Drug repurposing and the prior art patents of competitors

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Teaser: Companies filing patents for drug repurposing do this in a significantly different way than competitors who strived to protect the same indications shortly before. Nevertheless, later filings often fail due to other aspects.

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Drug repurposing, i.e. finding novel indications for established substances, has received increasing attention in industry. One challenge of repositioned drugs is obtaining effective patent protection; especially if the 'novel' indications have already been claimed by competitors within the same drug class. An analysis of the case of phosphodiesterase type 5 (PDE5) inhibitors shows that patentees of later filed patents on novel indications, even when they could not observe prior patenting of their direct competitors, filed patents for which patent examiners did not see the prior filed competitors' patents as relevant prior art, while these follower patent applications often failed due to other reasons.

Searching for new uses/indications for established drug substances is known as redirecting, repositioning, reprofiling, or repurposing of drugs [1]. The latter term is kept throughout this work. The benefits of such an approach is straightforward: as the substances have passed safety tests and have shown desirably pharmacokinetic and pharmacodynamic characteristics [2], time-to-market and the costs involved are lower than developing new molecular entities (NMEs, i.e. novel substances which had not been approved for human treatment before), which is appealing as the latter are associated with increasing development costs and about constant approval rates [2, 3]. Eighty-four percent of all drugs sold in the United States are addressing more than one indication, while an additional 6 percent have novel indications under development [4], and there are numerous examples of successful drug repurposing (e.g. [1, 5-7]). Overall, drug repurposing approaches are estimated to be accountable for industry revenues of about 20 billion US dollars in 2012 [8].

Due to the high costs involved in clinical drug development, patent protection is particularly relevant [2, 6, 9]. Companies typically file a range of new patents over the lifecycle of a product in order to extend exclusivity, often through line extensions (e.g. novel formulations addressing elderly in contrast to children) and repurposing [10 - 12], and here,

they even claim their competitors' substances from the same drug class[1] in order to block their development activities [12].

The patent system and patenting for repurposing

Before assessing the impact of such approaches on drug repurposing, a few clarifications about the patent system are in order. [2] Patentees define an invention via so-called patent claims that describe it as a combination of features, jointly defining the patents' scope. A patent application remains secret for 18 months before it gets published. Patent examination usually takes place afterwards. During this process, examiners assess novelty of the claims and their non-obviousness (i.e. the invention may not be obvious to the skilled person in the art). In case of very similar patent filings, the earlier one would be granted. Often times, patent applicants try to maximize the breadth of the patent by claiming topics broadly, which are then narrowed significantly during examination. For doing so, patent examiners search prior art (patents, scientific literature, etc.) in order to assess novelty and non-obviousness, building on published sources (and yet unpublished ones as far as on file with the same patent office), referencing back to them in their examination reports.

While patenting the same invention twice is forbidden, a later patent may be covered by the claims of an earlier one.[3] An illustrative example is a substance patent and a patent filed later claiming the use of that substance for a medical indication. As far as both patents belong to different parties, the substance patent-holder may not use its substance for the particular indication described in the later patent, and the later patents' owner may not use the substance from the earlier patent without permission (regardless of the indication).

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[1] A drug class refers to structurally similar molecules with also similar physiological effects.
[2] While patenting rules differ from country to country, the following procedures broadly describe the practice in the U.S. and Europe.
[3] As far as the later invention is novel and non-obvious in the light of the earlier one, the patent office is not concerned with this situation.

For many companies being limited in their operations by owning such dependent patents is undesired, and it may deter them from commercializing their affected products. One way to assure freedom-to-operate is early defensive publishing/strategic disclosure, i.e. publishing topics broadly (giving, for instance, many examples of use) either anonymously or attributably (linked to the publisher) to create prior art. It can take place in an easily accessible form (as scientific publication, database entry, etc.) or somewhat hidden (e.g. as a dissertation in a foreign language) [13 - 14]. As a consequence, only somewhat more specific – and narrower – patents filed later (by competitors or by the same company) may get granted – with limited exclusionary power – that then can be circumvented more easily.

Looking at patent practice in pharmaceuticals, and there, into activities taking place within a class of drugs, a patent claiming the use of a particular substance for a specific indication may be non-obvious if the use of another substance from the same class has been described for the same indication before. In fact, *"[…] many composition of matter compound patents claim a very large number of uses for the compound, even indications well beyond those initially demonstrated by the data, and therefore the "new" indication may be previously disclosed in the compound patent simply by referring them as possibilities."* [15, p. 43]. Hence, these earlier filings assure freedom-to-operate, and eventually allow obtaining broad patent protection.

Owners of such follow-on drugs inside a class, however, may change the formulation or dosing of repurposed drugs [5 - 6, 15 - 16], and, by doing so, assure novelty and non-obviousness. Proactively adjusting formulation or dosing to outmanoeuvre earlier prior art from direct competitors could mean that followers might frequently receive patents on their inventions even in the light of earlier patents claiming the same indication inside the same drug class. But do companies actually have to become proactive, or do they "naturally" file such patents?

Methodology, field of research, and data

The assessment of proactive versus "natural" filing behaviour can be accomplished by taking into account the time-lag of 18 month during which a patent application is yet unpublished. If two competitors file patents for the same indication within 18 months, and patent examiners do not consider the earlier-filed application as constituting prior art, then this would favour the "natural" filing hypothesis.

The data for the analysis builds on [12] who found the above-mentioned blocking activities. It relates to the class of phosphodiesterase type 5 (PDE5) inhibitors. Only substances were considered for the analysis that had been approved in the United States by 2011, namely sildenafil, vardenafil, and tadalafil. These substances were searched in the Chemical Abstracts (CA) database using the CAS-number, a unique ID for these substances that is supposed to be assigned for any chemical patent document, to identify all relevant patent filings. In order to elicit which content was actually claimed (unbiased by examination results), the analyses are primarily based on patent applications for assessing patentability of the later patents, and granted earlier patents to assess the legal dependence of the follower patents.

The results from the search in the CAS database were transferred to the Minesoft PATBASE database to determine which of the patents found belong to the same patent family (i.e. are based on the same idea). Manual data cleaning took place, eliminating patents that, e.g., mentioned these substances coincidentally. Patent claims were investigated in more detail for each published US patent document and the first patent document of a patent family (either an application at the European Patent Office (EPO) or via the Patent Cooperation Treaty (PCT)) to identify the nature of the claims (focusing on substances, dosing/formulations, indications, etc.). From in total 72 patent families stemming from Pfizer, Lilly, and Bayer, 58 patent families comprised indications and were, therefore, analysed. In

addition to the prior-mentioned steps, examination reports from the USPTO's Patent Application Information Retrievel (PAIR) system (where not available, from the EPO) were screened for the selected documents to elicit references made by examiners from later applications to assess their patentability.

In order to further investigate indications mentioned within the patent documents, the indications found were manually structured according to the hierarchical MeSH classification (Medical Subject Headings, a controlled thesaurus provided by the US National Library of Medicine). The MeSH thesaurus provides alternative terms/synonyms for identical indications, while its hierarchical structure also allows assessing if the terms used refer to narrower or broader indication categories, such as cardiovascular diseases in contrast to its sub-category heart failure. Taking such hierarchy into account is important for assessing the novelty of an indication. For instance, when treatment of diseases has been claimed on a superior level, it is unlikely that, later, a disease on a lower level can be still claimed successfully. However, this must not be the case the other way round, as higher level diseases may involve much more mechanisms being relevant for a disease. In case the applicant used a continuation-in-part application (CIP), which allows adding novel matter to an older, still pending patent from the same patent family, while examiners do not consider older content from the same patent family as novelty destroying or non-obvious, the new priority date for the newly added content was used, as indicated with the term CIP in the patent number column in Table 1.

Results

In total, about 180 different indications were mentioned in the dataset with, on average, about six indications in every US patent document (which have at least one indication), and each indication is mentioned in about 2.5 patent families. Four patent families have more than 40

indications and may have been filed defensively to establish freedom-to-operate as none of them was granted. Fifty indications were mentioned by at least two competitors, from which ten patent – patent pairs for eight indications were filed within a timeframe shorter than 18 months (see Table 1), with one of them involving autoimmune diseases and depression at the same time (as indications overlap, the latter relationship is indirectly also represented by the last two patent pairs). Three early patents occur twice, while among the follower patents, one appears four times in this role.

In eight of the ten patent-patent pairs, the follower patent was not granted. Overall, Table 1 reveals that the first and follower patents were, in general, of different types. There was not a single case where patent examiners considered the first patent-filings as prior art while using the earlier filing for successfully arguing against the followers' filing, and there was no situation resulting in dependent patents. For cancer as an indication, the follower patent considered cancer not as an indication for treatment, but a predecessor for fibrosis, which was supposed to be treated with PDE5 inhibitors. A somewhat similar situation occurred for the treatment of neuropathies, where the first patent considered diseases of the eye to be treated that were accompanied by neuropathies, while the follower patent explicitly discussed treatment of neuropathies.

{insert Table 1 about here}

Subsequently, three cases will be discussed for which the claims are illustrated in Table 2: two where the follower patent was granted and one case where it was not. The first case relates to autoimmune diseases. Here, the first patent application from Lilly claimed PDE5 inhibitors, including vardenafil (written with a typo) for, among others, treatment of autoimmune diseases. The second patent application from Bayer (finally not granted) claimed PDE5 inhibitors (including vardenafil as well) for treating, among others, autoimmune diseases. So far, one should expect the first patent to be considered as prior art. The patent

examination report of the followers' patent application reveals that eight patent families and three scientific publications were considered as relevant prior art. While two of the scientific publications could not be accessed (which, however, related to coronary diseases and not to autoimmune diseases), from the remaining prior art documents only one document appears to be of some relevancy regarding the focus indication: multiple sclerosis is mentioned in one Pfizer patent that the examiner cited. Interestingly, this patent was not found during the database search for assembling the dataset, and it had a priority date *later* than the filing date of the Lilly patent application. So its validity for assessing novelty and non-obviousness in this case are dubious. A further cited document deals with treating mental dysfunctions as a cause of multiple sclerosis, but it does not deal with directly treating this autoimmune disease. The follower patent application finally failed at the EPO due prior art regarding further claimed indications and was subsequently abandoned at both the EPO and the USPTO.

The second case relates to the above-mentioned example of neuropathies. In both patents sildenafil was mentioned as the substance for treatment, even the dosing areas overlap to some degree. However, in the first filing, ocular diseases are treated that are accompanied by neuropathies, while the latter are the primary indication in the second patent filing. The patent examiner once even cited the first patent filing, arguing that the eye diseases would represent neuropathies. The patentee, however, successfully argued that the mentioned eye diseases are no neuropathies. Hence, the examiner dropped this argument in later communications and focused on other mentioned indications.

In the third case, benign prostate hypertrophy is mentioned as one of several indications. The first patent refers to vardenafil as a substance, the second one to tadalafil in combination with further substances. Unfortunately, no examination report was available for this case to more thoroughly assess the situation from the examiners' perspective. It can only

be speculated that the combination of a PDE5 inhibitor with another substance was sufficient to represent non-obviousness here.

Next, the patent examiners' arguments are briefly examined for the remaining document pairs. In case of cancer, due to the above mentioned points no further check took place. For epilepsy, the examiner did not cite any other patent with the focus indication. Regarding fibrosis, the examiner of the follower patent from Bayer cited another Bayer patent on treating fibrosis that was even older than the first fibrosis patent from Pfizer. This earlier patent was not classified accordingly in the Chemical Abstracts database. However, as also a Bayer patent was cited as prior art, the commercial impact of this citation on Bayer may have been limited. For bladder disorders, the cited documents do not contain this disorder, while the examiner refers to e.g. hypertension as an indication which was also claimed. With female sexual dysfunction, the examiners did not find a relevant prior art document relating to this indication, but one of the opponents during the respective procedure at the European Patent Office came up with a document filed from a third party briefly before the Bayer patent.[4] For depression, in both cases the examiner did not cite any document on treating this indication. Remarkably, seven of the eight patents, the new indication was one of many (a scenario that was also mentioned in [15]), without discussions on specific experimental data to support the claims. For the granted patents, this was only the case for benign prostate hypertrophy, while neuropathies were discussed in detail.

Overall, these findings indicate that prior art references hardly harm granting of later-filed patents regarding the specific indication. In one case, a critical reference was involved which came from a third party that had no product on the market. While direct competitors are unlikely to grant licenses to each other, third parties with relevant patents may explicitly be

[4] This document was uncovered after inspecting two of the 25 prior art references brought forward during the opposition procedure, and no further inspection of the remaining documents took place.

willing to out-license, so the impact regarding potential blocking from these parties may be limited. In general, during patent examination the patentees could have argued more based on the novel indications that were hardly addressed by the examiners. It can only be speculated that they did not due to limited clinical data to substantiate their claims here.

Among the 58 patent families inside the drug class relating to indications, only one from Lilly, which filed relatively early for tadalafil, was subsequently granted with over 30 indications (including angina, hypertension, irritable bowel syndrome, etc.) for tadalafil, exerting blocking power with respect to this substance and freedom-to-operate that should it have made also more complicated for the competitors to overcome non-obviousness when filing these indications for their own substances – which can also be seen as one form of weak blocking. However, despite extensive upfront patenting of various indications, the drugs were only approved for three indications, but in all cases, secondary patents allowed the companies to extend market exclusivity by a few years (see Table 3). In this line, apart from looking for novel indications, the patentees filed numerous process, formulation/dosing or combination patents with the potential to extend the lifecycle of their already approved products. Finally, this demonstrates that substantial patenting effort took place for drug repurposing; only few attempts reach the market.

Apart from prior art, negative findings on the commercial profile of a drug such as side effects or competitive activities in related fields may also influence the decision not to further pursue a patent from the patentees perspective. Vice versa, it was recently found that progress in patent examination accelerates clinical trials [17].

{insert Tables 2 and 3 about here}

Conclusion

Within the class of PDE5 inhibitors, 52 patent families were filed during the observation

period, with eight events in which followers filed patents on treating the same indications as competitors without being able to observe their activities. In one of these cases, a third party (no direct competitor) had already claimed the focus indication and was considered to represent prior art. In no case, the earlier filed competitor patents on the same indication constituted prior art for the followers, which were also all of a different type, claiming e.g. drug combinations and uses instead of processes. There were also no cases where dependent patents emerged. So, patentees in drug repurposing seemingly need to worry less about earlier, unobservable patent filings from their direct competitors inside the same class as they hardly represented relevant prior art. In the same vein, earlier-filed blocking patents from competitors seemingly can be outmanoeuvred relatively easily.[5] Patentees, however, have to worry more about popular indications claimed earlier that are jointly mentioned with the novel ones, which examiners are seemingly focusing on in their arguments. Overall, naming multiple indications in combination with little experimental support seems to be a risky strategy when pursuing patent protection for these indications seriously.

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[5] While some time has elapsed since the filing of the PDE5 patents, the mechanisms of the patent system that characterize the activities observed in the data are rather general and still valid today.

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Table 1: Pairs of early and late patents filed by different patentees within 18 months, including patentees, substances claimed, type of patent, outcome of the patent examination for the follower patent applications (with respect to evaluating the earlier patent filing as prior art), and dependence of later filings on earlier ones.

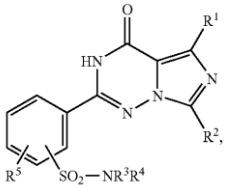
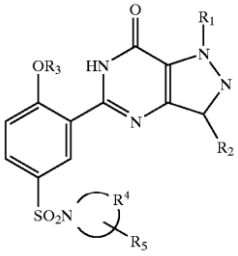
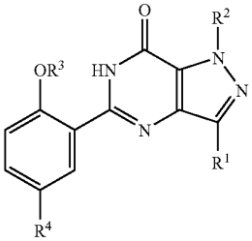
focus indication	first									follower									outcome of examination	follower patent dependent on first
	patent application#/ applicant + substance	granted patent#/ applicant+ substance	relevant priority date	publication date	type of patent application (1)	(2)	(3)	(4)	(5)	patent (appli-cation)#/ appli-cant+ substance	granted	relevant priority date	type of patent application (1)	(2)	(3)	(4)	(5)		
autoimmune disease & depression	US2006222647 (Lilly – a – CIP)	-	28-Jan-03	05-Oct-06		yes			yes	US2007299088 (Bayer – a)	no	6-Aug-04					yes	withdrawn without US exam report; EP exam report mentions other references	NA (first not granted)
neuropathy	US2002119974 (Pfizer – a)	-	28-Jul-99	29-Aug-02			yes		yes	US7338955 (Lilly - s)	yes	12-Oct-99					yes	mentions first patent application once, but not in further correspondence due to counter-arguments of patentee	No, as first does not involve direct neuropathy treatment
cancer	US2005234022 (Bayer – v)	US7276504 (Bayer – v)	27-Jul-01	20-Oct-05					yes	US2003216407 (Pfizer – a)	no	31-Jan-02			yes	yes	yes	mentioned other references cancer not directly addressed in 2nd filing as an indication but predecessor of indication	NA (first not granted)
epilepsy	US2004180941 (Pfizer – a)**	-	14-Mar-03	16-Sep-04	yes		yes	yes	yes	US2007299088 (Bayer – a)	no	6-Aug-04					yes	withdrawn without US exam report; EP exam report mentions other references	NA (first not granted)
fibrosis	US2003216407 (Pfizer – s)	-	31-Jan-02	20-Nov-03			yes	yes	yes	US2007299088 (Bayer – a)	no	6-Aug-04					yes	withdrawn without US exam report; EP exam report mentions other references	NA (first not granted)
bladder disorders*	US2005234022 (Bayer – v)	US7276504 (Bayer – v)	23-Jul-01	20-Oct-05					yes	US2003124150 (Pfizer – a)	no	6-Dec-01			yes		yes	mentioned other references	NA (first not granted)
	-	US6566360 (Bayer – v - CIP)	12-Nov-97	20-May-03					yes	US6143746 (Lilly – t)	yes	16-Sep-98				yes	yes	no exam report available; EP exam report not relevant, as indication was added via continuation-in-part application	No, as different substances are involved
female sexual dysfunction	-	US6566360 (Bayer – v)	12-Nov-97	20-May-03					yes	US2006142282 (Pfizer – s)	no	16-Dec-97				yes	yes	abandoned without examination in the US; granted in Europe, but was revoked during opposition. Neither the EP search report nor opponents cited the first patent	NA (first not granted)
depression	US2006222647 (Lilly – a – CIP)	-	28-Jan-03	05-Oct-06		yes			yes	US2004180941 (Pfizer – a)**	no	14-Mar-03	yes		yes	yes	yes	mentioned no references, EP report mentions other referen.	NA (first not granted)
	US2004180941 (Pfizer – a)**	-	14-Mar-03	16-Sep-04	yes		yes	yes	yes	US2007299088 (Bayer – a)	no	6-Aug-04					yes	withdrawn without US exam report; EP exam report mentions other references	NA (first not granted)

Types of patents: substance (1); process (2); dosing/formulation (3); combination (4); use (5)

* First line: bladder disorders/lower urinary tract syndrome (LUTS); second line: benign prostate hyperplasia (BPH).

** Other substance in combination with PDE5 inhibitors; NA – not applicable; s – sildenafil; v – vardenafil; t – tadalafil; a – PDE5 inhibitors in general

Table 2: comparison of first and follower claims

First patent family	Follower patent family
Autoimmune diseases – from Lilly 1. A method for modulating the enzymatic activity of PDE5, comprising contacting PDE5 with an effective amount of an agent that binds PDE5 and **activates or inhibits PDE5**. [claims 2-9 relate to binding mechanisms] 10. The method of claim 1 wherein the agent that binds PDE5 is selected from the group consisting of antibodies, peptides, proteins, oligonucleotides, antisense DNA and RNA, small interfering RNAs (siRNAs), non-peptide compounds, and small inorganic or organic molecules. [claim 11 relates to further binding substances] 12. The method of claim 10, wherein the agent that binds PDE5 is a small molecule selected from the group consisting of sildenafil, tadalafil, tildenafil, **vardenafit**, analogs thereof, and cGMP analogs. [claims 13-20 on methods to identify binding agents] 1. A pharmaceutical composition comprising the agent identified by any of the methods of claims 13-20 and a pharmaceutically acceptable carrier. [claims 22-28 relate to uses, recipients, routes of administration, etc.] 29. A method of treating stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, pulmonary arterial hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, malignant hypertension, pheochromocytoma, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, a peripheral vascular disease, a vascular disorder, thrombocythemia, an inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, a gut motility disorder, postpercutaneous transluminal coronary or carotid angioplasty, post-bypass surgery graft stenosis, osteoporosis, preterm labor, benign prostatic hypertrophy, irritable bowel syndrome, peptic ulcer, diseases characterized by disorders of gut motility, appetite, depression, anxiety, motor function, memory, immune function, inflammation, **autoimmune disease**, amelioration of reperfusion injury, sepsis, hypotension, and reversal of nitrovasodilator overdose including an overdose of viagra in a human or nonhuman animal subject, said method comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition of claim 21. [claim 30 relatives to routes of administration for claim 29]	*Autoimmune diseases – from Bayer* 1. The use of **PDE 5 inhibitors** for manufacturing a medicament for the treatment of cardiac ischemia, for achieving or improving a preconditioning effect, for the treatment of an acute myocardial infarction and of reperfusion damage, specifically following a myocardial infarction, for the treatment of male infertility, of Raynaud's syndrome, of intermittent claudication, of Peyronie's disease, for the treatment of fibrotic disorders, of arteriosclerosis, for improving sperm motility, for the treatment of depression, leukemia (e.g. of chronic lymphocytic leukemia), for the treatment of priapism, for the treatment of platelet adhesion and aggregation associated with renal ischemia, for supporting and promoting liver regeneration following surgical resection of the liver or associated with liver cancer, for inhibiting the contraction of esophageal muscles (e.g. associated with nutcracker esophagus or esophagospasms), for the treatment of achalasia, premature labor, female infertility and dysmenorrhea, for the treatment of liver disorders such as, for example, cirrhosis of the liver, portal hypertension, for the treatment of lupus, hypertensive systemic lupus erythematosus, scleroderma, for the treatment of multiple sclerosis, rheumatoid arthritis, allergy, **autoimmune diseases**, osteoporosis, cachexia, polycystic ovary syndrome, inflammatory bowel diseases such as, for example, Crohn's disease and ulcerative colitis, diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic cataract, hyperlipidemia and dyslipidemia, for promoting growth and improving survival of oocytes, zygotes, embryos or fetuses, for increasing the weight of premature babies, for increasing milk production in mammals, specifically in humans, for the treatment of migraine, incontinence, acute and chronic renal failure, of glomerular disease, of nephritis, tubulointerstitial disorders, glomuleropathy, hair loss, pancreatitis, amnesia, disturbances of consciousness, autism, speech disturbances, Lennox syndrome and epilepsy. 2. The use as claimed in claim 1 of compounds of the formula (I)  [… description of formula (including **vardenafil**) and R-placeholders …] [claims 3-5: further formulas and routes of administration]
Neuropathy – from Pfizer 1. A method of treating or preventing **central retinal or posterior ciliary artery occlusion** which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitor. 2. The method of claim 1 wherein the cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitor is a compound of Formula 1:  [… detailed description of chemical groups for the R-placeholders, which includes **sildenafil** as a substance…] [claims 3 – 7 describe compounds] 8. The method of claim 7 wherein the prophylactically or therapeutically effective amount of a compound of Formula 1 or a pharmaceutically acceptable salt or solvate thereof is from about	*Neuropathy – from Lilly* 1. A method for a chemotherapeutic **treatment of a neuropathy** characterized by administration to a patient suffering from neuropathy, from **1-100 mg/day** of a pharmaceutical agent comprising a compound of formula (I):  in which [… detailed description of chemical groups for the R-placeholders, which includes **sildenafil** as a substance…] wherein the neuropathy is selected from the group consisting of a peripheral diabetic polyneuropathy, gastroparesis, a toxic neuropathy, and a metabolic neuropathy. 2. The method of claim 1 wherein the pharmaceutical agent comprises a compound of formula (Ia): [… description of formula and R-placeholders …] 3. The method of claim 1 wherein the pharmaceutical agent comprises a compound of formula (III):

5 to about 250 mg/day.
[claims 9 and 10 limit the **mg/day range to 10-200 and 20-150** respectively]

1. A method of treating or preventing **central retinal vein occlusion** which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitor.

[claims 12 – 17 describe compounds comparable to claims 2-7]
[claims 18 – 21 replicate claims 8-11 with respect to claim 12]

22. The method of claim 21 wherein the patient is selected from the group consisting of: patients with elevated intraocular pressure; patients greater than about 50 years of age; **patients with family histories of optic neuropathy**; patients with hypertension; patients with diabetes; patients with family histories of diabetes or heart disease; patients who have used, or are currently using, corticosteroids that raise intraocular pressure; and patients who have undergone intraocular surgery.
23. The method of claim 21 wherein said **treating or preventing optic neuropathy does not affect the intraocular pressure of a patient**.

[claims 24-27 relate to types of neuropathies caused by different types of glaucomas]

28. The method of claim 21 wherein the cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitor is a compound of Formula 1:
[… detailed description of chemical groups for the R-placeholders, which includes **sildenafil** as a substance…]

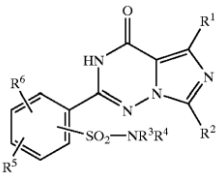
[claims 29 – 33 describe compounds]
[claims 34 – 36 replicate claims 8-10 with respect to claim 33]
[14 more claims on macular degeneration omitted here]

[formula, which is sildenafil]
or a pharmaceutically acceptable salt thereof.

4. The method of claim 1, wherein from 5-50 mg/day of said pharmaceutical agent is administered to the patient being treated.
5. The method of claim 1, wherein from 25-50 mg/day of said pharmaceutical agent is administered to the patient being treated.
6. The method of claim 1 wherein the neuropathy is selected from the group consisting of gastroparesis, a toxic neuropathy, and a metabolic neuropathy.
7. A method for a chemotherapeutic treatment of a peripheral diabetic polyneuropathy consisting of administration to a patient suffering from the polyneuropathy, from 1-100 mg/day of a pharmaceutical agent comprising a compound of formula (I):
[formula from claim 1].

Bladder disorders – BPH – from Bayer

1. A method of treating **hypertrophy of the prostate**, incontinence or female sexual dysfunction, comprising administering to a mammal an effective amount of a compound of the formula I

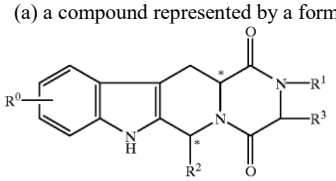


[… detailed description of chemical groups for the R-placeholders, which includes **vardenafil** as a substance…]

[… detailed description of chemical compounds and their groups for the R-placeholders, which includes **vardenafil** as a substance…]

Bladder disorders – BPH – from Lilly

1. A combination comprising:
(a) a compound represented by a formula (I)



[… detailed description of chemical groups for the R-placeholders, which includes **tadalafil** as a substance…]
(b) a second therapeutically active agent,
for simultaneous, separate, or sequential use in the treatment of condition where inhibition of a cGMP-specific PDE is of a therapeutic benefit.
[claim 2 on formulation of claim 1]
[claims 3-6 on the second active ingredient, comprising, among others, vasodilators]
[claims 7-11 on treating humans orally with PDE5 inhibitors for male and female sexual dysfunction]

12. A method of treating stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, malignant hypertension, pheochromocytoma, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, a peripheral vascular disease, a vascular disorder, thrombocythemia, an inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, a gut motility disorder, postpercutaneous transluminal coronary or carotid angioplasty, post-bypass surgery graft stenosis, osteoporosis, preterm labor, **benign prostatic hypertrophy**, or irritable bowel syndrome, in a human or nonhuman animal body, said method comprising administering to said body a therapeutically effective amount of a combination of claim 1.
13. The method of claim 12 wherein the combination is administered orally.

Table 3: Drugs inside the class of PDE5 inhibitors, indications approved in the US, and exclusivity extensions by secondary patents.

substance	indications			secondary patents	exclusivity expiration
	erectile dysfunction (ED)	pulmonary hypertension (PH)	benign prostatic hyperplasia (BPH)		
sildenafil	yes	yes		1x use patent on ED	2012 → 2019
vardenafil	yes			1x formulation patent	2018 → 2027
tadalafil	yes	yes	yes	1x substance patent	2016 → 2017
				3x formulation/dosing patent	2016 → 2020