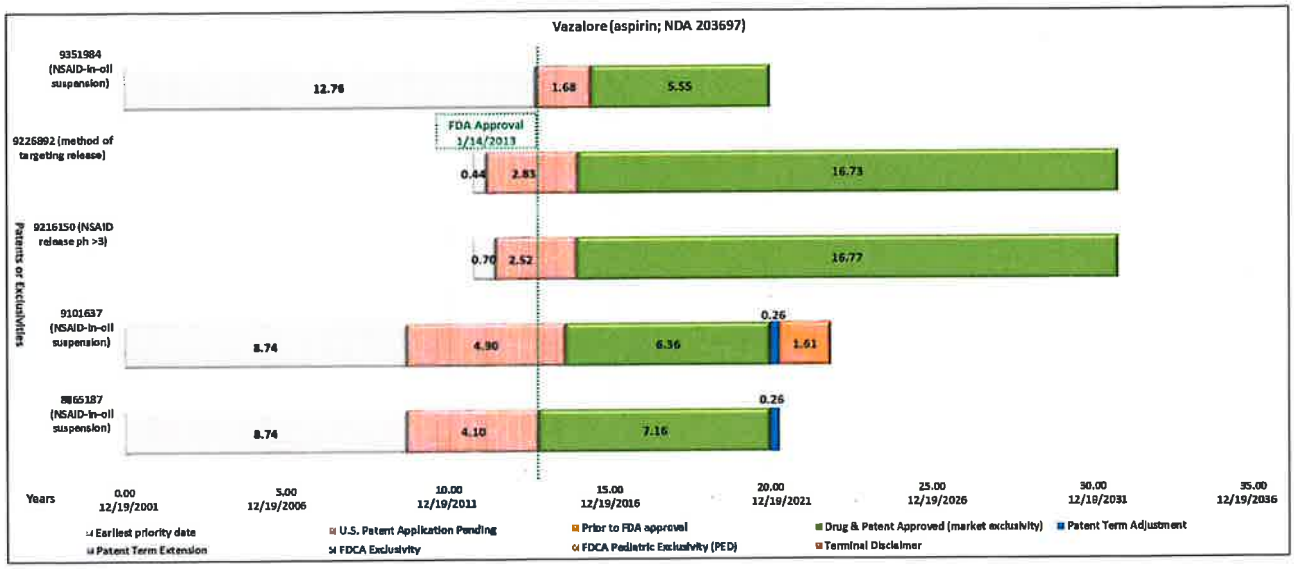


Figure 9. Bar chart of VAZALORE (NDA 203697) (325 mg) (Orange Book entries 2005-2018)

5. atorvastatin calcium (LIPITOR)

LIPITOR (NDA 020702) relates to drug products available in multiple strengths containing the active ingredient atorvastatin calcium in a tablet formulation. Atorvastatin calcium is in the statin class of drugs that block an enzyme that helps make cholesterol in the body. LIPITOR lowers cholesterol in the blood. The study includes LIPITOR because it was the most prescribed medication in 2017. It is considered one of the biggest blockbuster drugs of all time.[62]

As shown in the bar chart of Figure 10 below, LIPITOR was approved on December 17, 1996. The first atorvastatin generic (ANDA 76477) (for the 10 mg, 20 mg, and 40 mg products) was launched on November 30, 2011. The first generic was launched after the patent owner and the first-challenger generic entered into a settlement agreement of a Hatch-Waxman litigation. Thus, the NDA applicant enjoyed less than 15 years of market exclusivity (the period from the date of FDA approval until the generic launched).

As shown in Figure 10 below and in Table 6 of Appendix 4, the USPTO identified five patents listed in the Orange Book during the 2005 to 2018 time period for the 10 mg, 20 mg, and 40 mg products.[63] The exclusivities include three-year NCI exclusivities: new indications of use; labelling additions for prevention of heart disease (M-36); and dosing for patients requiring a large reduction in LDL-C (D-77) and children with heterozygous familial hypercholesterolemia ("HEFH") (M-204).

As shown in Figure 10 below, three of the listed patents cover various aspects of the drug compound. The first expiring compound patent covers the broad family of compounds, including atorvastatin; the second expiring compound patent covers the specific drug compound of atorvastatin in a salt form; and the last expiring compound patent covers specific crystalline forms of atorvastatin. The remaining two listed patents cover formulations including ingredients for stabilizing atorvastatin. All of the patents include pediatric exclusivities.

The first atorvastatin generic (ANDA 76477) was launched on November 30, 2011, after expiration of the atorvastatin salt patent (June 28, 2011), but prior to expiration of the

---

[62] Personal Finance (January 2, 2018), which is available online at: https://www.kiplinger.com/article/investing/t052-c000-s001-biggest-blockbuster-drugs-of-all-time.html.

[63] U.S. Patent Nos. 4,681,893; RE40667; and 5,686,104 were each filed prior to June 8, 1995, and were subject to a patent term of 17 years from the date of issuance.

formulation patents (i.e., May 11, 2015, including pediatric exclusivity) and the crystalline atorvastatin patent (July 8, 2016, including pediatric exclusivity).[64]

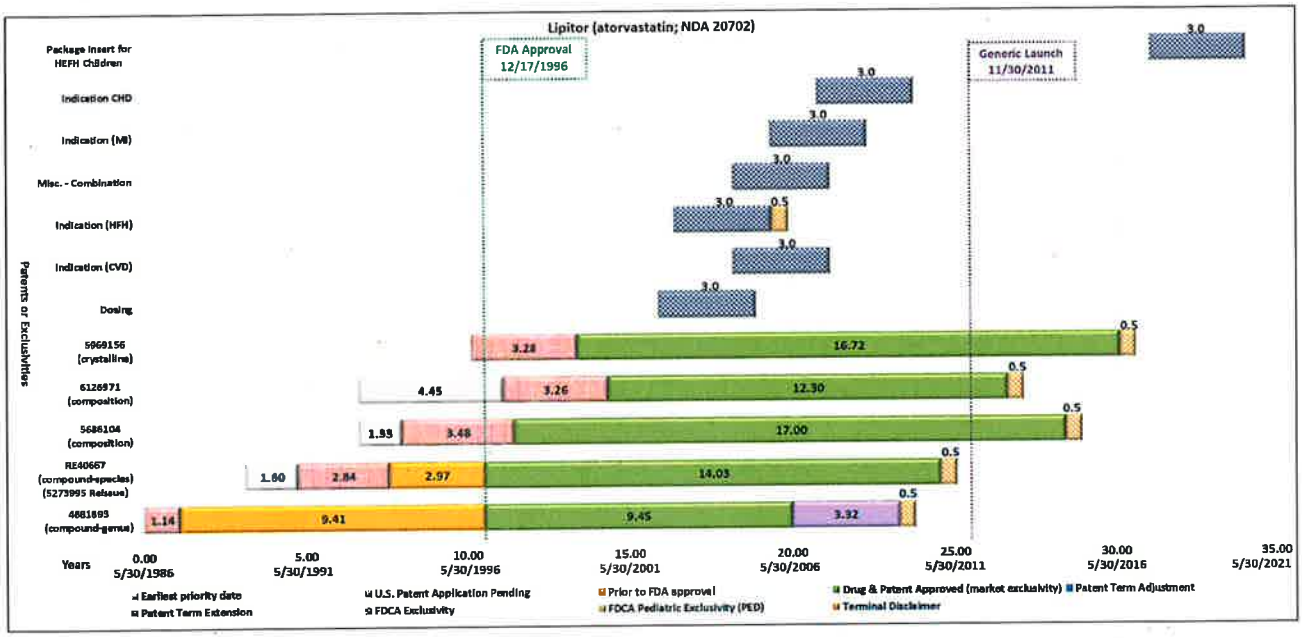


Figure 10. Bar chart of LIPITOR (NDA 20702) (10 mg, 20 mg, 40 mg) (Orange Book entries 2005-2018)

[64] U.S. Patent Nos. 6,087,511 and 6,274,740, which are not listed in the FDA Orange Book, were asserted during patent litigation related to a generic atorvastatin product. These patents are directed to methods of making amorphous atorvastatin calcium.

6. bictegravir sodium; emtricitabine; tenofovir alafenamide fumarate (BIKTARVY)

BIKTARVY is a combination drug treatment for HIV infection (including for pre-exposure prophylaxis) with three different active ingredients combined in one dosage form, a tablet available in two strengths. These types of multi-drug "cocktails" are now common in HIV treatment, and often combine a novel active ingredient, i.e., bictegravir, with older drugs, e.g., emtricitabine and tenofovir, each drug utilizing a different mechanism for treating HIV. The study includes BIKTARVY because I-MAK highlighted BIKTARVY in a report issued in 2022.

As shown in the bar chart of Figure 11 below, BIKTARVY was approved on February 7, 2018. At this time, no generic version of BIKTARVY is available.

BIKTARVY (NDA 210251) relates to an Orange Book-listed product containing the active ingredients bictegravir sodium, emtricitabine and tenofovir alafenamide fumarate in strengths of 30 mg/120 mg/15 mg and 50 mg/200 mg/25 mg, respectively. As shown in Figure 11 below and in Table 7 of Appendix 4, the USPTO identified nine patents and one exclusivity listed in the Orange Book during the 2005 to 2018 time period for the 50 mg/200 mg/25 mg product.[65] The exclusivity is a five-year NCE exclusivity for the new chemical entity bictegravir.

The nine patents shown in Figure 11 below are directed to the various components of this combination therapy. The earliest expiring patents relate to emtricitabine, the next expiring patents relate to tenofovir; and the last three expiring patents relate to the new compound, bictegravir (U.S. Patent Nos. 9,216,996 and 9,732,092, expiring December 19, 2033), and the approved drug product bictegravir sodium (U.S. Patent No. 9,708,342, expiring June 19, 2035).

[65] U.S. Patent Nos. 6,642,245 and 6,703,396 were each filed prior to June 8, 1995, and were subject to a patent term of 17 years from the date of issuance.

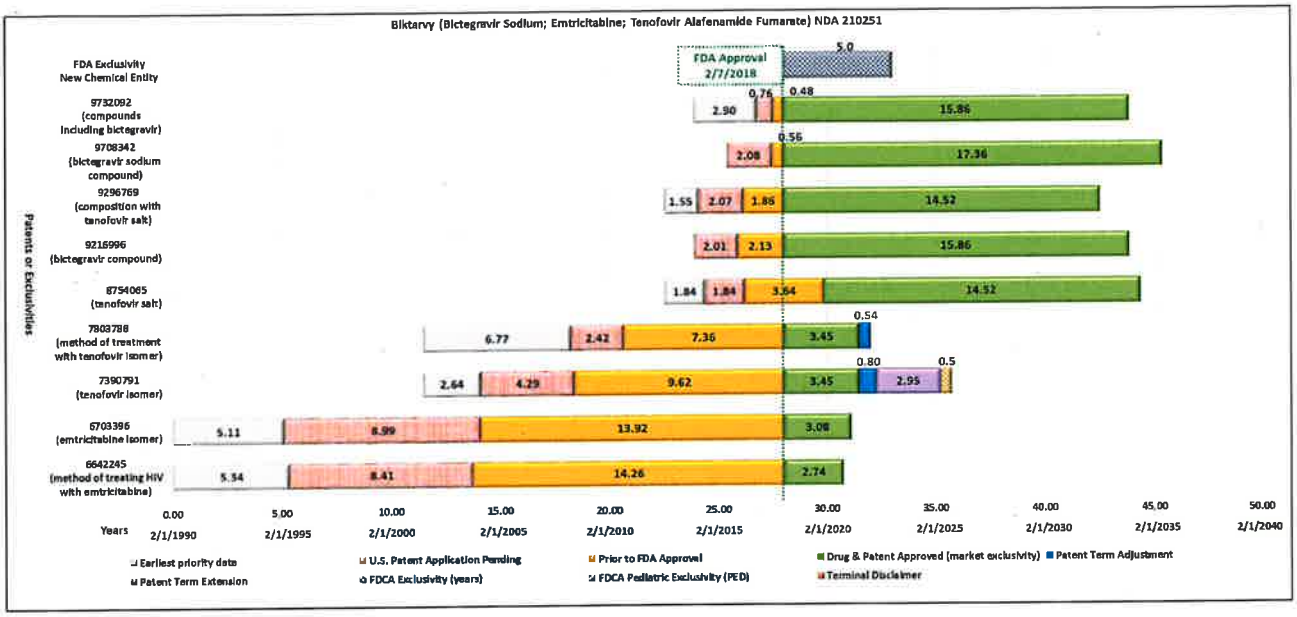


Figure 11. Bar chart of BIKTARVY (NDA 210251) (50 mg/200 mg/25 mg) (Orange Book entries 2005-2018)

7. ibrutinib (IMBRUVICA capsule and tablet)

IMBRUVICA relates to Orange Book-listed drug products containing the active ingredient ibrutinib: 1) IMBRUVICA capsule (NDA 205552) (140 mg (approved November 13, 2013) and 70 mg (supplemental approval August 2, 2017)) and 2) IMBRUVICA tablet (NDA 210563) (140 mg, 280 mg, 420 mg, and 560 mg).[66] IMBRUVICA is used to treat leukemia, lymphoma, and graft versus host disease. The study includes the IMBRUVICA products because I-MAK highlighted IMBRUVICA in a report ("Imbruvica's Patent Wall").

a) IMBRUVICA capsule

IMBRUVICA 140 mg capsule (NDA 205552): As shown in Figure 12 below and in Table 8 of Appendix 4, the USPTO identified 27 patents that were listed in the Orange Book between 2005 and 2018 for the 140 mg IMBRUVICA capsule, in addition to multiple exclusivities. The exclusivities include a five-year NCE exclusivity, three-year NCI exclusivities, and seven-year orphan-drug exclusivities (ODE). Drugs may be eligible for orphan-drug exclusivities if they are designated and approved for treating rare diseases and conditions.[67]

As shown in the bar chart of Figure 12 below, IMBRUVICA 140 mg capsule was approved on November 13, 2013. No generic ibrutinib products have been launched yet.[68]

The patents shown in Figure 12 below can be characterized as four families. Patents in each family have the same expiration dates due, in part, to terminal disclaimers. The first patent family, generally expiring on December 28, 2026, covers ibrutinib and other related compounds, and methods of treating different types of lymphomas. One of the compound patents received a patent term extension associated with the FDA approval process. The second patent family, generally expiring on June 3, 2031, covers different ibrutinib dose amounts for treating different lymphomas. The third patent family, generally expiring on June 3, 2033, covers different crystalline forms of ibrutinib and different formulations containing ibrutinib. The fourth patent family, generally expiring on October 24, 2034, covers methods of treating graft versus host disease.

Figure 12 below does not show pediatric exclusivities for the IMBRUVICA tablet product. This is because this study includes only patents and exclusivities listed in the Orange Book between January 2005 and December 2018. Additional information submitted to FDA, in March 2018 requesting to add pediatric exclusivities for IMBRUVICA (NDA 210563) tablet products wasn't reflected in the Orange Book until 2019.

---

[66] USPTO identified 29 total unique patents listed in the FDA Orange Book for the IMBRUVICA capsule and tablet products combined.

[67] See Appendix 3 for other exclusivities under the FD&C Act.

[68] See IMBRUVICA tablet for litigation information.

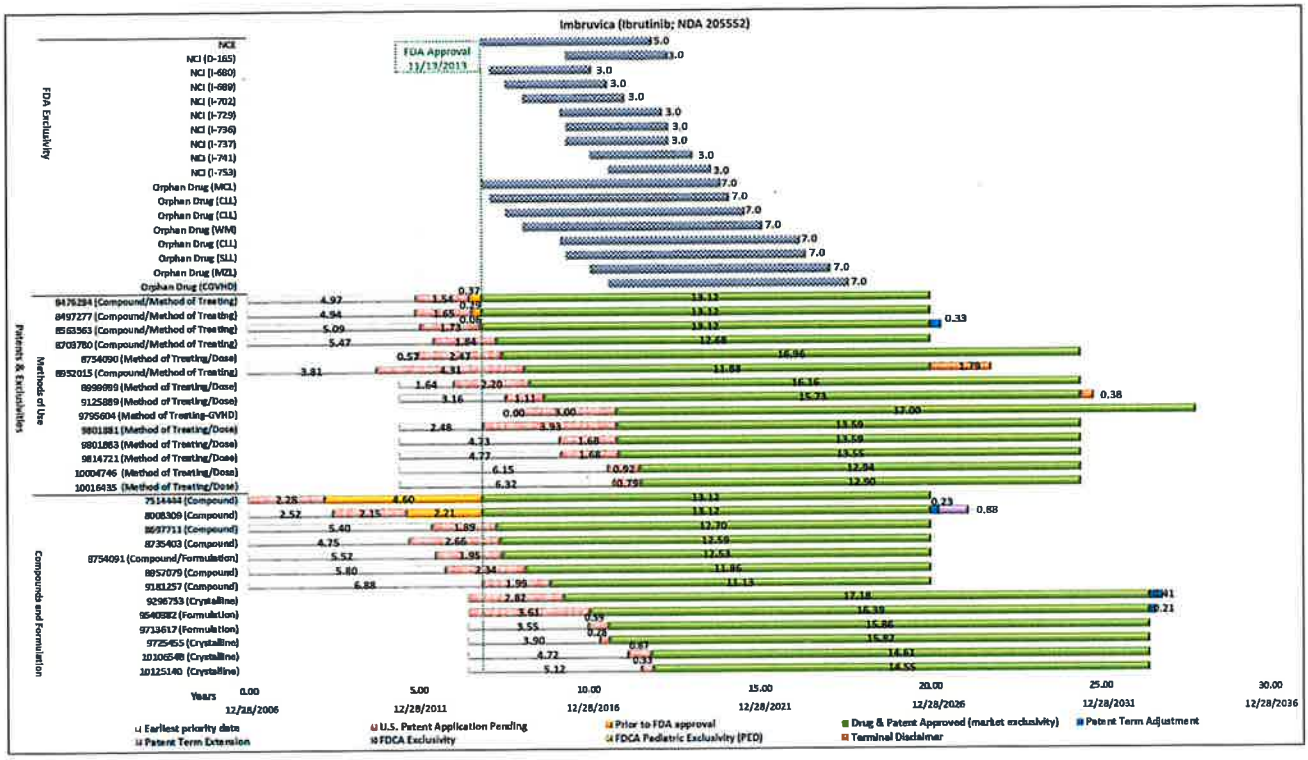


Figure 12. Bar chart of IMBRUVICA capsule (NDA 205552) (140 mg) (Orange Book entries 2005-2018)

b) IMBRUVICA tablet

IMBRUVICA tablet (ibrutinib) (NDA 210563) (140 mg, 280 mg, 420 mg, and 560 mg): As shown in Figure 13 below and in Table 9 of Appendix 4, the study identifies 27 patents and one exclusivity (NCE) associated with the four products listed in the Orange Book between 2005 and 2018.

As shown in the bar chart of Figure 13 below, the IMBRUVICA tablet was approved on February 16, 2018. The FDA tentatively approved a generic ibrutinib product in 2021 based on the generic applicant demonstrating it met the requirements for approval under the FD&C Act, but the applicant could not be fully approved because of the patent protection on the reference listed drug ("RLD"). The patent owner successfully enforced four of the listed IMBRUVICA patents, which a court determined were not invalid and were infringed by the generic ibrutinib product. The patent owner obtained a permanent injunction against generic launch prior to September 3, 2036 (U.S. Pat. No. 9,655,857, with PED exclusivity). As of the date of this report, no generic ibrutinib products have been launched.

The patents shown in the bar chart of Figure 13 below can be characterized into five different families of patents having the same expiration dates due, in part, to terminal disclaimers. The first patent family, generally expiring on December 28, 2026, covers ibrutinib and other related compounds, and methods of treating different types of lymphomas. One of the compound patents received a patent term extension associated with the FDA approval process. The second patent family, generally expiring on June 3, 2031, covers different ibrutinib dose amounts for treating different lymphomas. The third patent family, generally expiring on June 3, 2033, covers different crystalline forms of ibrutinib and different formulations containing ibrutinib. The fourth patent family, generally expiring on October 24, 2034, covers methods of treating graft versus host disease. The fifth patent family, generally expiring on March 3, 2036, covers different tablet formulations containing ibrutinib. The bar chart of Figure 13 also shows the five-year NCE exclusivity.

Figure 13 below does not show pediatric exclusivities for the IMBRUVICA tablet product. This is because this study includes only patents and exclusivities listed in the Orange Book between January 2005 and December 2018. Additional information submitted to FDA, in March 2018 requesting to add pediatric exclusivities for IMBRUVICA (NDA 210563) tablet products wasn't reflected in the Orange Book until 2019.

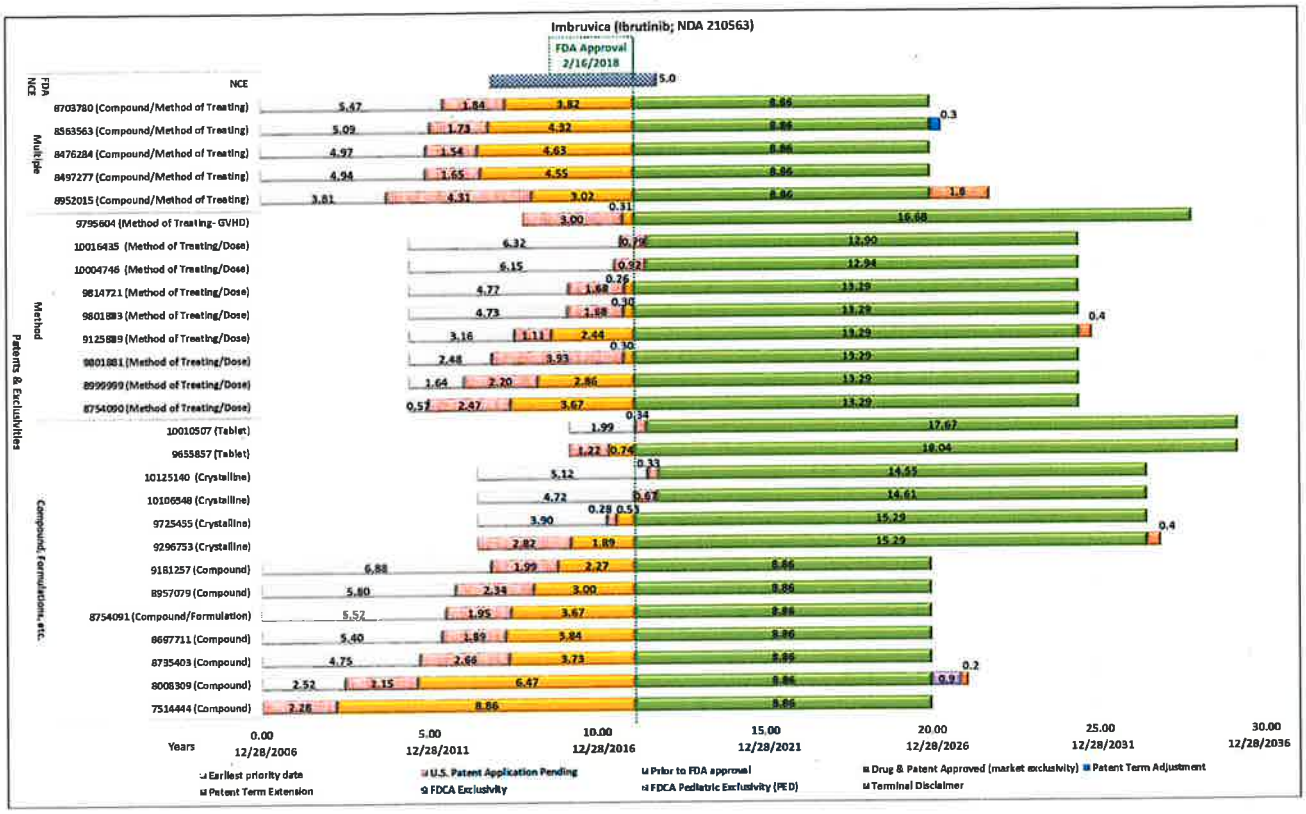


Figure 13. Bar chart of IMBRUVICA tablet (NDA 210563) (140 mg, 280 mg, 420 mg, 560 mg) (Orange Book entries 2005-2018)

8. lenalidomide (REVLIMID)

REVLIMID (NDA 021880) relates to products containing the active ingredient lenalidomide in capsule form. Lenalidomide is a thalidomide analog that may help the immune system kill abnormal blood cells or cancer cells. REVLIMID is used to treat multiple myeloma, lymphoma, and myelodysplastic syndromes. The study includes REVLIMID because it was one of the top grossing drugs of 2017.

As shown in the bar chart of Figure 14 below, REVLIMID was approved on December 27, 2005. The first generic was launched on March 3, 2022, after the expiration of patents listed in the Orange Book covering the drug compounds and compositions.[69] Due to settlement of multiple litigations, the generic launch came before the expiration of the method of treatment patents and the crystalline compound patents. Thus, the NDA applicant enjoyed a period of 16 years of market exclusivity (from the date of FDA approval until the generic launch).

As shown in Figure 14 below and in Table 10 in Appendix 4, USPTO identified 27 patents listed in the FDA Orange Book for the 5 mg and 10 mg (first-approved) REVLIMID products. The exclusivities included NCE, ODE, and NCI exclusivities. Although a single NDA is associated with REVLIMID, there are multiple strengths of the drug covered by the NDA that were approved on various dates. The FDA first approved the NDA for the 5 mg and 10 mg capsule for treatment of patients with transfusion dependent anemia due to myelodysplastic syndromes on December 27, 2005. This date and the corresponding five-year NCE exclusivity are shown on the bar chart of Figure 14.

Figure 14 shows that the earliest expiring patents relate to the drug compound and methods for reducing tumor necrosis factor α (TNFα) associated with inflammation. Later-filed patents relate to compositions containing the compound and they expired at the same time as the earliest-expiring patents due to terminal disclaimers. The two latest-expiring compound patents relate to a specific crystalline form of the active ingredient. There are several method of treatment patents relating to treating various conditions including: myelodysplastic syndrome (and associated anemia), multiple myeloma, mantle cell lymphomas, and non-Hodgkin's lymphoma, among other conditions. Finally, USPTO identified a group of patents that appear to relate to methods for delivering the drug under a Risk Evaluation and Mitigation Strategy ("REMS"). A REMS is a drug safety program that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.[70]

---

[69] U.S. Patent Nos. 7,977,357; 8,193,219; and 8,431,598, which are not listed in the FDA Orange Book, were asserted during patent litigation related to a generic lenalidomide product. These patents are directed to unsolvated crystalline lenalidomide.

[70] https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems.

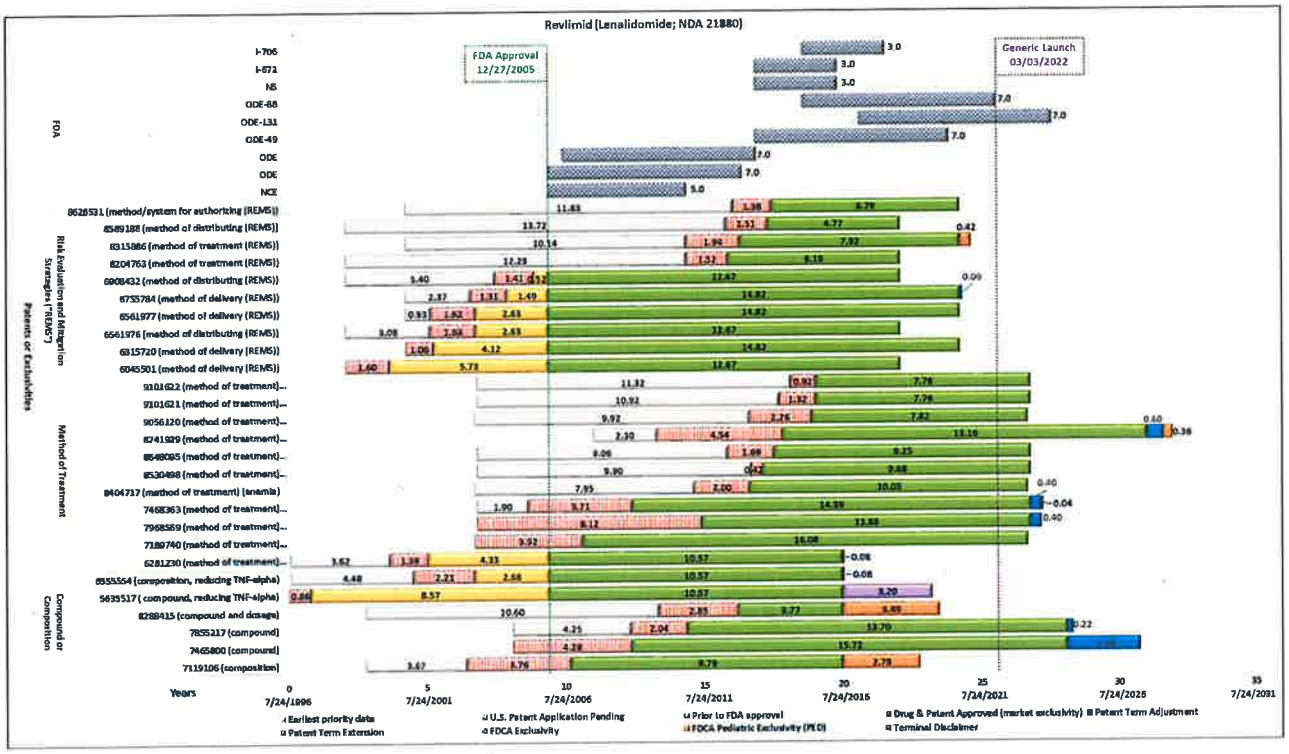


Figure 14. Bar chart of REVLIMID (NDA 21880) (5 mg, 10 mg) (Orange Book entries 2005-2018)

9. lopinavir; ritonavir (KALETRA CAPSULE, SOLUTION AND TABLET)

KALETRA relates to combination products containing the active ingredients lopinavir and ritonavir. The products listed in the Orange Book between 2005-2018 included: 1) KALETRA capsule (NDA 21226) (133.3 mg/33.3 mg), 2) KALETRA solution (NDA 21251) (80 mg/mL/20 mg/mL), and 3) KALETRA tablet (NDA 21906) (200 mg/50 mg and 100 mg/25 mg).[71] KALETRA is used with other antiretroviral medicines to treat HIV-1 infections. The study includes KALETRA because the products have been a focus of I-MAK's attention.[72]

a) KALETRA capsule

KALETRA capsule (NDA 21226) (133.3 mg/33.3 mg):

As shown in the bar chart of Figure 15 below, KALETRA capsule was approved on September 15, 2000. To date, there is no generic version of KALETRA capsule, which has been discontinued. But generics are available for the oral solution and tablet as described below.

As shown in Figure 15 below and in Table 11 of Appendix 4, the USPTO identified 16 patents and one three-year NCI exclusivity listed in the Orange Book between 2005 and 2018.[73]

KALETRA is a multi-drug treatment for HIV infection including two different drugs, lopinavir and ritonavir, combined in one dosage form. Lopinavir is a protease inhibitor ("PI") that prevents HIV from reproducing. Ritonavir was originally used as a direct inhibitor of HIV. Scientists later discovered that ritonavir boosts other HIV-PIs, by preventing the body from metabolizing PIs. Ritonavir-boosting of PIs decreased pill burden and frequency of dosing.[74] Accordingly, ritonavir is now commonly combined with PIs, such as lopinavir. The patent data illustrates this combination, as the earliest expiring patents relate to ritonavir and lopinavir as separate compounds, but later patents are directed to specific compositions and methods combining the two drugs as a fixed combination. As shown the Figure 15, of the 16 patents, five patents cover a formulation or compound, four cover specific formulations, five cover a method of treatment, one covers a flavoring system and one covers both methods and formulations.

---

[71] USPTO identified 28 total unique patents listed in the FDA Orange Book for the KALETRA Capsule, Solution, and Tablet products combined.

[72] See, e.g., I-MAK's Tahir Amin on Washington Business Tonight Discussing the Case Against Abbott's Drug KALETRA – I-MAK, which is posted on their website at https://www.i-mak.org/2010/03/04/i-maks-tahir-amin-on-washington-business-tonight-discussing-the-case-against-abbotts-drug-kaletra/.

[73] U.S. Patent Nos. 5,541,206; 5,635,523; 5,648,497; and 5,674,882 were each filed prior to June 8, 1995, and were subject to a patent term of 17 years from the date of issuance.

[74] M. Hull and J. S. G. Montaner, "Ritonavir-boosted protease inhibitors in HIV therapy," 43(5) Annals of Medicine 375-388 (2011).

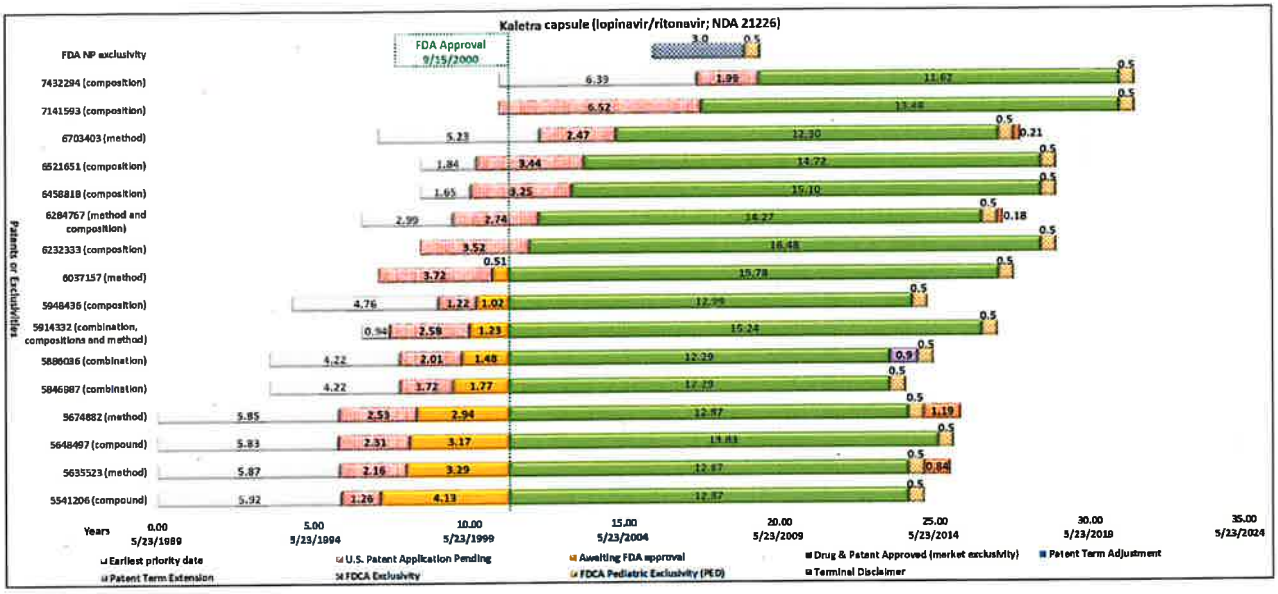


Figure 15. Bar chart of KALETRA capsule (NDA 21226)(133 mg/33.3 mg) (Orange Book entries 2005-2018)

b) KALETRA solution

KALETRA solution (NDA 21251) (80 mg/mL/20 mg/mL):

As shown in the bar chart of Figure 16 below, KALETRA solution was approved on September 15, 2000. A generic version of KALETRA solution was launched on January 23, 2017, prior to the expiration of the latest two-expiring patents which covered a formulation and flavoring system. The USPTO did not identify any litigation associated with these patents. Thus, the NDA applicant enjoyed 16 years of market exclusivity (from the date of FDA approval to the date of generic launch).

As shown in Figure 16 below and in Table 12 of Appendix 4, the USPTO identified 14 patents and two exclusivities listed in the Orange Book between 2005 and 2018. The exclusivities include a three-year NCI exclusivity for a new dosing regimen for therapy naïve adult patients (D-99) and a three-year NCI exclusivity for a once daily dosing regimen in adult patients with less than three lopinavir resistance-associated substitutions (D-124). The 14 patents included eight patents covering formulations or compounds, six patents covering methods of treatment, and a patent on a flavoring system.[75] At least one of the patents covers both formulations and methods of treatment.

[75] U.S. Patent Nos. 5,484,801; 5,541,206; 5,635,523; 5,648,497; and 5,674,882 were each filed prior to June 8, 1995, and were subject to a patent term of 17 years from the date of issuance.

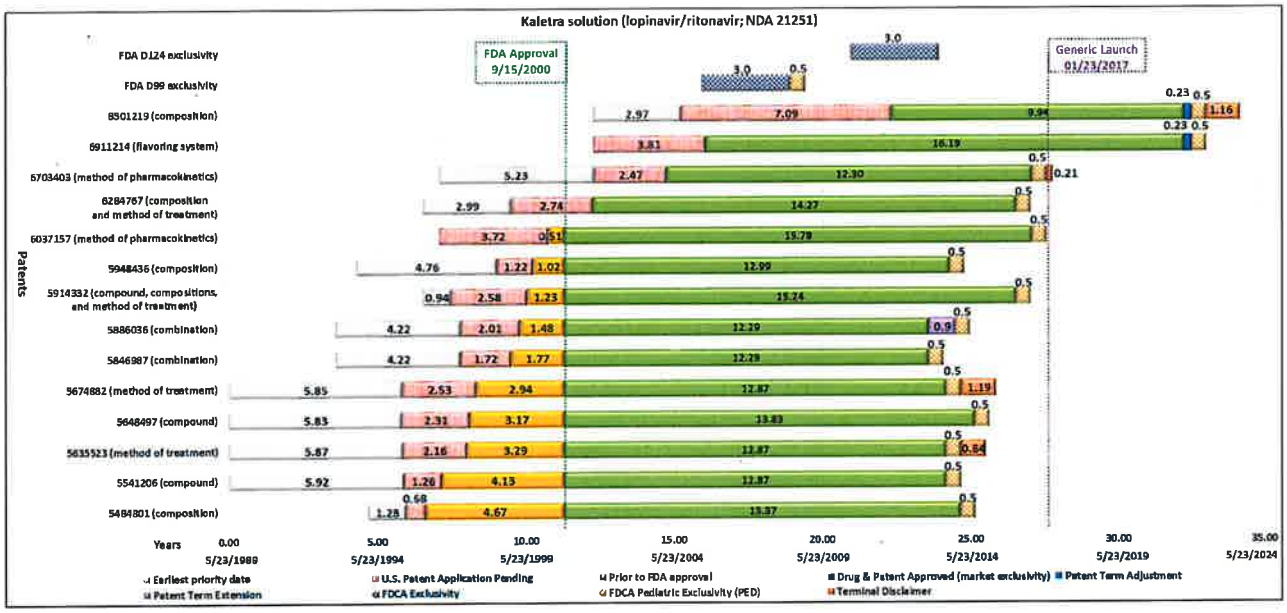


Figure 16. Bar chart of KALETRA solution (NDA 21251) (80 mg/mL/20 mg/mL) (Orange Book entries 2005-2018)

c) KALETRA tablet

KALETRA tablet (NDA 21906) (200 mg/50 mg and 100 mg/25 mg):

As shown in the bar chart of Figure 17 below, KALETRA tablet was approved on October 28, 2005. A generic version of KALETRA tablet was launched on June 7, 2021, prior to expiration of the latest expiring patents in April 2029. Thus, the NDA applicant enjoyed 16 years of market exclusivity (from the date of FDA approval until the date of generic launch).

As shown in Figure 17 below and in Table 13 of Appendix 4, the USPTO identified 19 patents and one three-year NCI exclusivity for a new dosing regimen (D-124) listed in the Orange Book between 2005 and 2018. As shown in Figure 17 below, of the 19 patents, at least three patents claimed a pharmaceutical composition, one of which was granted patent term extension under 35 U.S.C. § 156 (U.S. Patent No. 5,886,036), six patents claimed a specific dosage form or formulation, and nine patents claimed a method of treatment.[76] One listed patent covers a transgenic mouse. In 2015, one patent that had been previously listed in the Orange Book was reexamined by the USPTO and all claims were canceled. Because the patent was listed in the Orange Book during the period covered by this report, it is included in the bar chart even though it would have been subsequently removed from the Orange Book.

[76] U.S. Patent Nos. 5,541,206; 5,648,497; and 5,648,597 were each filed prior to June 8, 1995, and were subject to a patent term of 17 years from the date of issuance.

As of March 23, 2020, the KALETRA brand owner, AbbVie, announced it would no longer enforce patent rights related to KALETRA due to the COVID-19 pandemic.[77] They also statutorily disclaimed most of the patents.

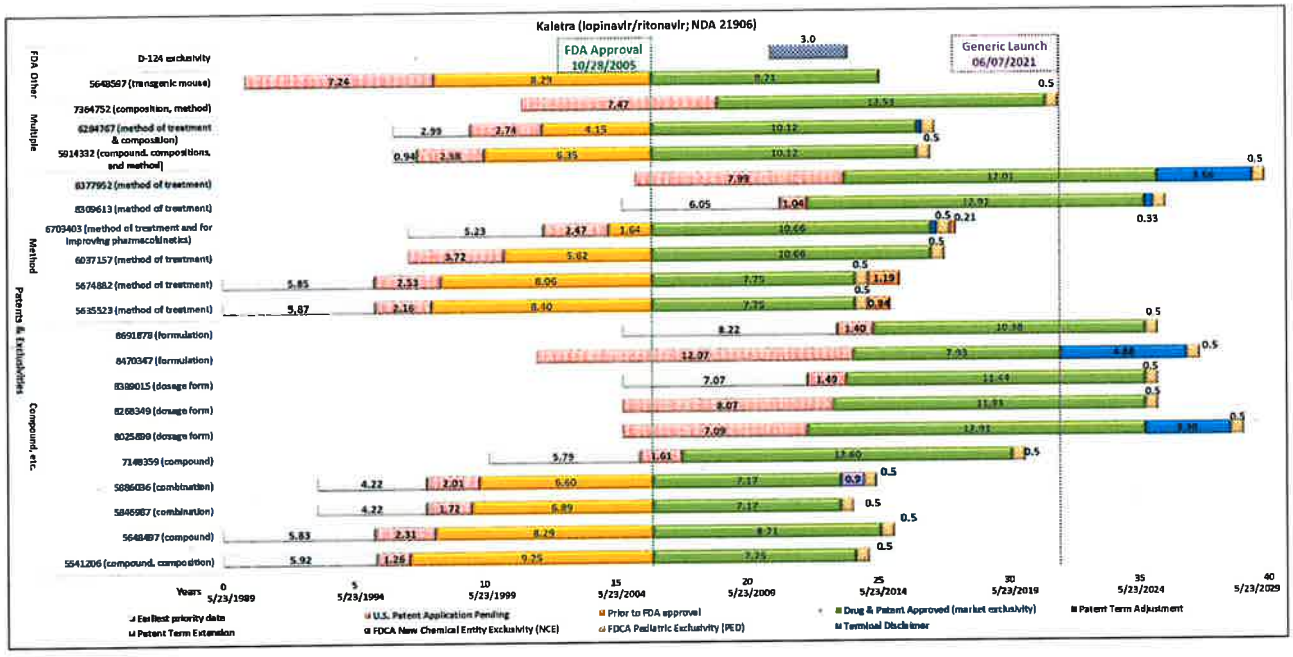


Figure 17. Bar chart of KALETRA tablet (NDA 21906) (200 mg/50 mg and 100 mg/25 mg) (Orange Book entries 2005-2018)

10. pramipexole dihydrochloride (MIRAPEX and MIRAPEX ER)

MIRAPEX relates to two NDAs containing the active ingredient pramipexole dihydrochloride. MIRAPEX (NDA 20667) relates to a tablet formulation with drug products approved in seven strengths (0.125 mg, 0.25 mg, 0.5 mg 0.75 mg, 1 mg, 1.25 mg, and 1.5 mg). MIRAPEX ER (NDA 22421) relates to an extended-release tablet with drug products approved in seven strengths (0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, and 4.5 mg), which were listed in the Orange Book between 2005 and 2018.[78] Pramipexole is used to treat symptoms of Parkinson's disease and restless leg syndrome (RLS), and is in the drug class dopaminergic anti-parkinsonism agents. Other drugs in this class are ropinirole, rotigotine, selegiline, and carbidopa. Pramipexole (MIRAPEX) is included in the study because it was widely prescribed during the period studied.

---

[77] See *AbbVie drops patent rights for Kaletra antiviral treatment*, Financial Times (March 23, 2020), which is available at https://www.ft.com/content/5a7a9658-6d1f-11ea-89df-41bea055720b.

[78] USPTO identified 6 total unique patents listed in the FDA Orange Book for the MIRAPEX and MIRAPEX ER products combined.

a) *MIRAPEX (NDA 20667)*

As shown in the bar chart of Figure 18 below, MIRAPEX NDA 20667 products (0.125 mg, 0.25 mg, 1 mg, 1.25 mg, and 1.5 mg) were first approved July 1, 1997. The 0.5 mg product was approved February 12, 1998, and the 0.75 mg product was approved July 30, 2007. The first generic pramipexole dihydrochloride products (0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and 1.5 mg) approved for treating Parkinson's disease were available on January 4, 2010.

The first generic pramipexole dihydrochloride products for treating Parkinson's disease were available on January 4, 2010, due to settlement of patent litigation. Thus, the NDA applicant enjoyed approximately 12.5 years of market exclusivity from the date of FDA approval to the date of generic launch. Additional generic pramipexole dihydrochloride products, also approved for treating Parkinson's disease, were launched on October 18, 2010 (shown in Figure 21 below), after expiration of U.S. Patent Nos. 4,843,086 and 4,886,812 and before expiration of the two patents covering the treatment of restless legs syndrome. USPTO did not identify any litigation associated with the patents covering the treatment of restless leg syndrome.

For five of the first-approved drug products (0.125 mg, 0.25 mg, 1 mg, 1.25 mg, and 1.5 mg), the USPTO identified four patents as well as two exclusivities as shown in Figure 18 below and in Table 14 of Appendix 4. As shown in Figure 18 below, the exclusivities included two, three-year exclusivities (I-517, M-104). The first-expiring patents relate to the drug compound and its method of use for treating Parkinson's disease, among other conditions.[79] The later-expiring patents relate to methods for treating restless leg syndrome by administering pramipexole.

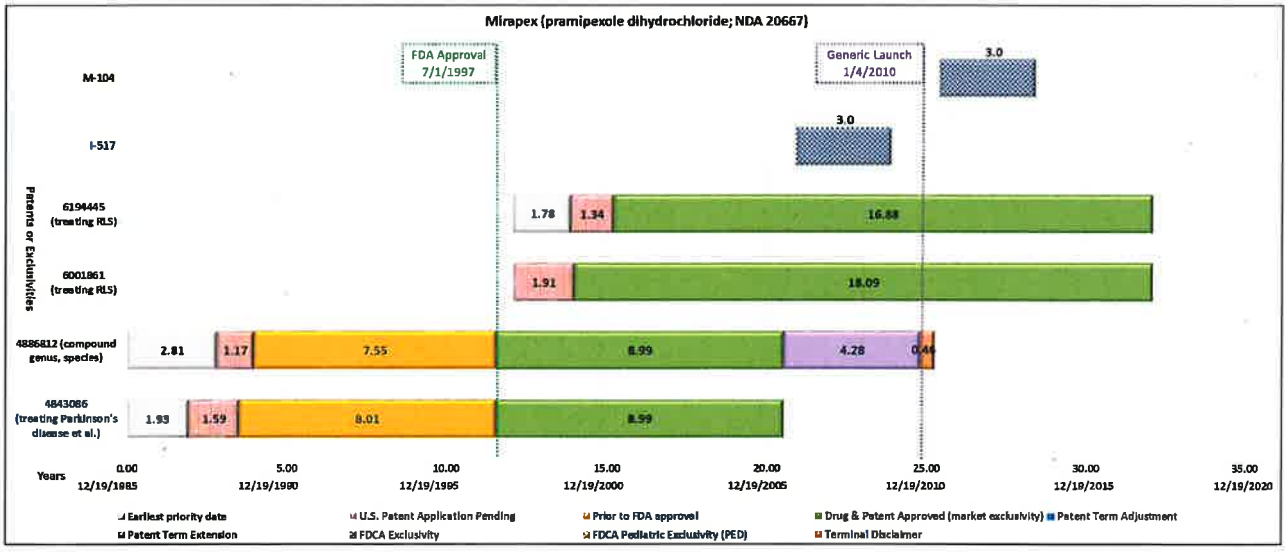


Figure 18. Bar chart of MIRAPEX (NDA 20667) (0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 1.5 mg) (Orange Book entries 2005-2018)

[79] U.S. Patent Nos. 4,843,086 and 4,886,812 were each filed prior to June 8, 1995, and were subject to a patent term of 17 years from the date of issuance.

b) MIRAPEX ER extended-release tablet (NDA 22421)

MIRAPEX ER (NDA 22421) is an extended-release tablet formulation of pramipexole dihydrochloride. The NDA includes drug products in seven strengths (0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, and 4.5 mg). Five products (0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg) were approved on February 19, 2010. The 2.25 mg and 3.75 mg products were approved on June 17, 2011.

As shown in the bar chart of Figure 19 below, MIRAPEX ER was approved on February 19, 2010. The first generic extended-release product (2.25 mg) was launched on November 20, 2015, after the exclusivities expired, but prior to the 2028 and 2029 expiration dates of the later expiring, extended-release formulation patents (listed for all strengths). Thus, the NDA applicant enjoyed approximately 5.5 years of market exclusivity from the date of FDA approval to the date of generic launch. The USPTO did not identify any litigation associated with the extended-release formulation patents.

As shown in Figure 19 below and in Table 15 of Appendix 4, the USPTO identified three patents and two NCI exclusivities for the first-approved MIRAPEX ER extended-release tablet products (0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg) during 2005 to 2018. The first expiring patent relates to the drug compound.[80] The later expiring patents relate to specific extended-release (sustained-release) formulations, and manufacturing methods for making the extended-release formulations.

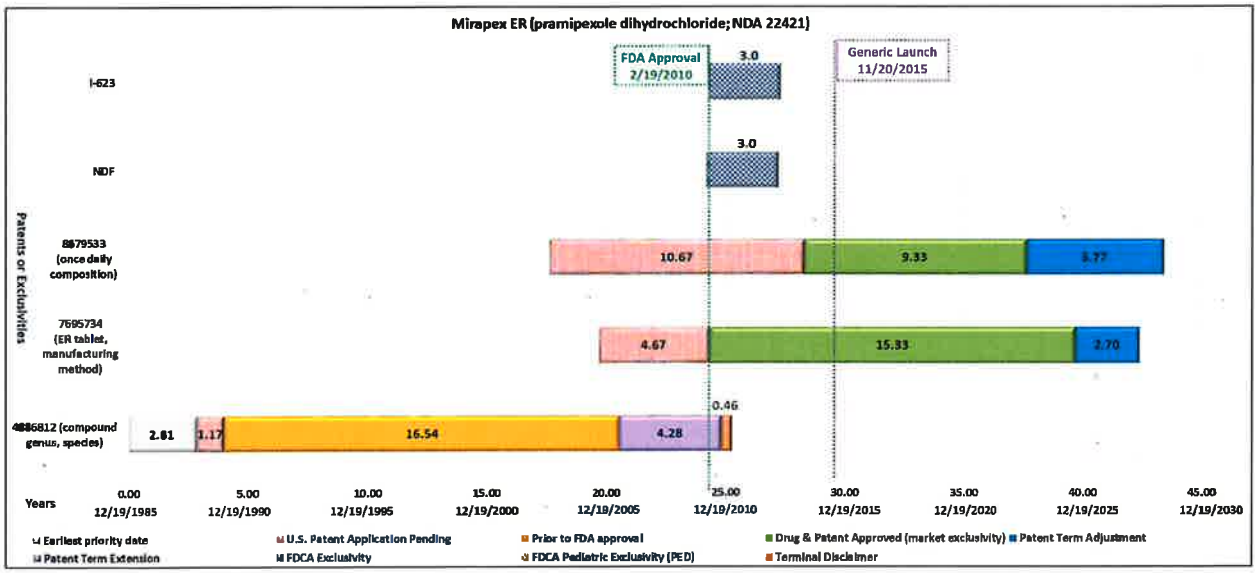


Figure 19. Bar chart of MIRAPEX ER (NDA 22421) (0.375 mg, 0.75 mg, 1.5 mg, 3 mg, 4.5 mg) (Orange Book entries 2005-2018)

[80] U.S. Patent No. 4,886,812 was filed prior to June 8, 1995, and was subject to a patent term of 17 years from the date of issuance.

11. pregabalin (LYRICA and LYRICA CR)

LYRICA relates to three NDAs containing the active ingredient pregabalin which were listed in the Orange Book between 2005 and 2018: 1) LYRICA capsule (NDA 021446), which includes eight drug products available in eight strengths (see below); 2) LYRICA solution (NDA 022488), which includes one drug product (20 mg/mL); and 3) LYRICA CR extended-release tablet (NDA 209501), which includes three drug products available in three strengths (82.5mg, 165 mg, and 330 mg).[81]

Pregabalin is an anti-epileptic drug in the drug class gamma-aminobutyric acid analogs. It may also be used to treat pain, such as that caused by fibromyalgia. The study includes LYRICA because it was one of the top grossing drugs of 2017.

a) LYRICA capsule

LYRICA capsule (NDA 21446):

As shown in the bar chart of Figure 20 below, the FDA first approved the NDA on December 30, 2004, with drug products in four strengths, 25 mg, 50 mg, 75 mg, and 100 mg. Additional strengths of 150 mg, 200 mg, 225 mg and 300 mg were approved in 2006. The patent and exclusivity information listed in the Orange Book was the same for each product during the 2005 to 2018 period. Generics (ANDA 091025 for all strengths approved) were launched on July 23, 2019, shortly after the expiration of the latest-expiring patent covering the pregabalin compound on June 30, 2019 (including patent term extension and a pediatric exclusivity). Thus, the NDA applicant enjoyed a little less than 15 years of market exclusivity for all strengths during the period from FDA approval to the date of generic launch.

As shown in Figure 20 below and in Table 16 of Appendix 4, the USPTO identified three patents and five exclusivities listed in the FDA Orange Book between 2005 and 2018. The exclusivities include one five-year NCE exclusivity and several three-year NCI exclusivities, including for clinical investigations to support two new indications, a new patient population, and an update to the label for treating adolescents with fibromyalgia (M-196). As shown in Figure 20 below, one patent covers the drug compound, one patent covers treating seizures, and one patent covers treating pain.[82] U.S. Patent No. RE 41,920 is a reissue of U.S. Patent No. 6,001,826. Both documents were listed in the FDA Orange Book between 2005 and 2018. The USPTO counted U.S. Patent No. 6,001,826 and U.S. Patent No. RE 41,920 as a single patent, because a patent owner must surrender the original patent prior to the USPTO issuing a

---

[81] USPTO identified 6 total unique patents listed in the FDA Orange Book for the LYRICA Capsule, LYRICA Solution, and LYRICA CR products combined.

[82] U.S. Patent Nos. 5,563,175 and 6,197,819 were each filed prior to June 8, 1995, and were subject to a patent term of 17 years from the date of issuance.

reissue patent and, thus, a reissue replaces the original patent and does not prolong the duration of the original patent grant.

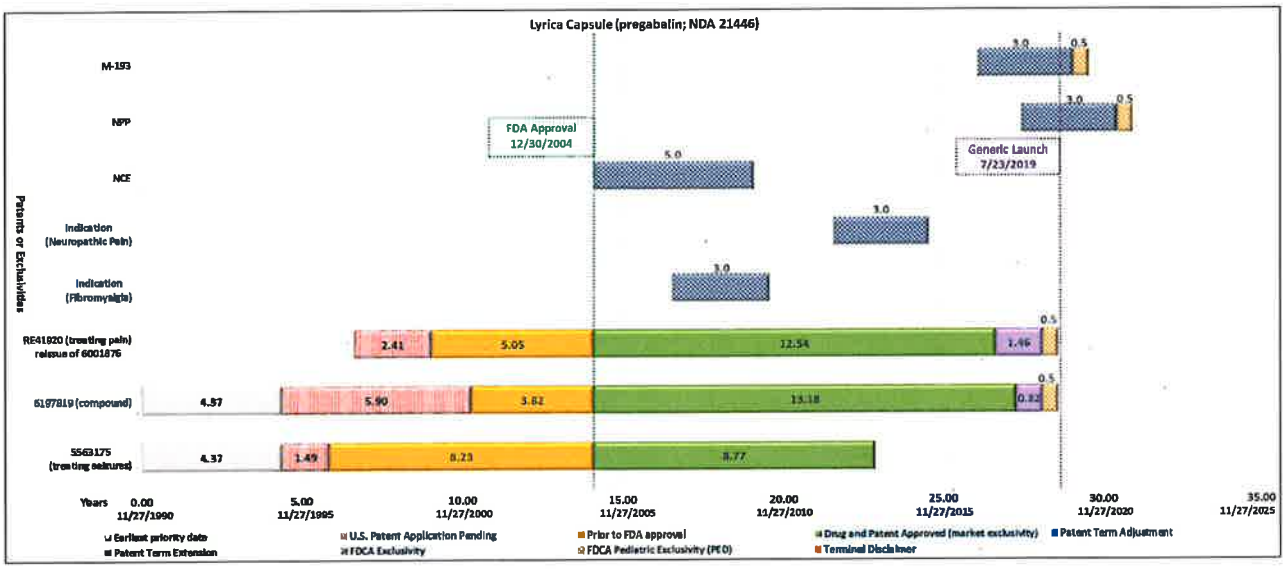


Figure 20. Bar chart of LYRICA capsule (NDA 21446) (25 mg, 50 mg, 75 mg, 100 mg) (Orange Book entries 2005-2018)

b) LYRICA solution

LYRICA solution (NDA 22488) (20 mg/mL):

As shown in the bar chart of Figure 21 below, LYRICA solution was approved on January 4, 2010. Generics were launched on July 23, 2019, shortly after the expiration of the latest-expiring patent covering the pregabalin compound. Thus, the NDA applicant enjoyed a little more than nine years of market exclusivity for the drug product available in a solution during the period from FDA approval to the date of generic launch.

As shown in Figure 21 below and Table 17 of Appendix 4, the USPTO identified three patents and five exclusivities listed in the Orange Book between 2005 and 2018. The exclusivities included one five-year NCE exclusivity, and several three-year NCI exclusivities, including two new indications, a new patient population, and an update to the label for treating adolescents with fibromyalgia (M-196). As shown in Figure 21 below, one patent covers the drug compound, one patent covers treating seizures, and one patent covers treating pain.[83]

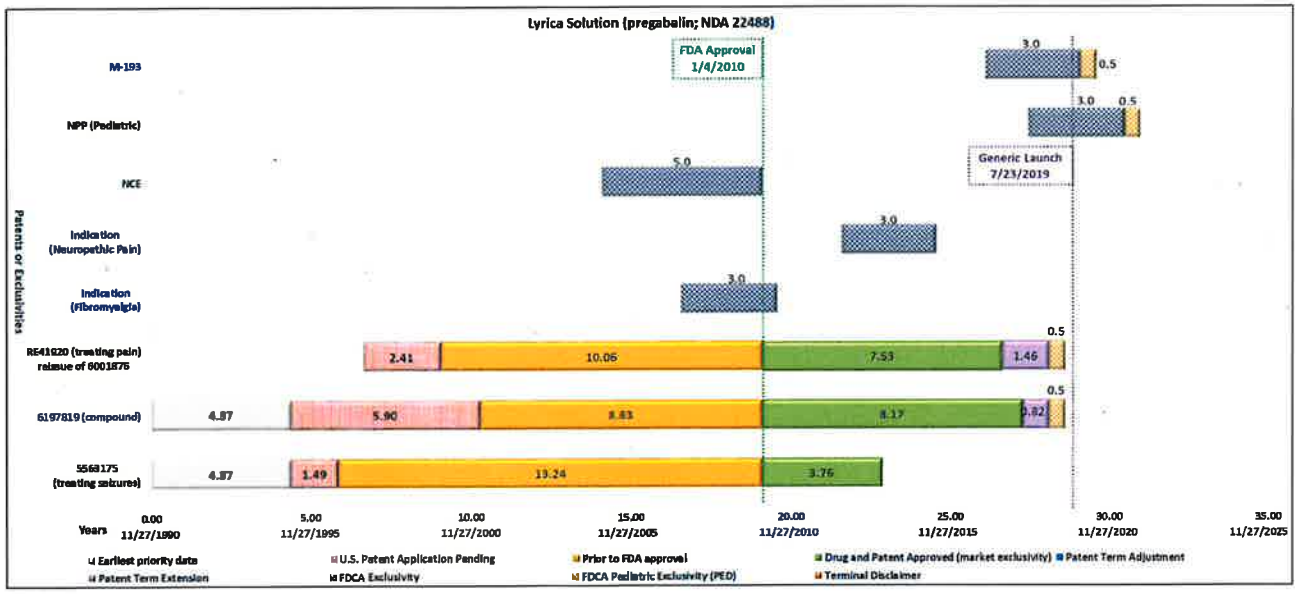


Figure 21. Bar chart of LYRICA solution (NDA 22488) (20 mg/mL) (Orange Book entries 2005-2018)

[83] U.S. Patent Nos. 5,563,175 and 6,197,819 were each filed prior to June 8, 1995, and subject to a patent term of 17 years from the date of issuance

c) *LYRICA CR extended-release tablet*

LYRICA CR extended-release tablet (NDA 209501):

As shown in the bar chart of Figure 22 below, the NDA for LYRICA CR was approved for all strengths (82.5 mg, 165 mg, and 330 mg) on October 11, 2017. Generic products for all strengths were launched on April 13, 2021, after expiration of exclusivity (including pediatric exclusivity) for the extended-release tablet but before the patents listed in the Orange Book for the controlled release formulation expired. The generic competitor obtained a judgment of non-infringement for its competing controlled release product.[84] Thus, the NDA applicant enjoyed a little more than three years of market exclusivity for its extended-release product during the period from FDA approval to generic launch.

As shown in Figure 22 below and in Table 18 of Appendix 4, the USPTO identified five patents and one exclusivity listed in the Orange Book between 2005 and 2018. The first two expiring patents cover the compound and treating pain, and three later-expiring patents cover controlled release formulations of the tablet. The controlled release formulation patents all expire on May 2, 2027 (including pediatric exclusivity).

The exclusivity includes a three-year NCI exclusivity for the new dosage form (extended-release tablet).

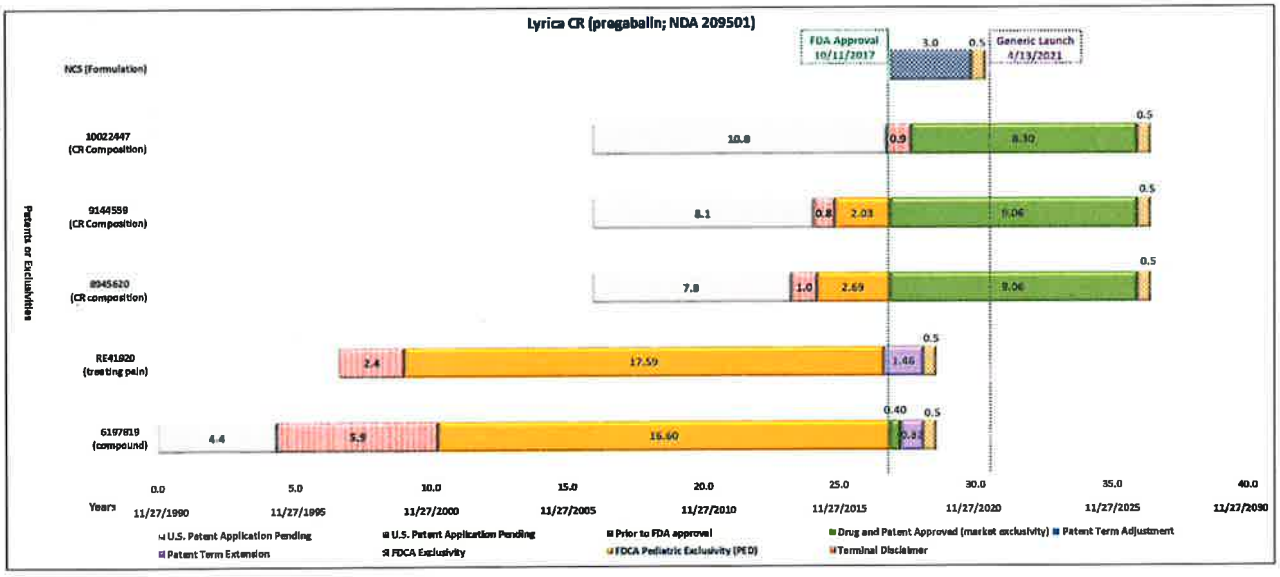


Figure 22. Bar chart of LYRICA CR (NDA 209501) (82.5 mg, 165 mg, 330 mg) (Orange Book entries 2005-2018)

[84] *Sun Pharm. Indus. Ltd. v. Pfizer Inc.*, No. 19-cv-09335-KM-SCM (D.N.J. August 13, 2020) ("the Court finds that Sun does not, through Sun's ANDA or Sun's ANDA Product, infringe any claim of the '620, '559, or '447 patents directly, indirectly, literally, or pursuant to the doctrine of equivalents.")

12. rivaroxaban (XARELTO tablets)

XARELTO relates to two NDAs containing the active ingredient rivaroxaban, which were included in the Orange Book between 2005 and 2018: 1) XARELTO tablet (NDA 22406) and 2) XARELTO tablet (NDA 202439). NDA 202439 was later consolidated with NDA 22406. Both NDAs were listed in the 2012 Orange Book, but only NDA 22406 has been listed in the Orange Book since 2013. This is an example that shows the Orange Book is not a static document as both product and patent listings are updated over time.

XARELTO contains the active ingredient rivaroxaban. Rivaroxaban is a Factor Xa inhibitor and is used to treat or prevent blood clots, including deep vein thrombosis, and to lower the risk of strokes caused by blood clots. Other Factor Xa inhibitors include apixaban (ELIQUIS, discussed above) and fondaparinux. The study includes XARELTO because it was listed in the 2017 I-MAK report.

a) XARELTO immediate release tablet

As shown in the bar chart of Figure 23 below, XARELTO immediate release tablet (NDA 22406) corresponds to four drug products: 10 mg tablet (approved July 1, 2011), 15 mg and 20 mg tablets (both approved November 4, 2011), and 2.5 mg tablet (approved October 11, 2018). During ANDA patent litigation, the compound patent (U.S. Patent No. 7,157,456) was found not invalid.[85] There are no generic versions of XARELTO immediate release tablet at this time.

As shown in Figure 23 below and Table 19 of Appendix 4, the USPTO identified five patents and two exclusivities listed in the FDA Orange Book in connection with the XARELTO tablet (10 mg) from 2005 to 2018. The patents relate to the compound, rapid release tablet formulations, and various methods of treatment. The formulation patents all expire on May 13, 2025 (including pediatric exclusivity), whereas the method patents are set to expire on August 18, 2034 (including patent term adjustment, and pediatric exclusivity). One method of treatment patent includes a patent term extension of 1,356 days, and another patent includes a patent term adjustment of 2,951 days.

The exclusivities include a five-year NCE exclusivity, and three, three-year NCI exclusivities (I-660, I-661, I-662).

---

[85] See *Bayer Intell. Prop. GmbH v. Aurobindo Pharma Ltd.*, No. CV 15-902, 2018 WL 3410020, at *1 (D. Del. July 13, 2018).

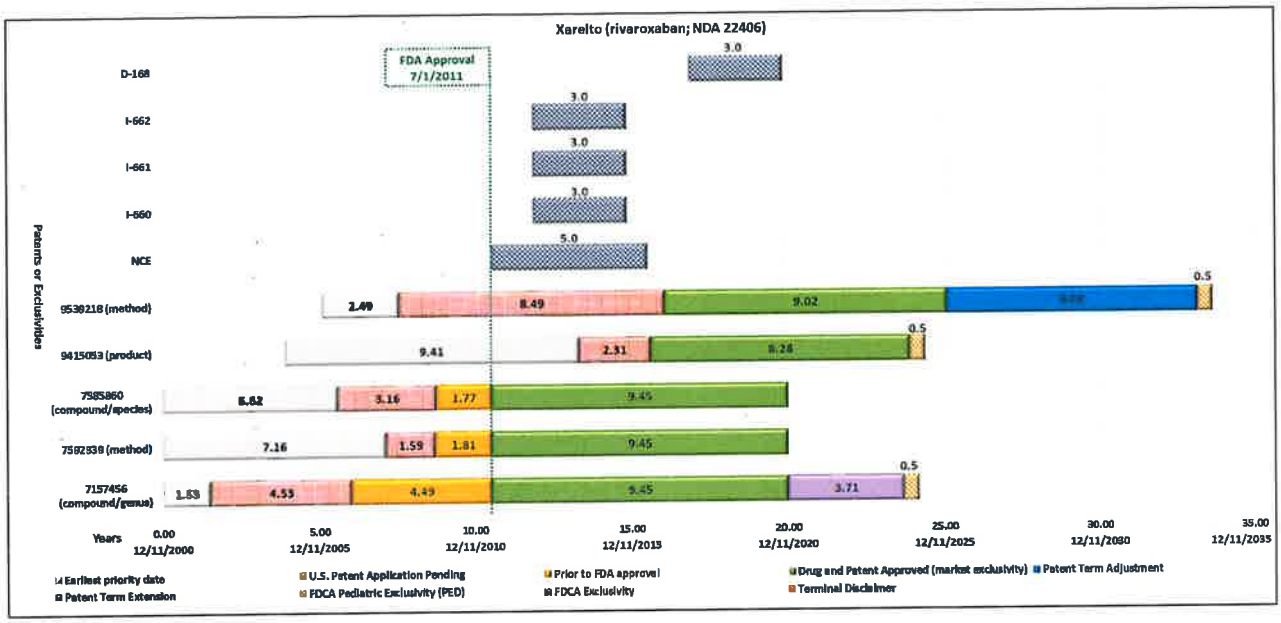


Figure 23. Bar chart of XARELTO (NDA 22406) (10 mg) (Orange Book entries 2005-2018)

b) XARELTO tablet

XARELTO tablet (NDA 202439, now NDA 22406) included two drug products, 15 mg and 20 mg.

As shown in the bar chart of Figure 24 below, XARELTO tablet was approved on November 4, 2011. No generics were approved for NDA 202439 before it was administratively consolidated with NDA 22406.

As shown in Figure 24 below and in Table 20 of Appendix 4, the USPTO identified three patents and two exclusivities associated with XARELTO tablet products (15 mg, 20 mg). One patent covers the drug compound genus, another the drug compound species and the third various methods of treatment. Although the three patents would have expired at the same time, one patent received a patent term extension of 1,356 days.

The exclusivities include an NCE exclusivity and an NCI exclusivity (I-643 (reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation)).

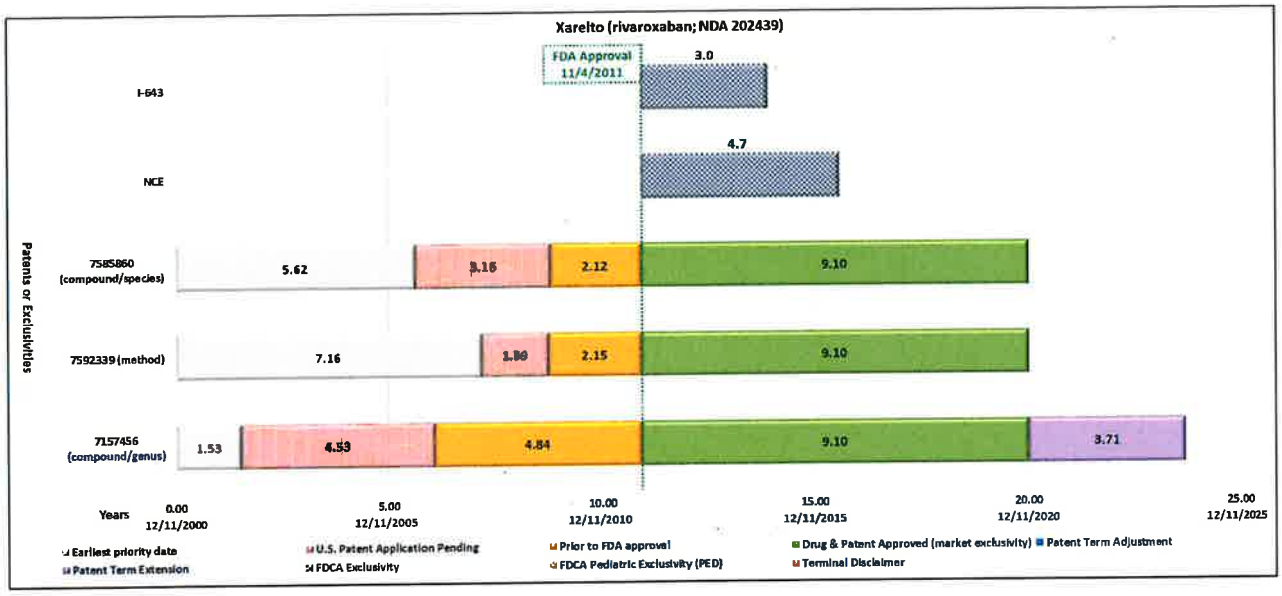


Figure 24. Bar chart of XARELTO (NDA 202439) (15 mg, 20 mg) (Orange Book entries 2005-2018)

13. zolpidem tartrate (AMBIEN (AMBIEN tablet and AMBIEN CR), INTERMEZZO, EDLUAR and ZOLPIMIST)

The UC Database lists five NDAs containing the active ingredient zolpidem tartrate: 1) AMBIEN (NDA 19908); 2) AMBIEN CR (NDA 21774); 3) INTERMEZZO (NDA 22328); 4) EDLUAR (NDA 21997); and 5) ZOLPIMIST (NDA 22196) which are addressed below. The report includes these five NDAs as an example of the types of innovation that may occur using the same active ingredient and illustrate the variety of products that may contain the same well-known active ingredient, yet not be determined to be therapeutically equivalent.

Zolpidem tartrate is a sedative used to treat insomnia in the drug classification: Miscellaneous anxiolytics, sedatives and hypnotics. Other active ingredients in this class include, among others, buspirone, doxylamine, diphenhydramine, chloral hydrate, doxepin, eszopiclone, and hydroxyzine. Other drug classes include drugs used to treat insomnia. These primarily include benzodiazepines and antihistamines.

AMBIEN, INTERMEZZO, EDLUAR, and ZOLPIMIST have immediate release forms to help people fall asleep. The extended-release form of AMBIEN CR has two layers, one that dissolves quickly to help you fall asleep, and another that dissolves slowly to help you stay asleep. INTERMEZZO is formulated to help you fall back asleep if you wake up in the middle of the night.

a) AMBIEN (tablet and CR)

AMBIEN relates to two Orange Book-listed NDAs containing the active ingredient zolpidem tartrate: 1) AMBIEN tablet (NDA 19908) and 2) AMBIEN CR extended-release tablet (NDA 21774).[86]

i. AMBIEN tablet

AMBIEN tablet (NDA 19908) (5 mg and 10 mg):

As shown in the bar chart of Figure 25 below, AMBIEN tablet was approved on December 16, 1992. Multiple generics for AMBIEN tablet (5 mg and 10 mg) were launched on April 27, 2007, after the Orange Book patent expired. Thus, the NDA applicant enjoyed less than 15 years of market exclusivity during the period between FDA approval and generic launch.

As shown in Figure 25 below and in Table 21 in Appendix 4, the USPTO identified one patent and one exclusivity for both strengths. The patent covers the drug compound and various methods of treatment.[87] The FDA approved the NDA for the drug compound on December 16, 1992, listing the 5 mg and 10 mg tablets.

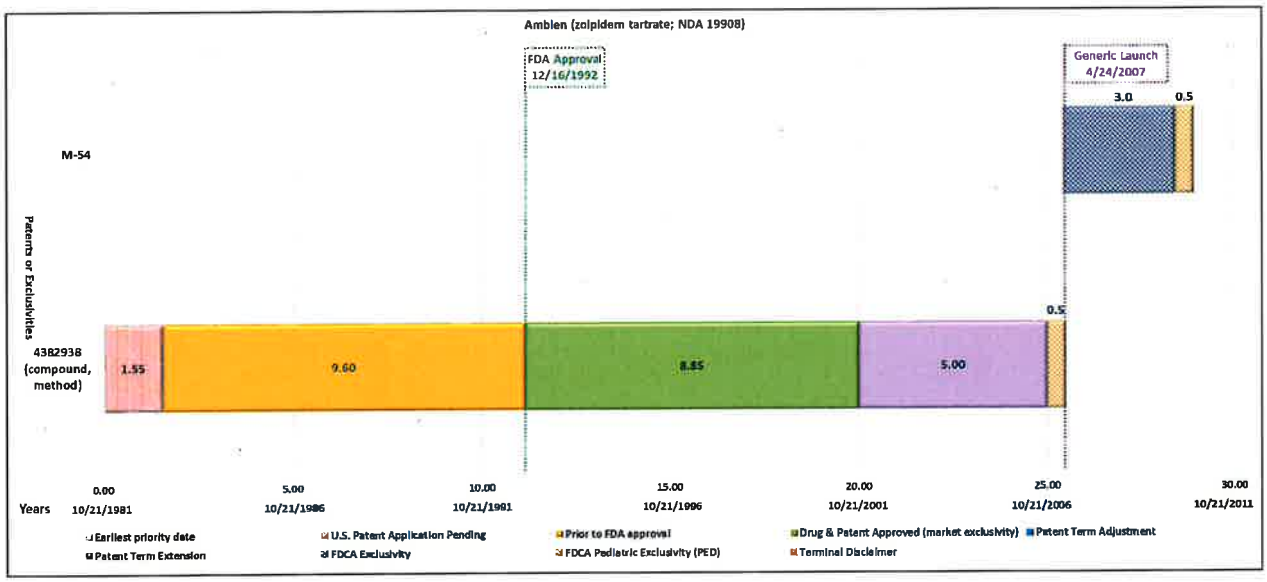


Figure 25. Bar chart of AMBIEN (NDA 19908) (Orange Book entries 2005-2018)

---

[86] USPTO identified two total unique patents listed in the FDA Orange Book for the AMBIEN and AMBIEN CR products combined.

[87] U.S. Patent No. 4,382,938 was filed prior to June 8, 1995, and subject to a patent term of 17 years from the date of issuance.

ii. AMBIEN CR extended-release tablet

AMBIEN CR (NDA 21774) (6.25 mg and 12.5 mg) extended-release tablet:

As shown in the bar chart of Figure 26 below, AMBIEN CR was approved on September 2, 2005. A generic to AMBIEN CR (6.25 mg) was launched on October 13, 2010, after expiration of the three-year NCI exclusivity, and six months of pediatric exclusivity.[88] Accordingly, a generic product was launched prior to expiration of U.S. Patent No. 6,514,531, covering controlled release formulations. Thus, the NDA applicant enjoyed about five years of market exclusivity during the period between FDA approval and generic launch for the 6.25 mg dosage form.

As shown in Figure 26 below and explained in Table 22 of Appendix 4, the USPTO identified two patents and one exclusivity, a three-year NCI (new dosage form). The patents include one patent covering the compound and methods of using the compound, and one patent covering controlled release formulations.[89]

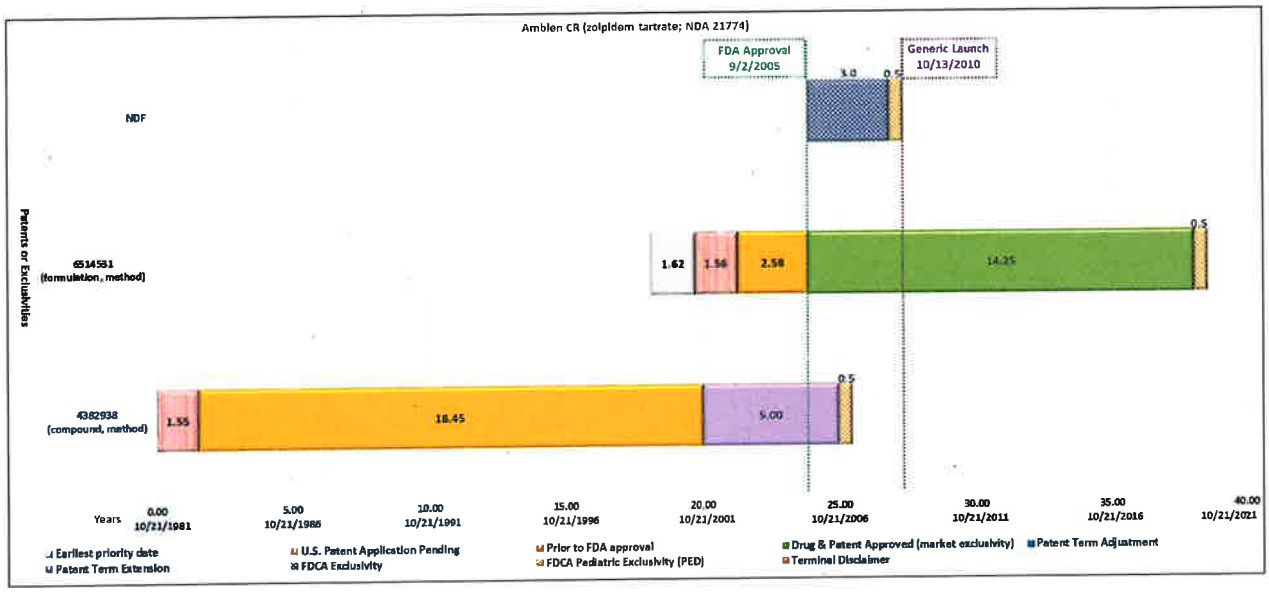


Figure 26. Bar chart of AMBIEN CR (NDA 21774) (6.25 mg) (Orange Book entries 2005-2018)

---

[88] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/078179s000ltr.pdf.

[89] U.S. Patent No. 4,382,938 was filed prior to June 8, 1995, and subject to a patent term of 17 years from the date of issuance.

b) EDLUAR

EDLUAR (NDA 21997) (5 mg and 10 mg) sublingual tablet:

As shown in the bar chart of Figure 27 below, EDLUAR (5 mg and 10 mg) was approved on March 13, 2009. There are no generics currently available.

As shown in Figure 27 below and in Table 23 of Appendix 4, the USPTO identified four patents that were listed in the Orange Book between 2005 and 2018. The USPTO confirmed that there were no exclusivities listed for EDLUAR (5 mg and 10 mg) during this period.

The patents include a product patent related to the sublingual tablet and three method patents, including one related to sublingually administering a sublingual tablet formulation, and two related to treating insomnia by administering a sublingual tablet containing zolpidem. The latest expiration date is February 25, 2031.

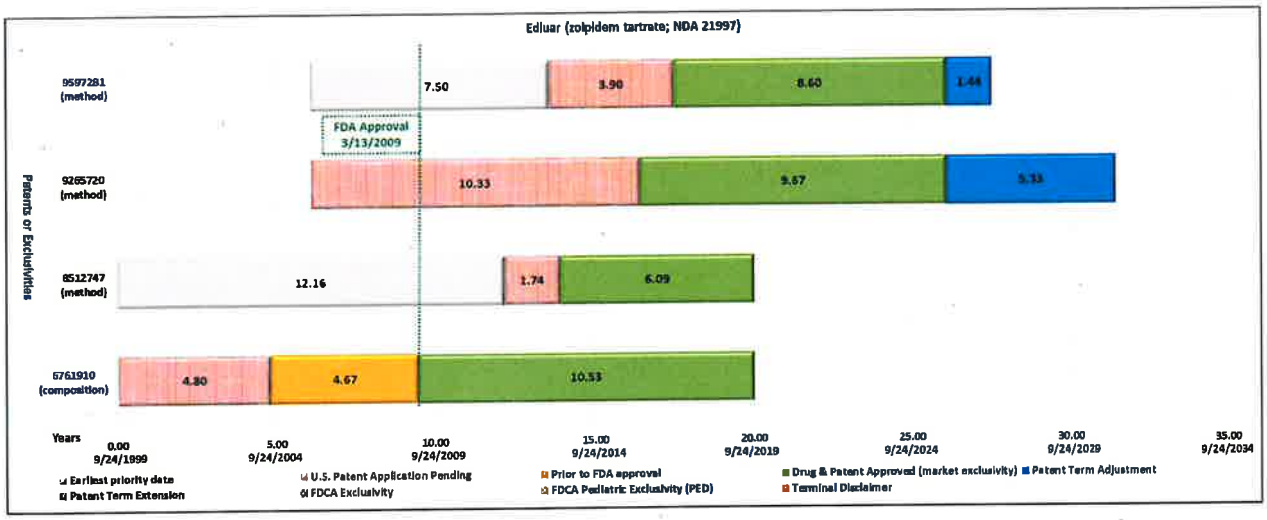


Figure 27. Bar chart of EDLUAR (NDA 22197) (Orange Book entries 2005-2018)

c) *INTERMEZZO*

INTERMEZZO (NDA 22328) (1.75 mg and 3.5 mg) sublingual tablet:

As shown in the bar chart of Figure 28 below, INTERMEZZO was approved on November 23, 2011. Generic versions of both strengths of INTERMEZZO were launched on March 23, 2016, after all of the Orange Book-listed patents were found noninfringed or invalid during litigation.[90] Thus, the NDA applicant enjoyed about four years of market exclusivity for INTERMEZZO during the period from FDA approval to generic launch.

As shown in Figure 28 below and in Table 24 of Appendix 4, the USPTO identified one, three-year NCI exclusivity (NP) and four patents for both strengths. The two earlier-filed patents relate to sublingual formulations containing zolpidem and a buffer and methods of administering the formulations. The two later-filed patents relate to formulations and methods for treating middle of the night (MOTN) insomnia.

The FDA approved the NDA for the sublingual tablet on November 23, 2011, with a recommended maximum dose of 1.75 mg for women and 3.5 mg for men. The term of the last patent was due to expire on March 26, 2029 (including Hatch-Waxman patent term extension and patent term adjustment). The product is currently listed as discontinued.

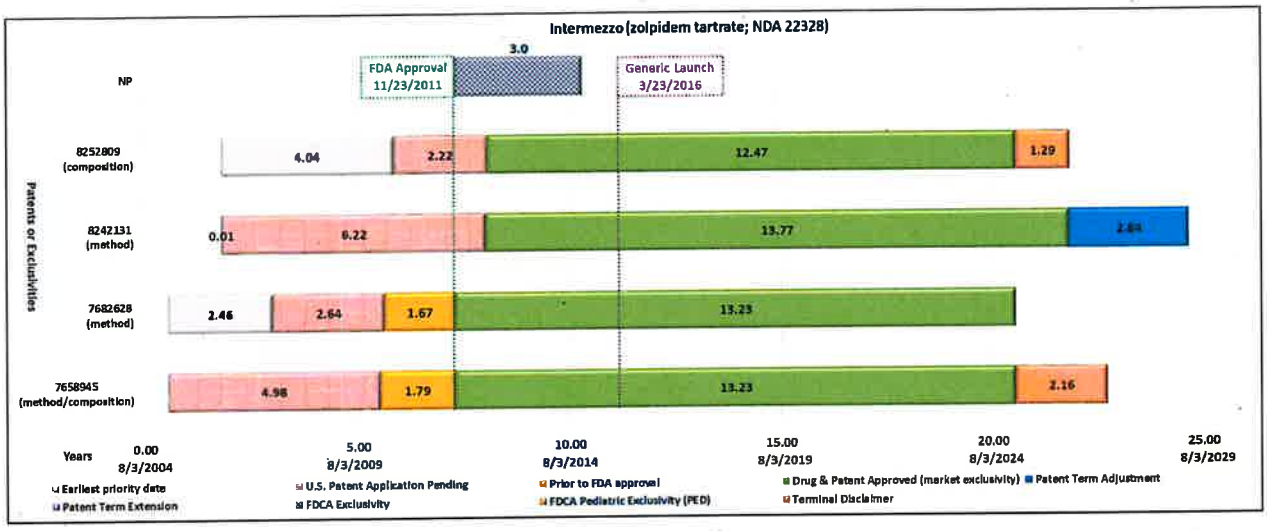


Figure 28. Bar chart of INTERMEZZO (NDA 22328) (Orange Book entries 2005-2018)

[90] See *Purdue Pharm. Prod. L.P. v. Actavis Elizabeth LLC*, No. CIV.A. 12-5311 JLL, 2015 WL 5032650 (D.N.J. Aug. 25, 2015); U.S. Patent No. 7,658,945.

d) ZOLPIMIST

ZOLPIMIST (NDA 22196)(5 mg) metered spray:

As shown in the bar chart of Figure 29 below, ZOLPIMIST was approved on December 19, 2008. ZOLPIMIST was discontinued and there is no generic version.

As shown in Figure 29 below and Table 25 of Appendix 4, the USPTO identified two patents that were listed in the Orange Book between 2005 and 2018. The USPTO confirmed that there were no exclusivities listed for ZOLPIMIST (5 mg/spray) during this period.

Both patents cover methods of treating insomnia by spraying a specific formulation to the inside of the mouth (oral mucosa). Figure 29 below shows that the patents issued after FDA approval. Additionally, both patents are subject to terminal disclaimers, meaning that they expire on the same date as related patents that are not Orange Book-listed (covering spray formulations for different drugs).

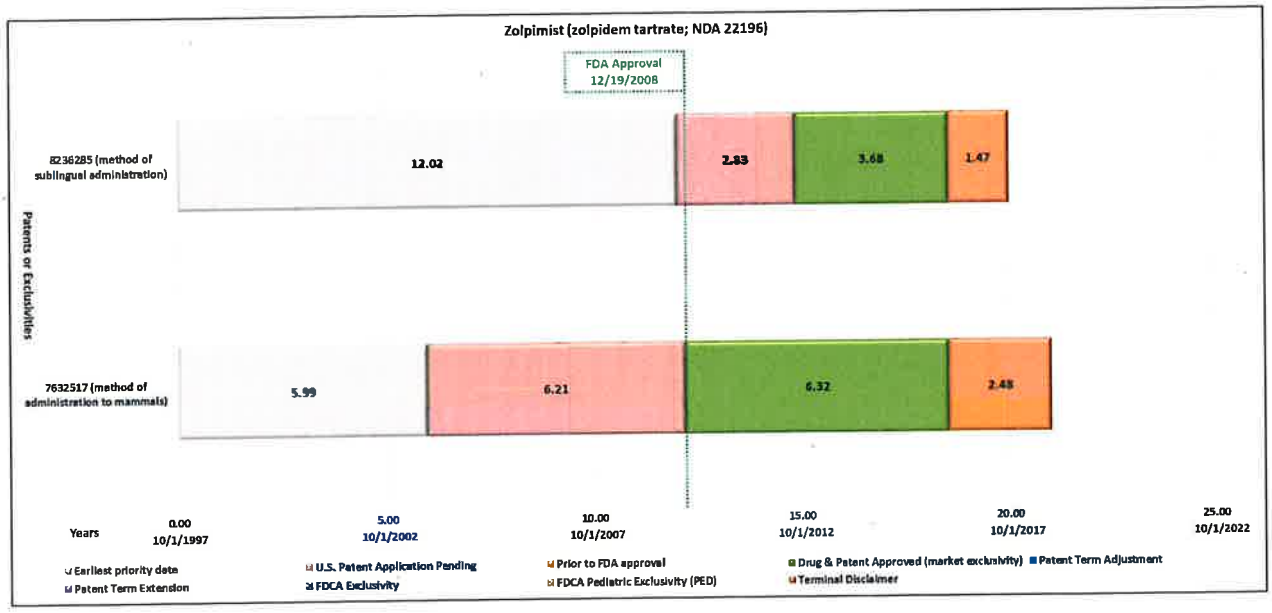


Figure 29. Bar chart of ZOLPIMIST (NDA 22196) (Orange Book entries 2005-2018)

CONCLUSION

This study surveys market exclusivity, based on patent protection and FD&C Act exclusivities, for a selection of drug products included in the Orange Book from 2005 to 2018. The drug products were chosen because they were among the top grossing products by revenue, among the most commonly prescribed, or contained well known active ingredients in 2017 (the year covered by the first I-MAK report mentioned in the letter from Senator Tillis). For the chosen drug products with identified generic competition, the market exclusivity of the drug products ranged from about 3 to about 16 years.[91] The sample size limits generalizations that can be drawn from the study and the conclusions that follow focus on observations about the studied products.

This study maps a baseline approach for examining the number of years from the time an NDA is first approved until the first launch of a generic. The results illustrate that simply quantifying raw numbers of patents and exclusivities is an imprecise way to measure the intellectual property landscape of a drug product because not every patent or exclusivity has the same scope. For example, one patent could contain different sets of claims directed to: (1) a pharmaceutical product, (2) a method of using the product, and (3) a process for manufacturing the product. Alternatively, separate patent applications could have been filed for each aspect of the invention, resulting in issuance of three patents instead of one patent. Thus, simple counts of patents can be misleading when every patent is counted equally, because the number of patents does not provide a clear picture of the landscape without a review of the scope of the claims in each patent.

Some research methodologies, such as that adopted by the UC Database, appear to rely on patent "use codes" corresponding to information provided by NDA holders to the FDA as a proxy for the scope of a patent. However, this study does not incorporate use codes. Not all Orange Book-listed patents have associated use codes—only those claiming a method of using the drug product—and use codes are not a replacement for a detailed analysis of a patent claim's scope. Moreover, newer methods of use protected by a patent may be carved out[92] from generic drug product labels and thus may not necessarily prevent a generic launch for other uses for which patent protection has expired. For example, a generic version of MIRAPEX (see Figure 18) was launched after expiration of the exclusivity under the FD&C Act

---

[91] For comparison, the mean and medium patent term across all technology areas from issuance to expiration is 17.17 years and 17.8 years, respectively, including any patent term adjustment and assuming the fees to maintain a patent in force are paid. M. Lemley, and J. Reinecke, "Our More-Than-Twenty-Year Patent Term" (July 31, 2023). Available at SSRN: https://ssrn.com/abstract=4529670 or http://dx.doi.org/10.2139/ssrn.4529670. See e.g., 35 U.S.C. § 154(b)(1)(B).

[92] Section 505(j)(2)(A)(viii) of the FDCA (which is codified at 21 U.S.C. § 355(j)(2)(A)(viii)) allows ANDA applicants to omit or "carve out" uses claimed in a patent and only seek approval for uses that are not claimed in the patent, and thereby avoid needing to make a certification for that patent.

without infringing later issued and non-expired method of use patents (directed to treating restless-leg syndrome).

Many of the products in this study were associated with multiple patents issued over a period of time. For several products studied, generics were launched before the expiration of all applicable Orange Book-listed patent and exclusivity time periods for that product (see, e.g., LIPITOR (settlement agreement), LYRICA CR (noninfringement judgment[93]), KALETRA (statutory disclaimer), REVLIMID (settlement agreement)).

The study shows instances where no generic has launched despite the expiration of Orange Book-listed patent(s), though in some cases other drug products with the same active ingredient were available in the market during the time period studied (see, e.g., VENTOLIN HFA, AMBIEN). The study also notes some instances where no generic has launched, but there are other available therapies with different active ingredients and indications for the same disease or condition were available to patients (see, e.g., NORVASC, XARELTO). In addition, the study includes an older active ingredient, aspirin, patented in a new formulation. Although patents listed in the Orange Book for an NDA for an over-the-counter aspirin containing product (VAZALORE) are identified in this study, these patents did not impact the continued availability of other products containing aspirin during the period of the listed patents. Instead, the scope of the patents was limited to the specific innovative formulation, and countless alternative aspirin-containing products continued to be available and marketed to consumers.

While outside the scope of this study and the USPTO's expertise, a comprehensive analysis of the product landscape might also consider other drug products available to practitioners and patients, such as treatment alternatives with the same active ingredient that are not therapeutically equivalent. Further studies of competition in the drug market may wish to explore the impact of other approved drug products that use the same active ingredient as well as approved drug products with different active ingredients that are indicated for the same disease or conditions, on market power and price. As noted above, however, this study does not address pricing.

Similarly, while outside the scope of this study and the USPTO's role, a comprehensive analysis of all the patents and pending patent application claims that, if issued in a patent, could reasonably be asserted against an ANDA applicant could provide a more fulsome picture of the general competitive landscape for a drug product.

With respect to multiple patents that cover a single product, multiple patents associated with a single marketed product are not unique to the pharmaceutical industry and are a common practice in many innovative industries, especially for complex products. Among the products

---

[93] *Sun Pharm. Indus. Ltd. v. Pfizer Inc.*, No. 19-cv-09335-KM-SCM (D.N.J. August 13, 2020) (finding that the generic product did not infringe the later issued patents).

included in the study, there is a large variance in the number of patents associated with a drug product. In some instances, a higher number of patents may not necessarily delay a generic launch (see, e.g., REVLIMID).[94] When multiple patent applications are filed by the same patentee to novel but obvious variations of related inventions, the doctrine of non-statutory double patenting prevents patents on these inventions from issuing with a different patent expiration date.[95] Accordingly, the patents tied by terminal disclaimers will have the same patent term (see, e.g., IMBRUVICA).

The study observes that patent expiration dates, like the number of patents, may not be predictive of the timing of actual launch of competing products (see, e.g., LIPITOR, LYRICA, AMBIEN CR), because not all listed patents may be infringed by a generic product or the patent owner and generic drug applicant agree upon a launch date before patent expiration. Likewise, the study observed instances where products with patent and exclusivity barriers[96] have no competition (see, e.g., IMBRUVICA, ELIQUIS) and instances of products with no generic competition that may face competition from other branded drug products with the same active ingredient (see, e.g., VENTOLIN HFA). Accordingly, policy makers may benefit from more comprehensive and broader studies that examine these issues across a broader scope of products to further analyze the potential impact of number of patents and timing of listing of patents on the actual timing of launch of generic products. Future research might also consider topics not addressed in this study, such as other data that may be indicative of potentially anticompetitive behavior.

As the USPTO's study shows, pharmaceutical market exclusivity from the time of NDA approval to the launch of a first generic competitor is influenced by a complex interplay of patent law and FDA statutes and regulations. In some cases, however, the timing of the entry of generic products is not fully reflected by a computation of patents and exclusivities and competition could be affected by other factors.

---

[94] C. Chien, et al., "Distinguishing and Predicting Drug Patents" (Nature Biotechnology, March 2023, which is available at https://www.nature.com/articles/s41587-023-01703-0, *supra* note 9.

[95] The patent examination process for treating patent applications and patents with patentably indistinct claims is described in Manual of Patent Examining Procedure, Section 804, and which is available on the USPTO website at https://www.uspto.gov/web/offices/pac/mpep/s804.html.

[96] See, e.g., ERG Report, *supra* note 13, for a discussion of barriers to generic drug development and market entry and considered a range of incentives to mitigate these barriers. Barriers addressed include patents, the possible introduction of an altered version of the brand drug, the possibility of an authorized generic, market manipulation by pharmacy benefit managers such as not including a generic drug in a formulary and uptiering of generic drugs in formularies (moving a generic from a tier where the co-payment, for example, is on average $12 to a tier where the copayment is an average of $124), among others.

APPENDIX 1: LETTERS FROM SENATOR TILLIS

THOM TILLIS
NORTH CAROLINA
113 DIRKSEN SENATE OFFICE BLDG
WASHINGTON, DC 20510
PH: (202) 224-6342

https://tillis.senate.gov

United States Senate
WASHINGTON, DC 20510

COMMITTEES
ARMED SERVICES
BANKING, HOUSING, AND URBAN DEVELOPMENT
JUDICIARY
VETERANS' AFFAIRS

VIA ELECTRONIC TRANSMISSION

January 31, 2022

Dr. Janet Woodcock
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

Mr. Drew Hirshfeld
Commissioner for Patents
Performing the functions and duties of the
Undersecretary for Intellectual Property and Director
United States Patent and Trademark Office
600 Dulany Street
Alexandria, Virginia 22314

Dear Dr. Woodcock and Mr. Hirshfeld:

I write you today in my capacity as Ranking Minority Member of the Senate Judiciary Committee Subcommittee on Intellectual Property. As the Ranking Member—and as a Senator from a State with a number of leading innovative biotech, pharmaceutical, and medical device companies—I am keenly aware of the role that strong intellectual property rights play in enabling the development of lifesaving, innovative biopharmaceuticals and other medical treatments.

Unfortunately, I am also aware of the false narrative being advanced by some that patents are being systemically used in ways not contemplated by our patent laws to delay generic drug competition. While I share the important goal of lowering drug prices for all Americans, I also believe it is imperative that any proposed solutions are fact-driven, objective, and take into account the many facets of this highly complex issue. Any solutions to this difficult and important issue must ensure that we do not undermine the robust intellectual property protections needed to enable the development of new medicines in the first place.

In order to ensure an objective, measured, and appropriate approach to this issue, it is fundamental that assumptions and premises be based on accurate facts and data from reliable, unbiased sources. Sadly, it has recently come to my attention that several of the main sources driving the narrative that patents are to blame for high drug prices do not appear to meet these fundamental criteria. Specifically, I am referring to research from the Initiative for Medicines,

CHARLOTTE OFFICE:
9300 HARRIS CORNERS PKWY
SUITE 170
CHARLOTTE, NC 28269
PH: (704) 509-9087

RALEIGH OFFICE:
310 NEW BERN AVE
SUITE 122
RALEIGH, NC 27601
PH: (919) 856-4630

HIGH POINT OFFICE:
1840 EASTCHESTER DR
SUITE 200
HIGH POINT, NC 27265
PH: (336) 885-0685

GREENVILLE OFFICE:
1694 E ARLINGTON BLVD
SUITE B
GREENVILLE, NC 27858
PH: (252) 329-0371

HENDERSONVILLE OFFICE:
1 HISTORIC COURTHOUSE SQ
SUITE 112
HENDERSONVILLE, NC 28792
PH: (828) 693-8750

Access & Knowledge (I-MAK) and a separate project from the University of California (UC) Hastings Law School project called the "Evergreen Drug Patent Search."[1]

I-MAK appears to be a primary source of data regarding the role of patents in drug pricing that is cited during these debates. I-MAK concludes that all of the top-selling drugs are protected by dozens or hundreds of patents that supposedly have the effect of blocking generic competition for an average of 30 to 50 years each.[2] But according to at least one new analysis that looks more closely at I-MAK's figures, the organization does not transparently disclose or explain its underlying data, and the data differs by orders of magnitude from public sources like the US Orange Book and court filings.[3] It also appears that many of the drugs alleged to be protected by "patent thickets" blocking competition for decades to come have already gone generic, in some cases before the reports making these allegations were even published.

The "Evergreen Drug Patent Search" database similarly suggests that nearly every FDA-approved drug has amassed unduly large numbers of "protections" that "artificially extend" exclusivity far into the future. As with the I-MAK reports, however, a subsequent analysis of this source has raised concerns about inaccuracy in the underlying data, inadequate transparency, and flawed methodology, and warns that the database risks causing policymakers to be "misled by the statistics."[4] As one illustration, the database apparently contains multiple entries for aspirin and suggests that it is still enjoying exclusivity under an "evergreening" strategy, even though aspirin has been available in generic form for over 100 years.

Both drug pricing, and matters of patent law and policy that impact the development of innovative medicines, are too important to this country to rely on sources whose accuracy and reliability are in question. For this reason, I request that your agencies conduct an independent assessment and analysis of the sources and data that are being relied upon by those advocating for patent-based solutions to drug pricing. It is my hope and belief that a clearer and more accurate picture of the underlying facts will help to reveal whether, and to what extent, patent-related issues are really contributing to high drug prices, and help to focus future policymaking in the right areas.

It is my hope that such an independent assessment and study will be completed by no later than December 31, 2022. Having this valuable information before we begin a new Congress will ensure that lawmakers are armed with all the key facts and data needed to make sound public policy decisions regarding drug pricing. Thank you for your attention to this matter. If you have any questions, please do not hesitate to contact me.

---

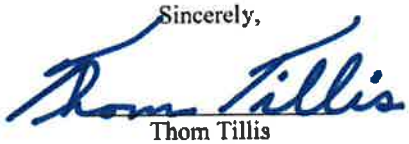
[1] *See* https://sites.uchastings.edu/evergreensearch/about/#.YfbYL-rMKkw

[2] *See, e.g.*, I-MAK, *Overpatented, Overpriced: How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving Up Drug Prices* (2018); https://www.i-mak.org/overpatented-overpriced-excessive-pharmaceutical-patenting-extending-monopolies-driving-drug-prices/ .

[3] Mossoff, Adam, *Unreliable Data Have Infected the Policy Debates Over Drug Patents,* Hudson Institute.

[4] George Mason University Center for Intellectual Property x Innovation Policy, UC Hastings' Evergreen Drug Patent Search Database: A Look Behind the Statistics Reveals Problems with this Approach to Identifying and Quantifying So-Called "Evergreening."

Sincerely,



Thom Tillis
Ranking Member
Subcommittee on Intellectual Property

THOM TILLIS
NORTH CAROLINA
113 Dirksen Senate Office Bldg
Washington, DC 20510
PH: (202) 224-6342

https://tillis.senate.gov

United States Senate

WASHINGTON, DC 20510

COMMITTEES
ARMED SERVICES
BANKING, HOUSING, AND URBAN DEVELOPMENT
JUDICIARY
VETERANS' AFFAIRS

VIA ELECTRONIC TRANSMISSION

April 1, 2022

The Honorable Dr. Robert Califf, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Mr. Drew Hirshfeld
Commissioner for Patents
Performing the functions and duties of the
Under Secretary of Commerce for Intellectual Property and Director
United States Patent and Trademark Office
600 Dulany Street
Alexandria, Virginia 22314

Dear Dr. Califf and Mr. Hirshfeld,

I write you again regarding several sources that are often cited to advance the false narrative that patent protections are to blame for high drug prices.[1] I remain concerned that these sources are based on opaque methodologies, and appear to contain inaccurate or incomplete information that may be misleading policymakers.[2] In my previous letter, I requested that your agencies conduct an independent assessment of the accuracy and reliability of those sources.

As I explained in that letter, these commonly referenced sources claim that biopharmaceuticals are often protected by dozens or hundreds of patents each, with an alleged effect of blocking generic competition for 30 to 50 years or longer per drug. However, researchers who have analyzed these claims have identified what appear to be serious flaws, inaccuracies, and biases in the methods and calculations of those advancing the claims.

I am specifically concerned about work from the Initiative for Medicines, Access & Knowledge (I-MAK). When I last wrote you, I also sent a letter to I-MAK inviting it to disclose its underlying data set, or at least to provide a detailed explanation of its methods to enable others to check the accuracy of I-MAK's alleged patent count, and to assess the credibility of its other assertions. While I had hoped to receive a constructive response, I-MAK unfortunately declined

[1] *See, e.g.*, I-Mak, *Overpatented, Overpriced*, August 2018; and *America's Overspend*, October 25, 2017. https://www.i-mak.org/overpatented-overpriced-excessive-pharmaceutical-patenting-extending-monopolies-driving-drug-prices/; *see also Evergreen Drug Patent Database*

[2] *See* Letter from Senator Tillis to Acting Commissioner Woodcock and Commissioner/Performing Functions of Director Hirschfeld, dated January 31, 2022.

CHARLOTTE OFFICE:
10150 Mallard Creek Rd
Suite 508
Charlotte, NC 28262
PH: (704) 509-9087

RALEIGH OFFICE:
310 New Bern Ave
Suite 122
Raleigh, NC 27601
PH: (919) 856-4630

HIGH POINT OFFICE:
1840 Eastchester Dr
Suite 200
High Point, NC 27265
PH: (336) 885-0685

GREENVILLE OFFICE:
1694 E Arlington Blvd
Suite B
Greenville, NC 27858
PH: (252) 329-0371

HENDERSONVILLE OFFICE:
1 Historic Courthouse Sq
Suite 112
Hendersonville, NC 28792
PH: (828) 693-8750

to disclose its data, and instead largely repeated the same explanations it employs in its reports.[3] I have enclosed a copy of their response for your review.

I-MAK attempts to justify its refusal to disclose its data on the basis that anyone "familiar with patent searching techniques would be able to replicate" its methods to "arrive at the same or very similar datasets."[4] Its failure to disclose this information raises a new question that you may wish to include in the analysis I previously requested—namely, whether you can, by employing standard "patent searching techniques," in fact credibly arrive at similar patent numbers and similar effective patent terms as those claimed in I-MAK's reports.

However, other assertions and admissions in I-MAK's response to my office would seem to cast serious doubt on that possibility. For example, in its letter, I-MAK acknowledges that it is counting patent applications among its figures. But, in its October 2017 report on three cancer drugs, for instance, I-MAK calculates a figure that it terms "total patents," but this number includes not just patents, but also pending patent applications, and even fully abandoned patent applications.[5] My understanding is that others employing "patent searching techniques" certainly would not conflate pending and abandoned patent applications with granted patents and call them all "total patents."

With respect to the periods of market exclusivity that I-MAK claims extend for 30 to 50 years for most drugs, it represented to me that its reports "clearly state that the number of years of patent protection for each drug studied is [merely] the drugmakers' attempt or potential to extend its monopoly period that could block competition."[6] This is another admission that does not appear to be an accurate representation of what I-MAK's reports attempt to show. In its 2018 report, I-MAK's key metrics are the "years block competition," and not the attempted or potential patent term. I-MAK concedes in its response to my letter at least six of the twelve drugs in its 2018 report indeed face generic competitors today, years before its key metric of "years blocking competition." I also understand that two of the three drugs in its 2017 report are already generic, including one that, like one in the 2018 report, was indeed generic long before the report's publication date.[7]

As you can see, there remain concerns with I-MAK's work and methodology. Those concerns are much more fundamental than challenging a single or even several errors. Instead, my concern

---

[3] I-Mak Letter to Senator Thom Tillis, March 9, 2022.
[4] *Id.*
[5] *See* I-Mak, *America's Overspend*, October 25, 2017 at 3 (Alleging that "105 patents cover the various hematology cancers and indications for which Revlimid has been approved," of which 29 are "abandoned patent applications," and another 10 are pending applications); *id.* at 5 (Alleging that a "total of 45 patents" protect Sovaldi,® of which 16 are "abandoned patent applications" and 2 are pending applications); *id.* at 7 (Alleging that "a total of 73 patents" cover Gleevec, of which the majority (44) are "abandoned applications" and another is a pending application).
[6] I-Mak Letter to Senator Thom Tillis, March 9, 2022.
[7] According to public sources, Revlimid went generic this month, contrary to the report's claims that the "patents enable a minimum exclusivity period from 2019 through 2028." *America's Overspend* at 7. Gleevec went generic in early 2016, almost two years before the report was published, despite the report's suggestion that is protected until 2029.

is to ensure that policymaking in this critical area is based on accurate, reliable, and replicable facts and evidence. Accordingly, I reiterate my request that your agencies conduct an independent assessment and study of these matters that will be completed by no later than December 31, 2022.

Please reply to me by May 1, 2022 indicating that you will conduct such an assessment. Having this valuable information before we begin a new Congress will ensure that lawmakers are armed with all the key facts and data needed to make sound public policy decisions regarding drug pricing. Thank you for your attention to this matter. If you have any questions, please do not hesitate to contact me.

Sincerely,

Thom Tillis
United States Senator

APPENDIX 2: THE CYCLE OF INNOVATION

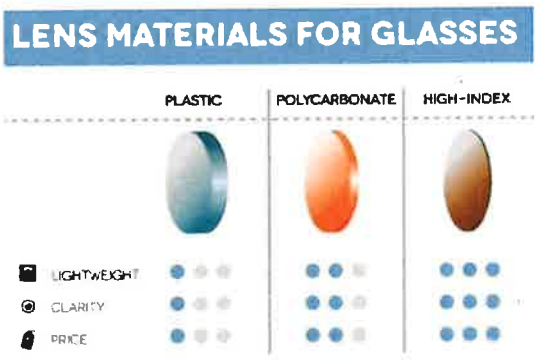
In the cycle of innovation, inventors build upon the knowledge and advancements of those that came before them. The patent system helps accelerate this cycle through disclosure of these innovations and in incentivizing research and development. Using the patent system to protect these later innovations that build upon earlier patented inventions is a common business practice in many, if not all, industries. Although the eyeglasses industry is not directly analogous to that in the pharmaceutical industry, it can be an instructive example. Eyeglasses and their related technologies are a well-established product area, eyewear companies continue to innovate and are granted patents for inventions in this area.

The evolution of eyeglass technology is one illustration of the cycle of innovation. One of the earliest patents to eyeglasses was awarded to Owen Aves by the British Patent Office in 1908 for the manufacturing process and design of progressive addition lenses.[97] In the ensuing years, many innovative advancements directed to new uses and structural improvements received their own patent protections.

A wide variety of applications define the eyewear landscape, including eyewear for correcting vision, shielding eyes from infrared radiation or blue light, protecting against physical harm, and even for stylistic purposes. Within the eyewear landscape are also improvements to the structure of the eyewear, including improvements to lenses, frames, bridges, hinges, temples, and nose pads.[98] These applications and structural improvements illustrate some of the novel and non-obvious improvements in eyewear protected by intellectual property rights despite the long history of using eyeglasses to correct vision.

Even today, patents continue to be granted for eyewear when the claimed invention meets the standards for patentability even though eyewear itself has existed for centuries.

Many recent patents from the field of eyewear also benefit society with their innovative improvements to previous technology. Corrective eyewear, contact lenses, and laser eye surgery—among other advancements—are products of continual development and innovation that benefits the public. For example, corrective lenses were once made from glass, which was expensive to manufacture and posed a serious risk of injury to



[97] G.B. Patent No. 15,735 (filed in 1907 and issued in 1908).

[98] In fact, it would not be unusual for a single pair of eyeglasses to be covered by multiple patents directed to different aspects of the product, including the lenses, frames, hinges, methods of manufacturing, materials used, etc.

wearers. The introduction of plastic lenses significantly improved lens technology by lowering cost and risk to the user. Today, users have even more options, including polycarbonate and high-index lenses and additional features such as anti-reflective or scratch-resistant coatings. As shown in Figure 1, high-index lenses decrease lens thickness and weight but increase the clarity of the lenses in comparison to plastic or polycarbonate. These improvements are notable, and even necessary for some users with strong prescriptions.

Innovative improvements in eyewear are conceptually analogous to innovative improvements in the pharmaceutical field as both ground-breaking and incremental innovations can improve the product to the benefit of the user.[99] For example, a known active pharmaceutical ingredient with a new extended-release formulation that reduces the necessary dose frequency may be shown in clinical trials to benefit a patient by, among other things, simplifying dosing regimens and improving adherence to the prescribed drug, and a new use of an old drug may be shown in clinical trials to provide a new, effective treatment for a disease.

Such improvements, when deemed patentable, are entitled to patent protection, which is limited in scope to the patentable improvement. Importantly, once the original patent expires, the public may use the technology covered by the expired patent. Patents on the improvements only prevent the public from using the new technology until the new patents expire. As noted above, multiple patents on similar inventions (i.e., patentably indistinct inventions) are statutorily permitted so long as a terminal disclaimer is filed to ensure that the patents remain commonly owned and have the same original expiration date. The patent on the invention that is not patentably distinct cannot extend the duration of exclusivity of the other patents.

[99] The eyeglasses example is intended to demonstrate the cycle of innovation and is not a direct analogy to drugs.

APPENDIX 3: KEY CONCEPTS RELATED TO PATENTS AND EXCLUSIVITIES

USPTO's Role

Examination of patent applications

Examination of patent applications in any discipline involves ensuring that the application, including the claims, complies with the patent statutes, regulations, other office guidance, and relevant case law. At a high level, a claimed invention, as presented in a patent application, must have utility and be eligible for patenting (35 U.S.C. § 101), be novel and non-obvious over the prior art[100] (35 U.S.C. §§ 102 and 103), and be adequately described and disclosed so that another person skilled in that art can make and use the claimed invention (35 U.S.C. § 112).[101] These conditions of patentability are not limited to pharmaceutical and biotechnology patents and apply to all technology areas.

During the patent examination process, patent examiners make determinations of whether the claimed invention presented in a patent application complies with the statutory provisions enumerated above. Part of that process involves conducting a prior art search, comparing relevant prior art to the claimed invention, and making determinations on novelty and obviousness of the claimed invention. Examiners, then, upon analyzing the prior art and comparing it to the claimed invention, either reject the claimed invention if it is known or obvious in view of the prior art, or grant a patent if the claimed invention is novel and nonobvious in view of the prior art (and meets the other patenting requirements enumerated above).

Continuation patents

The patent laws allow patent applicants to file for continuation patent applications to seek protection for inventions disclosed, but not claimed, in earlier patents.[102] It is important to note that continuation patents, by statute, cannot extend the 20-year term of a parent (i.e., original) patent. The term of a continuation patent will expire at the same time the original patent will expire, except for any patent term adjustment or patent term extension of the continuation patent, if applicable. Specifically, the law provides for adjustments or extensions

---

[100] Prior art is comprised of information that has been publicly disclosed prior to the filing date of a patent application as well as certain patent applications that were filed before the patent application under examination.

[101] MPEP, chapter 2100.

[102] 35 U.S.C. §§ 120, 121.

of a patent beyond the 20-year term in two situations. First, if the USPTO does not meet examination timeframes set by statute, the term may be adjusted by the period of delay, less any applicant delay, to ensure that the patent owner does not unfairly lose patent term. This is called "patent term adjustment" or "PTA." Second, the 20-year term may be extended as a result of time taken for FDA review of a drug product after issuance of the patent. This is called "patent term extension" or "PTE."

Once a patent term ends, the claimed inventions are in the public domain, regardless of whether any continuation applications were filed.

Moreover, a patent applicant cannot be granted two patents for identical inventions. If an applicant files a continuation application seeking a patent for an obvious variation of an applicant's existing patent, the application will be rejected for "double patenting." The applicant can overcome this rejection by filing a terminal disclaimer to agree that the patents will remain commonly owned, and to limit the term of protection of the later-filed patent to the term remaining in the existing patent. This disclaimer of patent term prevents the improper timewise extension of patent term to the later-filed patent. Patent term for the later-filed patent ends the same day as the existing patent.

New patents relating to an already patented drug

In accordance with the patent laws noted above, in order to obtain a patent with a separate and potentially later expiring term, the inventions claimed must be novel and nonobvious. To obtain a patent with a separate and potentially later expiring term, the invention cannot merely be a trivial variation of existing technology. It must be an invention that a person of ordinary skill in that technological area would not consider to be obvious.[103]

In the pharmaceutical or biotechnology area, a new patent may be granted on innovations, such as new and nonobvious changes to an existing drug product. These changes could make an existing drug significantly safer and/or more effective. Additionally, if an inventor finds a novel and nonobvious use for an existing drug, the inventor may obtain a patent on the new method of use. For example, looking for new uses for existing drugs has become one of the key ways to search for effective treatments of a variety of diseases, from AIDS to heart disease to multiple sclerosis. These types of innovations often provide important treatment options for patients, and may lead to new patents consistent with the patent laws.

The USPTO applies the statute on obviousness (35 U.S.C. § 103) and the case law interpreting and applying this statute to determine whether a claimed invention is obvious over the prior art. Various Supreme Court and Federal Circuit decisions have provided instruction to the

---

[103] For instance, changes in size, shape, proportion, or sequence of adding ingredients are generally not considered to be patentable changes to prior art inventions.

USPTO on how to determine obviousness, including for formulation changes or new uses for drugs.[104]

Exclusivity periods under the FD&C Act

Exclusivity refers to certain delays and time limited prohibitions on the acceptance or approval of applications for competitor drugs. Under the FD&C Act a drug may be eligible for exclusivity if statutory requirements are met. (See 21 CFR 314.108, 316.31, 316.34 and sections 505A, 505E, 505(c)(3)(E), 505(j)(5)(B)(iv), 505(j)(5)(B)(v), 505(j)(5)(F) and 527 of the FD&C Act.) Periods of exclusivity and patent terms may or may not run concurrently. Exclusivity generally attaches upon approval of a drug product if the statutory requirements are met. Exclusivity was designed to promote a balance between drug innovation and competition, including incentives to challenge patents and greater public access to drugs that result from generic drug competition which is facilitated by the framework established in the Drug Price Competition and Patent Term Restoration Act (Hatch Waxman Act).[105]

The duration of an exclusivity period depends on what type of exclusivity is at issue.[106]

- Orphan-drug exclusivity (ODE) – seven years
- New Chemical Entity Exclusivity (NCE) – five years
- Generating Antibiotic Incentives Now (GAIN) Exclusivity – five years added to certain exclusivities (this exclusivity is available to designated Qualified Infectious Disease Products only)
- New Clinical Investigation Exclusivity – three years
- Pediatric Exclusivity (PED) – six months added to certain existing exclusivities and patent-based restrictions on approval. Pediatric exclusivities are not a separate form of protection from the FDA exclusivity or patent to which they are added.[107]
- Patent Challenge (PC) Exclusivity – 180 days (this exclusivity is available to ANDAs only)

---

[104] See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

[105] See, e.g., FDA/CDER Chronicles, "Patents and Exclusivity" (May 19, 2015) which is available at https://www.fda.gov/media/92548/download.

[106] The current complete list of exclusivity codes used in the Orange Book is available at: http://www.accessdata.fda.gov/scripts/cder/ob/results_exclusivity.cfm.

[107] See Section 505A of the FD&C Act. For a discussion of the complexities of pediatric exclusivities, see "Pediatric Exclusivity: Amazingly Powerful, Essentially Ironclad . . . and Often Overlooked," which is available at https://www.thefdalawblog.com/2015/07/pediatric-exclusivity-amazingly-powerful-essentially-ironclad-and-often-overlooked/.

- Competitive Generic Therapy (CGT) Exclusivity - 180 days (this exclusivity is available to ANDAs only)

See 21 CFR 314.108, 316.31, 316.34 and sections 505A, 505E, 505(c)(3)(E), 505(j)(5)(B)(iv), 505(j)(5)(B)(v), 505(j)(5)(F), and 527 of the FD&C Act.

New Chemical Entity (NCE) Exclusivity is provided for under section 505(c)(3)(E) and 505(j)(5)(F) of the FD&C Act and is a five-year period of exclusivity available for New Drug Applications for products containing a new chemical entity, i.e., a drug that contains an active moiety never previously approved by FDA either alone or in combination. No 505(b)(2) application or ANDA may be submitted during the five-year exclusivity period except that such applications may be submitted after four years if they contain a certification of patent invalidity or noninfringement.

New Clinical Investigation (NCI) Exclusivity is provided for under section 505(c)(3)(E) and 505(j)(5)(F) of the FD&C Act and is a three-year period of exclusivity available for a drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the sponsor that were essential to approval of the application, and prevents the approval of other applications for the exclusivity-protected conditions of approval for this period of time. For example, changes to the active ingredient(s), strength, dosage form, route of administration or conditions of use of an approved drug product such as use of the drug in a new patient population (NPP) may be eligible for exclusivity if new clinical investigations conducted or sponsored by the applicant were essential to approval of the application containing those changes.[108] NCI exclusivity is reflected in the Orange Book by various exclusivity abbreviations that provide general shorthand descriptions of the nature of the exclusivity-protected conditions or change. For example, the abbreviation "NPP" is used to describe NCI exclusivity related to a new patient population, "NP" is used to describe NCI exclusivity related to a new product, and "I" codes are used to describe NCI exclusivity related to a new indication.

Orphan-drug exclusivity (ODE) is provided for under section 527 of the FD&C Act. ODE is a seven-year period of exclusivity available to certain orphan drugs, which are drugs used to prevent, diagnose, or treat rare diseases or conditions. A rare disease is a disease or condition that affects fewer than 200,000 persons in the U.S., or for which there is no reasonable expectation that the costs of development will be recovered through sales in the U.S.[109] For eligible drugs, ODE prevents the approval of other applications for the same drug for the same

---

[108] Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity | FDA, response to questions 1 and 6, which is available at https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-new-drug-product-exclusivity.

[109] 21 U.S.C. § 360bb.

use or indication within the orphan-designated disease or condition. Under section 527(c), if a sponsor seeks ODE for a drug that is otherwise the same as a previously approved drug for the same use or indication, then to be eligible for ODE, the sponsor must demonstrate that its drug is clinically superior to any previously approved drug that is otherwise the same and approved for the same use or indication.[110]

Pediatric exclusivity is a six-month period added to certain exclusivities and patent-based restrictions on approval on all applications held by the sponsor for that active moiety (e.g., all formulations, dosage forms and indications). Pediatric exclusivity does not stand alone, but attaches to existing patents and exclusivities. When pediatric exclusivity attaches, the patent is shown twice in the patent column of the Orange Book—once with the patent expiration date and a second time with a date reflecting the six-month period of pediatric exclusivity linked to that particular patent. Because pediatric exclusivity does not stand alone and instead attaches to existing protections, it has been listed a single time in the tables in Appendix 4.

Other exclusivities referenced in the list above were not applicable to the NDAs included in this study. These include Generating Antibiotic Incentives Now (GAIN) Exclusivity, which was not observed during the studied period for the NDAs included in this study, as well as Patent Challenge (PC) and Competitive Generic Therapy (CGT) Exclusivity, which are only applicable to ANDAs.

[110] See Food and Drug Administration Reauthorization Act of 2017 (FDARA), Public Law No.: 115-52 (Aug. 18, 2017) § 607.

APPENDIX 4: SUMMARY OF INFORMATION IN BAR CHARTS

Template for tables

Drug Product name (NDA ######)	USPTO findings
NDA Approval Date:	
U.S. Patents in Orange Book (2005 to 2018)	
Patent Term Extensions in Orange Book (2005 to 2018)	
Exclusivities in Orange Book (2005 to 2018)	

In compiling the patents and FD&C Act exclusivities, the USPTO did not independently search to identify patents that were not listed in the Orange Book but should have been, or review the scope of the claims to determine whether a patent was properly listed. Instead, the USPTO compiled all of the patents and exclusivities that had been listed at one point during the 2005 to 2018 period. For patent and exclusivity information between 2005 and 2015, the USPTO used the dataset compiled by Robin Feldman on OPENICPSR.org.[111] For patent and exclusivity information in 2016, 2017 and 2018, the USPTO relied upon the Orange Book archives.[112] Patents that were removed from the Orange Book during or after the 2005 to 2018 period were retained in USPTO's dataset for this report.

Drug Product name: This refers to the brand (or proprietary) name in the Orange Book for the New Drug Application (NDA).

NDA: The New Drug Application number is a five- or six-digit number assigned by the FDA and which is indicated in the Orange Book. The same active ingredient may be associated with

---

[111] R. Feldman, "Identifying Extensions of Protection in Prescription Drugs: Navigating the Data Landscape for Large-Scale Analysis," OPENICPSR, https://www.openicpsr.org/openicpsr/project/104781/version/V2/view?path=/openicpsr/104781/fcr:versions/V2/Orange_Book.csv&type=file (last updated Dec. 7, 2018, 12:33 PM).

[112] Old, or historic, versions of the Orange Book are not available on FDA's website. One place to view older versions of the Orange Book and monthly supplements is the Orange Book archives, which are available at: https://www.thefdalawblog.com/orange-book-archives/.

multiple NDAs, usually for different formulations. Because each NDA has a different entry in the Orange Book, a separate chart is included for different NDAs with the same active ingredient. Each product approved under the same NDA is accorded a sequential product number (001, 002, etc., beginning with the first product approved). Products approved after the NDA approval date are found in the Orange Book with additional product numbers. Where these subsequent approvals had different patents, because for example, they were approved after the expiration date of a patent, or different exclusivities, for example, because they were approved after the expiration date of the NCE exclusivity, these are not shown in the bar chart. Some formulations of an active ingredient may be combination drug products containing other active ingredients. The scope of this study did not permit every drug product in every NDA studied to be included.

NDA Approval Date: This refers to the date when the NDA was first approved by the FDA. The USPTO checked the date in the UC Database and against the historic Orange Book Data, as compiled in the ICPSR database, and the Orange Book archives.

As explained above, in determining whether a patent or exclusivity should be included, the USPTO used the ICPSR database which scraped data from the Orange Book from 2005 to 2015 and the Orange Book archives.

U.S. Patents in Orange Book (2005 to 2018): The USPTO provides the patent numbers which appeared in the Orange Book during the 2005 to 2018 time period, together with the USPTO's calculation of the projected expiration date of the patent and any patent term extension. Use codes[113] are not listed in the table. The patent expiration dates provided assume all maintenance fees are paid, and there is no subsequent terminal disclaimer. As explained above, the patent expiration dates that are included in the Orange Book are the dates communicated to the FDA by the NDA applicant. The USPTO independently determined the patent and patent term extension expiration dates and these expiration dates may be different due to changes in the patent term adjustment after the patent was granted or due to a later filed terminal disclaimer. The expiration dates of any pediatric exclusivities are also shown.

Patent Term Extensions in Orange Book (2005 to 2018): Pursuant to 35 U.S.C. § 156(b), the rights derived from a PTE are different than during the original patent. The length of the patent term extension as shown in official USPTO records, and the projected expiration date of the patent term extension as calculated by the USPTO are provided. The expiration date of any pediatric exclusivities is also shown.

---

[113] Use codes correspond to a short explanation of the method claims of a patent which is provided by the NDA sponsor to the FDA and may help explain the scope of a patent's protection, as it is relevant to the approved product.

Exclusivities in Orange Book (2005 to 2018): All exclusivities in the ICPSR dataset or OB Archives from 2016–2018 with the expiration date indicated in the Orange Book.[114]

[114] Pediatric exclusivity is added to existing market exclusivities or patent protections, and, in general, cannot be given if there is no existing market exclusivity or patent protection. More information on pediatric exclusivity is available here: https://www.fda.gov/drugs/development-resources/qualifying-pediatric-exclusivity-under-section-505a-federal-food-drug-and-cosmetic-act-frequently.

Tables

Table 1: albuterol sulfate (VENTOLIN HFA) (single strength: 0.09 mg/inhale)

VENTOLIN HFA (NDA 20983)	USPTO Findings
Approval Date	4/19/2001
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 6,131,566 (exp. 4/14/2015, PED 10/14/2015) 6,161,724 (exp. 1/16/2018, PED 7/16/2018) 6,170,717 (exp. 12/23/2017, PED 6/23/2018) 6,315,173 (exp. 12/23/2017, PED 6/23/2018) 6,431,168 (exp. 6/8/2018, PED 12/8/2018) 6,435,372 (exp. 1/16/2018, PED 7/16/2018) 6,510,969 (exp. 12/23/2017, PED 6/23/2018) 6,532,955 (exp. 4/14/2015, PED 10/14/2015) 6,558,651 (exp. 12/19/2016, PED 6/19/2017) 6,596,260 (exp. 8/10/2014, PED 2/10/2015) 6,743,413 (exp. 6/1/2021, PED 12/1/2021) (17-year term) 6,938,796 (exp. 1/16/2018, PED 7/16/2018) 6,966,467 (exp. 12/23/2017, PED 6/23/2018) 6,997,349 (exp. 1/16/2018, PED 7/16/2018) 7,107,986 (exp. 1/20/2019, PED 7/20/2019) 7,143,908 (exp. 1/16/2018, PED 7/16/2018) 7,350,676 (exp. 8/24/2018, PED 2/24/2019) 7,500,444 (exp. 2/26/2026, PED 8/26/2026) 7,832,351 (exp. 6/19/2023, PED 12/19/2023) 9,861,771 (exp. 10/11/2020)
Patent Term Extensions in Orange Book (2005 to 2018)	None
Exclusivities in Orange Book (2005 to 2018):	None

Table 2: amlodipine besylate (NORVASC) (2.5 mg, 5 mg, 10 mg)

NORVASC (NDA 19787)	USPTO Findings
Approval Date	7/31/1992
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 4,572,909 (exp. 2/25/2003) (17-year term) 4,879,303 (exp. 11/7/2006, PED 5/7/2007) (17-year term)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 4,572,909 (1,252 days, exp. 7/31/2006, PED 1/31/2007)
Exclusivities in Orange Book (2005 to 2018)	NPP (exp. 1/8/2007, PED 7/8/2007) I-472 (exp. 9/28/2008)

Table 3: amlodipine besylate ODT (2.5 mg, 5.0 mg, 10.0 mg)

amlodipine besylate ODT (NDA 22026)	**USPTO Findings**
Approval Date	9/27/2007
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent No.: 6,828,339 (exp. 11/20/2022)
Patent Term Extensions in Orange Book (2005 to 2018)	None
Exclusivities in Orange Book (2005 to 2018)	None

Table 4: apixaban (ELIQUIS) (2.5 mg)

ELIQUIS (NDA 202155)	USPTO Findings
Approval Date	12/28/2012
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 6,413,980 (exp. 12/22/2019) 6,967,208 (exp. 11/21/2026) 9,326,945 (exp. 2/24/2031)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No.: 6,967,208 (1,526 days)
Exclusivities in Orange Book (2005 to 2018)	NCE (exp. 12/28/2017) I-681 (exp. 3/3/2017) I-661 (exp. 8/21/2017) I-690 (exp. 8/21/2017) I-691 (exp. 8/21/2017)

Table 5: aspirin (VAZALORE)

VAZALORE (NDA 203697)	**USPTO Findings**
Approval Date	1/14/2013
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos. 8,865,187 (exp. 3/23/2022) 9,101,637 (exp. 3/23/2022) 9,216,150 (exp. 9/29/2032) 9,222,892 (exp. 9/29/2032 9,351,984 (exp. 12/19/2021)
Patent Term Extensions in Orange Book (2005 to 2018)	None
Exclusivities in Orange Book (2005 to 2018)	None

Table 6: atorvastatin calcium (LIPITOR) (10 mg and 20 mg)

LIPITOR (NDA 20702)	USPTO Findings
Approval Date	12/17/1996
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 4,681,893 (exp. 5/30/2006) (17-year term) RE 40,667 (exp. 12/28/2010, PED 6/28/2011) (17-year term) 5,686,104 (exp. 11/11/2014, PED 5/11/2015) (17-year term) 5,969,156 (exp. 7/8/2016, PED 1/8/2017) 6,126,971 (exp. 1/19/2013, PED 7/19/2013) *Orange Book listed both U.S. Patent No. 5,273,995 and its Reissue, U.S. Patent No. RE 40,667
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 4,681,893 (1,213 days, exp. 9/24/2009, PED 3/24/2010)
Exclusivities in Orange Book (2005 to 2018)	D-77 (exp. 4/22/2005) I-350 (exp. 10/18/2005, PED 4/18/2006) I-434 (exp. 7/30/2007) M-36 (exp. 7/30/2007) I-471 (exp. 9/21/2008) M-204 (exp. 6/23/2020)

Table 7: bictegravir sodium; emtricitabine; tenofovir alafenamide fumarate (BIKTARVY) (50 mg/200 mg/25 mg)

BIKTARVY (NDA 210251)	USPTO Findings
Approval Date	2/7/2018
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 6,642,245 (exp. 11/4/2020) (17-year term) 6,703,396 (exp. 3/9/2021) (17-year term) 7,390,791 (exp. 5/7/2022) 7,803,788 (exp. 2/2/2022) 8,754,065 (exp. 8/15/2032) 9,216,996 (exp. 12/19/2033) 9,296,769 (exp. 8/15/2032) 9,708,342 (exp. 6/19/2035) 9,732,092 (exp. 12/19/2033)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 7,390,791 (1,076 days, exp. 4/17/2025, PED 10/17/2025)
Exclusivities in Orange Book (2005 to 2018):	NCE (exp. 2/7/2023)

Table 8: ibrutinib (IMBRUVICA capsule) (140 mg)

IMBRUVICA (NDA 205552)	USPTO Findings
Approval Date	11/13/2013
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 7,514,444 (exp. 12/28/2026) 8,008,309 (exp. 12/28/2026) 8,476,284 (exp. 12/28/2026) 8,497,277 (exp. 12/28/2026) 8,563,563 (exp. 4/26/2027) 8,697,711 (exp. 12/28/2026) 8,703,780 (exp. 12/28/2026) 8,735,403 (exp. 12/28/2026) 8,754,090 (exp. 6/3/2031) 8,754,091 (exp. 12/28/2026) 8,952,015 (exp. 12/28/2026) 8,957,079 (exp. 12/28/2026) 8,999,999 (exp. 6/3/2031) 9,125,889 (exp. 6/3/2031) 9,181,257 (exp. 12/28/2026) 9,296,753 (exp. 10/24/2034) 9,540,382 (exp. 8/18/2033) 9,713,617 (exp. 6/3/2033) 9,725,455 (exp. 6/3/2033) 9,795,604 (exp. 10/24/2034) 9,801,881 (exp. 6/3/2031) 9,801,883 (exp. 6/3/2031) 9,814,721 (exp. 6/3/2031) 10,004,746 (exp. 6/3/2031) 10,016,435 (exp. 6/3/2031) 10,106,548 (exp. 6/3/2033) 10,125,140 (exp. 6/3/2033)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 8,008,309 (320 days, exp. 11/13/2027)

Exclusivities in Orange Book (2005 to 2018)	NCE (exp. 11/13/2018) D-165 (exp. 5/6/2019) I-680 (exp. 2/12/2017) I-689 (exp. 7/28/2017) I-702 (exp. 1/29/2018) I-729 (exp. 3/4/2019) I-736 (exp. 5/6/2019) I-737 (exp. 5/6/2019) I-741 (exp. 1/18/2020) I-753 (exp. 8/2/2020) ODE-55 (MCL) (exp. 11/13/2020) ODE-60 (CLL) (exp. 2/12/2021) ODE-72 (CLL) (exp. 7/28/2021) ODE-86 (WM) (exp. 1/29/2022) ODE-109 (CLL) (exp. 3/4/2023) ODE-117 (SLL) (exp. 5/6/2023) ODE-128 (MZL) (exp. 1/18/2024) ODE-152 (CGVHD) (exp. 8/2/2024)

Table 9: ibrutinib (IMBRUVICA tablet) ((140 mg, 280 mg, 420 mg, 560 mg)

IMBRUVICA (NDA 210563)	USPTO Findings
Approval Date	2/16/2018
Patents	U.S. Patent Nos.: 7,514,444 (exp. 12/28/2026) 8,008,309 (exp. 12/28/2026) 8,476,284 (exp. 12/28/2026) 8,497,277 (exp. 12/28/2026) 8,563,563 (exp. 4/26/2027) 8,697,711 (exp. 12/28/2026) 8,703,780 (exp. 12/28/2026) 8,735,403 (exp. 12/28/2026) 8,754,090 (exp. 6/3/2031) 8,754,091 (exp. 12/28/2026) 8,952,015 (exp. 12/28/2026) 8,957,079 (exp. 12/28/2026) 8,999,999 (exp. 6/3/2031) 9,125,889 (exp. 6/3/2031) 9,181,257 (exp. 12/28/2026) 9,296,753 (exp. 6/3/2033) 9,655,857 (exp. 3/3/2036) 9,725,455 (exp. 6/3/2033) 9,795,604 (exp. 10/24/2034) 9,801,881 (exp. 6/3/2031) 9,801,883 (exp. 6/3/2031) 9,814,721 (exp. 6/3/2031) 10,004,746 (exp. 6/3/2031) 10,010,507 (exp. 3/3/2036) 10,016,435 (exp. 6/3/2031) 10,106,548 (exp. 6/3/2033) 10,125,140 (exp. 6/3/2033)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 8,008,309 (320 days, exp. 11/13/20217)
Exclusivities in Orange Book (2005 to 2018)	NCE (exp. 11/13/2018)

Table 10: lenalidomide (REVLIMID) (5 mg, 10 mg)

REVLIMID (NDA 21880)	USPTO Findings
Approval Date	12/27/2005
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 5,635,517 (exp. 7/24/2016) 6,045,501 (exp. 8/28/2018) 6,281,230 (exp. 7/24/2016) 6,315,720 (exp. 10/23/2020) 6,555,554 (exp. 7/24/2016) 6,561,976 (exp. 8/28/2018) 6,561,977 (exp. 10/23/2020) 6,755,784 (exp. 11/26/2020) 6,908,432 (exp. 8/28/2018) 7,119,106 (exp. 7/24/2016) 7,189,740 (exp. 4/11/2023) 7,465,800 (exp. 4/27/2027) 7,468,363 (exp. 10/7/2023) 7,855,217 (exp. 11/24/2024) 7,968,569 (exp. 10/7/2023) 8,204,763 (exp. 8/28/2018) 8,288,415 (exp. 7/24/2016) 8,315,886 (exp. 10/23/2020) 8,404,717 (exp. 4/11/2023) 8,530,498 (exp. 5/15/2023) 8,589,188 (exp. 8/28/2018) 8,626,531 (exp. 10/23/2020) 8,648,095 (exp. 5/15/2023) 8,741,929 (exp. 3/8/2028) 9,056,120 (exp. 4/11/2023) 9,101,621 (exp. 5/15/2023) 9,101,622 (exp. 5/15/2023)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 5,635,517 (1,167 days, exp. 10/4/2019)
Exclusivities in Orange Book (2005 to 2018)	NCE (exp. 12/27/2010) 5 ODE (exp. 12/27/2012, 6/29/2013, 6/5/2020, 2/22/24, 2/17/2022)

	I-672 (exp. 6/5/2016) I-706 (exp. 2/17/2018)

Table 11: lopinavir; ritonavir (KALETRA capsule) (133 mg/33.3 mg)

KALETRA Capsule (NDA 21226)	USPTO Findings
Approval Date	9/15/2000
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 5,541,206 (exp. 7/30/2013, PED 1/30/2014) (17-year term) 5,635,523 (exp. 7/30/2013, PED 1/30/2014) (17-year term) 5,648,497 (exp. 7/15/2014, PED 1/15/2015) (17-year term) 5,674,882 (exp. 7/30/2013, PED 1/30/2014) (17-year term) 5,846,987 (exp. 12/29/2012, PED 6/29/2013) 5,886,036 (exp. 12/29/2012) 5,914,332 (exp. 12/13/2015, PED 6/13/2016) 5,948,436 (exp. 9/13/2013, PED 3/13/2014) 6,037,157 (exp. 6/26/2016, PED 12/26/2016) 6,232,333 (exp. 11/7/2017, PED 5/7/2018) 6,284,767 (exp. 12/13/2015, PED 8/15/2016) 6,458,818 (exp. 11/7/2017, PED 5/7/2018) 6,521,651 (exp. 11/7/2017, PED 5/7/2018) 6,703,403 (exp. 6/26/2016, PED 12/26/2016) 7,141,593 (exp. 5/22/2020, PED 11/22/2020) 7,432,294 (exp. 5/22/2020, PED 11/22/2020)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 5,886,036 (325 days, exp. 11/19/2013, PED 5/19/2014)
Exclusivities in Orange Book (2005 to 2018)	D-99 (4/29/2008, PED 10/29/2008)

Table 12: lopinavir; ritonavir (KALETRA solution) (80 mg/mL/20 mg/mL)

KALETRA solution (NDA 21251)	USPTO Findings
Approval Date	9/15/2000
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 5,484,801 (exp. 1/28/2014, PED 7/28/2014) (17-year term) 5,541,206 (exp. 7/30/2013, PED 1/30/2014) (17-year term) 5,635,523 (exp. 7/30/2013, PED 1/30/2014) (17-year term) 5,648,497 (exp. 7/15/2014, PED 1/15/2015) (17-year term) 5,674,882 (exp. 7/30/2013, PED 1/30/2014) (17-year term) 5,846,987 (exp. 12/29/2012, PED 6/29/2013) 5,886,036 (exp. 12/29/2012) 5,914,332 (exp. 12/13/2015, PED 6/13/2016) 5,948,436 (exp. 9/13/2013, PED 3/13/2014) 6,037,157 (exp. 6/26/2016, PED 12/26/2016) 6,284,767 (exp. 12/13/2015, PED 6/13/2016) 6,703,403 (exp. 6/26/2016, PED 12/26/2016) 6,911,214 (exp. 11/28/2021, PED 5/28/2022) 8,501,219 (exp. 11/28/2021, PED 5/28/2022)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 5,886,036 (325 days, exp. 11/19/2013, PED 5/19/2014)
Exclusivities in Orange Book (2005 to 2018)	D-99 (exp. 4/29/2008, PED 10/29/2008) D-124 (exp. 4/27/2013)

Table 13: lopinavir; ritonavir (KALETRA tablet) (200 mg/50 mg; 100 mg/25 mg)

KALETRA tablet (NDA 21906)	USPTO Findings
Approval Date	10/28/2005
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 5,541,206 (exp. 7/30/2013, PED 1/30/2014) (17-year term) 5,635,523 (exp. 7/30/2013, PED 1/30/2014) (17-year term) 5,648,497 (exp. 7/15/2014, PED 1/15/2015) (17-year term) 5,648,597 (exp. 7/15/2014) (17-year term) 5,674,882 (exp. 7/30/2013, PED 1/30/2014) (17-year term) 5,846,987 (exp. 12/29/2012, PED 6/29/2013) 5,886,036 (exp. 12/29/2012) 5,914,332 (exp. 12/13/2015, PED 6/13/2016) 6,037,157 (exp. 6/26/2016, PED 12/26/2016) 6,284,767 (exp. 2/15/2016) 6,703,403 (exp. 6/26/2016, PED 12/26/2016) 7,148,359 (exp. 7/19/2019, PED 1/19/2020) 7,364,752 (exp. 11/10/2020, PED 5/10/2021) 8,025,899 (exp. 12/14/2027, PED 6/14/2028) 8,268,349 (exp. 8/25/2024, PED 2/25/2025) 8,309,613 (exp. 12/24/2024, PED 6/24/2025) 8,377,952 (exp. 10/20/2028, PED 4/20/2029) 8,399,015 (exp. 8/25/2024, PED 2/25/2025) 8,470,347 (exp. 4/17/2026, PED 10/17/2026) 8,691,878 (exp. 8/25/2024, PED 2/25/2025)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 5,886,036 (325 days, exp. 11/19/2013, PED 5/19/2014)
Exclusivities in Orange Book (2005 to 2018)	D-124 (exp. 4/27/2013)

Table 14: pramipexole dihydrochloride (MIRAPEX) (0.125 mg, 0.25 mg, 1 mg)

MIRAPEX (NDA 20667)	USPTO Findings
Approval Date	7/1/1997
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 4,843,086 (exp. 6/27/2006) (17-year term) 4,886,812 (exp. 6/27/2006) (17-year term) 6,001,861 (exp. 1/16/2018) 6,194,445 (exp. 1/16/2018)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 4,886,812 (1,564 days, exp. 10/8/2010)
Exclusivities in Orange Book (2005 to 2018)	I-517 (exp. 11/7/2009), M-104 (exp. 5/13/2014)

Table 15: pramipexole dihydrochloride (MIRAPEX ER Extended-Release) (0.375 mg, 0.75 mg, 1.5 mg, 3 mg, 4.5 mg)

MIRAPEX ER (NDA 22421)	USPTO Findings
Approval Date	3/19/2010
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 4,886,812 (exp. 6/27/2006) (17-year term) 7,695,734 (exp. 4/26/2028) 8,679,533 (exp. 5/1/2029)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 4,886,812 (1,564 days, exp. 10/8/2010)
Exclusivities in Orange Book (2005 to 2018)	NDF (exp. 2/19/2013), I-623 (exp. 3/19/2013)

Table 16: pregabalin (LYRICA) (25 mg, 50 mg, 75 mg, 100 mg)

LYRICA Capsule (NDA 21446)	**USPTO Findings**
Approval Date	12/30/2004
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 5,563,175 (exp. 10/8/2013) (17-year term) RE 41,920 (exp. 7/16/2017) 6,197,819 (exp. 3/6/2018) (17-year term) *Orange Book listed both U.S. Patent No. 6,001,876 and its reissue, U.S. Patent No. RE 40,667.
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent Nos.: RE 41,920 (533 days, exp. 12/31/2018, PED 7/1/2019) 6,197,819 (300 days, exp. 12/31/2018, PED 7/1/2019)
Exclusivities in Orange Book (2005 to 2018)	NCE (exp. 12/30/2009) I-535 (exp. 6/21/2010) I-651 (exp. 6/20/2015) M-193 (exp. 12/22/2019, PED 6/22/2020) NPP (exp. 5/3/2021, PED 11/3/2021)

Table 17: pregabalin (LYRICA solution) (20 mg/mL)

LYRICA Solution (NDA 22488)	USPTO Findings
Approval Date	1/4/2010
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 5,563,175 (exp. 10/8/2013) (17-year term) RE 41,920 (exp. 7/16/2017) 6,197,819 (exp. 3/6/2018) (17-year term)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent Nos.: RE 41,920 (533 days, exp. 12/31/2018, PED 7/1/2019) 6,197,819 (300 days, exp. 12/31/2018, PED 7/1/2019)
Exclusivities in Orange Book (2005 to 2018)	NCE (expired 12/30/2009) I-535 (expired 6/21/2010) I-651 (expired 6/20/2015) M-193 (exp. 12/22/2019, PED 6/22/2020) NPP (exp. 5/3/2021, PED 11/3/2021)

Table 18: pregabalin (LYRICA CR extended-release tablet) (82.5 mg, 165 mg, 330 mg)

LYRICA CR (NDA 209501)	USPTO Findings
Approval Date	10/11/2017
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: RE 41,920 (exp. 7/15/2017) 6,197,819 (exp. 3/6/2018) (17-year term) 8,945,620 (exp. 11/2/2026, PED 5/2/2027) 9,144,559 (exp. 11/2/2026, PED 5/2/2027) 10,022,447 (exp. 11/2/2026, PED 5/2/2027)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent Nos.: RE 41,920 (533 days, exp. 12/31/2018, PED 6/30/2019) 6,197,819 (300 days, exp. 12/31/2018, PED 7/1/2019)
Exclusivities in Orange Book (2005 to 2018)	NP (exp. 10/11/2020, PED 4/11/2021)

Table 19: rivaroxaban (XARELTO immediate release tablet) (10 mg)

XARELTO (NDA 22406)	USPTO Findings
Approval Date	7/1/11
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 7,157,456 (exp. 12/11/2020) 7,585,860 (exp. 12/11/2020) 7,592,339 (exp. 12/11/2020) 9,415,053 (exp. 11/13/2024, PED 5/13/2025) 9,539,218 (exp. 2/17/2034, PED 8/17/2034)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 7,157,456 (1,356 days, exp. 8/28/2024, PED 2/28/2025)
Exclusivities in Orange Book (2005 to 2018)	NCE (exp. 7/1/2016), I-660 (exp. 11/2/2015), I-661 (exp. 11/2/2015), I-662 (exp. 11/2/2015), D-168 (exp. 10/27/2020)

Table 20: rivaroxaban (XARELTO tablet) (15 mg, 20 mg)

XARELTO (NDA 202439)	**USPTO Findings**
Approval Date	11/4/2011
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 7,157,456 (exp. 12/11/2020) 7,585,860 (exp. 12/11/2020) 7,592,339 (exp. 12/11/2020)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 7,157,456 (1,356 days, exp. 8/28/2024)
Exclusivities in Orange Book (2005 to 2018)	NCE (exp. 7/1/2016), I-643 (exp. 11/4/2014)

Table 21: zolpidem tartrate (AMBIEN tablet) (5, 10 mg)

AMBIEN (NDA 19908)	USPTO Findings
Approval Date	12/16/1992
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent No. 4,382,938 (exp. 10/21/2001) (17-year term)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 4,382,938 (1,826 days, exp. 10/21/2006, PED 4/21/2007)
Exclusivities in Orange Book (2005 to 2018)	M-54 (exp. 3/29/2010, PED 9/29/2010)

Table 22: zolpidem tartrate (AMBIEN CR extended-release tablet) (6.25 mg, 12.5 mg)

AMBIEN CR (NDA 21774)	**USPTO Findings**
Approval Date	9/2/2005
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 4,382,938 (exp. 10/21/2001) (17-year term) 6,514,531 (exp. 12/1/2019, PED 6/1/2020)
Patent Term Extensions in Orange Book (2005 to 2018)	U.S. Patent No. 4,382,938 (1,826 days, exp. 10/21/2006, PED 4/21/2007)
Exclusivities in Orange Book (2005 to 2018)	NDF (expires 9/2/2008, PED 3/2/2009)

Table 23: zolpidem tartrate (EDLUAR) (5 mg and 10 mg)

EDLUAR (NDA 21997)	USPTO Findings
Approval Date	3/13/2009
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 6,761,910 (exp. 9/24/2019) 8,512,747 (exp. 9/24/2019) 9,265,720 (exp. 2/25/2031) 9,597,281 (exp. 4/6/2027)
Patent Term Extensions in Orange Book (2005 to 2018)	None
Exclusivities in Orange Book (2005 to 2018)	None

Table 24: zolpidem tartrate (INTERMEZZO sublingual tablet) (1.75 mg and 3.5 mg)

INTERMEZZO (NDA 22328)	USPTO Findings
Approval Date	11/23/11
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 7,658,945 (exp. 2/16/2025) 7,682,628 (exp. 2/16/2025) 8,242,131 (exp. 3/26/2029) 8,252,809 (exp. 2/16/2025)
Patent Term Extensions in Orange Book (2005 to 2018)	None
Exclusivities in Orange Book (2005 to 2018)	NP (exp. 11/23/2014)

Table 25: zolpidem tartrate (ZOLPIMIST) (5 mg)

ZOLPIMIST (NDA 22196)	USPTO Findings
Approval Date	12/19/2008
U.S. Patents in Orange Book (2005 to 2018)	U.S. Patent Nos.: 7,632,517 (exp. 4/12/2016) 8,236,285 (exp. 4/12/2016)
Patent Term Extensions in Orange Book (2005 to 2018)	None
Exclusivities in Orange Book (2005 to 2018)	None