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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KNOPP BIOSCIENCES, MICHAEL E. BOZIK, THOMAS PETZINGER JR., and VALENTIN GRIBKOFF[1]

Appeal 2019-000551
Application 13/942,695
Technology Center 1600

Before JOHN G. NEW, RYAN H. FLAX, and JAMIE T. WISZ, *Administrative Patent Judges.*

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] We use the word "Appellant" to refer to the "applicant" as defined in 37 C.F.R. § 1.142. Appellant identifies Knopp Biosciences LLC as the real party-in-interest. App. Br. 2.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Non-Final Rejection of claims 12–15 and 44–50 as unpatentable under 35 U.S.C. § 103(a) as being obvious over the combination of Lee et al. (WO 2004/010999 Al, February 5, 2004) ("Lee), Hall et. al. (US 6,156,777, December 5, 2000) ("Hall"), and Bennet et al. (WO 2003/049705 A3, June 19, 2003) ("Bennett"), as evidenced by U.S. Department of HHS FDA CDER (Guidance for Industry (July 2005)) ("FDA").

We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

NATURE OF THE CLAIMED INVENTION

Appellant's invention is directed to compositions of (R)-pramipexole and methods and kits of using such compositions for the treatment of neurodegenerative diseases, or those related to mitochondrial dysfunction or increased oxidative stress are disclosed. Abstr.

REPRESENTATIVE CLAIM

Claim 12 is representative of the claims on appeal and recites:

> 12. A single unit dose pharmaceutical composition comprising a therapeutically effective amount of R(+) pramipexole or pharmaceutically acceptable salt thereof and optionally a noneffective amount of S(-) pramipexole or pharmaceutically acceptable salt thereof, wherein the therapeutically effective amount of R(+) pramipexole or pharmaceutically acceptable salt thereof is greater than 100 mg and up to 3,000 mg and the non-effective amount of S(-) pramipexole or pharmaceutically acceptable salt thereof is less than 0.05 mg in the pharmaceutical composition, and wherein the

> pharmaceutical composition is formulated for a single unit dose administration to a human and wherein the pharmaceutical composition is therapeutically effective in treating a disease upon administration to the human.

App. Br. 17.

ISSUES AND ANALYSES

We adopt the Examiner's findings, reasoning, and conclusion that the claims on appeal are *prima facie* obvious over the cited prior art. We address the arguments raised by Appellant below.

Issue 1:

Appellant argues the Examiner erred in not providing sufficient reasons to combine the references. App. Br. 7.

Analysis

The Examiner finds that Lee teaches that S(-) pramipexole[2] is a potent dopamine agonist effective for the treatment of Parkinson's disease. Non-Final Act. 5.

The Examiner finds that Hall, like Lee, teaches that S(-) pramipexole is known to be effective to treat Parkinson's disease and other dopamine-related conditions such as Alzheimer's disease, Huntington's Chorea, vascular dementia, etc. Non-Final Act. 6 (citing Hall col. 1, ll. 20–33). The Examiner finds that Hall also teaches that the R(+) pramipexole enantiomer

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[2] Pramipexole is 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole. "S(-)" and "R(+)" (or simply "-" and "+" are its enantiomers). *See, e.g.*, Hall col. 1, ll. 14–16.

also has neuroprotective effects. *Id.* (citing Hall col. 1, ll. 52–54, col. 4, ll. 15–21). The Examiner finds that Hall teaches methods for preventing or treating neuronal damage-associated diseases comprising administering an effective amount of pramipexole as its S(-) enantiomer or R(+) enantiomers. *Id.* (citing Hall col. 2, ll. 1–14). The Examiner finds that Hall teaches a preferred dose of R(+) pramipexole of 1 mg/kg to 2 mg/kg PO, which the Examiner calculates to be 80 mg to 160 mg for an 80 kg adult, and the preferred total dose level for neuroprotection is 0.5 mg/kg/day to 20 mg/kg/day (*see* column 3, lines 5–11), which calculates to be 40 mg/day to 1600 mg/day for an 80 kg adult. *Id.* (citing Hall col. 3, ll. 5–11). The Examiner finds that Hall further teaches oral formulations in the form of tablets or capsules comprising pharmaceutically acceptable carriers. *Id.* (citing Hall col. 2, ll. 49–57).

The Examiner further finds that Bennett teaches that both enantiomers of pramipexole are effective in treating neurological diseases. Non-Final Act. 7 (citing, e.g., Bennett 1, 11). The Examiner finds that Bennett teaches that dosing of the S(-) enantiomer in humans must be limited due to its dopamine agonist activity; however the R(+) enantiomer has very little dopamine agonist activity, but, as disclosed by Hall, it retains its efficacy against neurodegenerative diseases. *Id.* (citing Bennett 4, ll. 17–23, 12, ll. 1–7). As such, the Examiner finds Bennett teaches compositions comprising either one of the enantiomers or compositions comprising mainly the R(+) enantiomer, in which the R(+) enantiomer is present from greater than 80% to greater than 99%. *Id.* (citing Bennett 9–10, ll. 16–5). The Examiner finds that Bennett also teaches that, due to its lack of dopaminergic agonistic activity, the R(+) enantiomer can be administered in

much larger quantities than the S(-) enantiomer. *Id.* (citing Bennett 12, ll. 1–7).

The Examiner finds that Bennett teaches dosages of pure (i.e., 100%) R(+) pramipexole for the treatment of either Alzheimer's disease or Parkinson's disease of about 10 mg to about 500 mg per day. Non-Final Act. 7 (citing Bennett 13–14, ll. 17–5). The Examiner finds that Bennett teaches different types of formulations, including tablet formulations for oral administration, and that the formulations can comprise pharmaceutically acceptable carriers. *Id.* (citing Bennett, e.g., 12, ll. 25–30, 15, ll. 14–23).

The Examiner concludes that, based upon the combined teachings of the cited references, it would have been *prima facie* obvious for a person of ordinary skill in the art to prepare single unit dose pharmaceutical compositions comprising between 10 mg and 650 mg of R(+) pramipexole, or 40 mg/day to 1600 mg/day, which overlaps with Appellant's claimed range of between 100 mg and 3,000 mg, as recited in Appellant's claim 12. Non-Final Act. 8.

Appellant argues that that the R(+) and S(-) enantiomers of pramipexole are used for different purposes, and that each enantiomer has different inherent activities. App. Br. 8. Appellant asserts that S(-) pramipexole is used for its dopamine agonist activity and beneficial effect in treating diseases characterized by pathologically low levels of dopamine, such as Parkinson's disease, whereas, R(+) pramipexole has been shown to have neuroprotective activity and to be useful in treating non-dopamine-dependent diseases, such as neurodegenerative diseases. *Id.* According to Appellant, S(-) pramipexole has never been shown to be useful for treating neurodegenerative diseases in humans and has only been shown to be useful

in treating neurodegenerative diseases *in vitro* and in mammals at doses and exposures that would be toxic or lethal in humans. *Id.* As such, Appellant contends, a person skilled in the art would need to limit or eliminate the amount of S(-) pramipexole in a composition when treating a non-dopamine dependent disease to avoid harmful results. *Id.*

Appellant argues that the state of the art, at the time of the present invention, was to limit the amount of S(-) pramipexole, NOT to combine it with R(+) pramipexole. App. Br. 8. Therefore, Appellant asserts, administering a composition of more than 100 mg of R(+) pramipexole would have been outside the acceptable scope of one skilled in the art at the time of the invention. *Id.*

Appellant argues further that there was no teaching or guidance in the cited prior art that would enable a skilled artisan to develop a single unit dose composition of R(+) pramipexole in an amount of greater than 100 mg and up to 3,000 mg. App. Br. 8. Appellant asserts that, at the time of the invention, such an artisan would have believed that a unit dose composition of R(+) pramipexole in such an amount would contain a dangerous amount of inherent dopamine agonist activity when administered as a single unit dose. *Id.* at 8–9. According to Appellant, the discovery that greater than 100 mg of R(+) pramipexole (up to the 3,000 mg) could be formulated into a pharmaceutical composition that is safe and effective for administration to a subject, such as a human, was completely unexpected and surprising, based upon the teachings of the prior art. *Id.* at 9. Appellant asserts that, prior to Appellant's discovery, a person skilled in the art would not have been motivated to arrive at a composition that contained greater than 100 mg and up to 3,000 mg of R(+) pramipexole specifically synthesized to contain less

than 0.05 mg of S(-) pramipexole in that composition as set forth in claim 12. *Id.*

Appellant argues further that the Examiner has the burden of identifying a teaching in the prior art that would guide or suggest to the artisan to arrive at the claimed composition. App. Br. 9. Appellant asserts that the art teaches the skilled artisan to make only a composition containing less than 100 mg of R(+) pramipexole from the large batch because only amounts less than that had any potential for viable use. *Id.*

Appellant also argues that the Examiner rejected relevant evidence that a person skilled in the art at the time of the invention would not have had any reasonable expectation of success in developing a single unit dose pharmaceutical composition containing greater than 100 mg of R(+) pramipexole. App. Br. 9. Appellant points to our reviewing court's holding in *In re Stepan Co.*, 868 F.3d 1342, 1350 (Fed. Cir. 2017), that:

> [W]hether a rejection is based on combining disclosures from multiple references, combining multiple embodiments from a single reference, or selecting from large lists of elements in a single reference, there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan would not arrive at the claimed combination.

Stepan, 868 F.3d at 1350

Appellant argues that, in the present appeal, the claimed combination is the large amount of R(+) pramipexole and little to no S(-) pramipexole. App. Br. 9. Appellant asserts that the Examiner has failed to provide the necessary references to support how one skilled in the art would have any expectation of success when arriving at the claimed single unit dose pharmaceutical composition. *Id.* To the contrary, argues Appellant, the

Examiner has been presented with evidence that one skilled in the art at the time of the invention would have had no reasonable expectation that a single unit dose of 100 mg or more of R(+) pramipexole would be therapeutic. *Id.* at 9–10. Rather, Appellant argues, the reasonable expectation of one skilled in the art at the time of the invention would have been to think that a single unit dose of 100 mg or more of R(+) pramipexole would be dangerous and not therapeutic. *Id.*

We do not find Appellant's argument persuasive. Hall teaches that:

> Pramipexole is shown to decrease slightly but significantly cAMP levels in cerebellar granular cells (3). This suggests the possible involvement of dopamine receptors (D2 family) in the mechanism of neuroprotection. To test this hypothesis, the (+) enantiomer was tested in a parallel experiment with [the (-) enantiomer of] pramipexole. The (+) enantiomer has been shown to be inactive in a battery of binding assays that involve adrenergic and serotonergic receptors, and less active in dopaminergic receptors. The results show that the (+) enantiomer is equally as potent and effective compared to pramipexole as a neuroprotective agent in this assay.
>
> The neuroprotective effects of pramipexole in L-dopa mediated toxicity in cerebellar granule cell does not appear to involve the activation of dopamine receptors.
>
> The (+) enantiomer of pramipexole shows utility as a neuroprotectant despite the fact that it shows little ability to bind to monoamine receptors.

Hall col. 4, ll. 10–27.

Bennett teaches that:

> Dosing with S(-) PPX [i.e., pramipexole] is limited in humans by its potent dopamine agonist properties and will restrict achievable brain drug levels. Because the R(+) enantiomer of PPX has very little dopamine agonist activity but may retain the

> desirable molecular/antioxidant properties of S(-) PPX, this compound is suggested herein as having utility as an effective inhibitor of the activation of cell death cascades and loss of viability that occurs in neurodegenerative diseases.

Bennett 4 (citing C.S. Schneider et al., *Dopamine Autoreceptor Agonists: Resolution and Pharmacological Activity of 2, 6 Diaminotetrahydro-benzothiazole and an Aminothlazole Analogue of Apomorphine*, 30 J. MED. CHEM. 494–498 (1987) ("Schneider")) (internal citations omitted). Bennett further teaches that:

> S(-) pramipexole, which is a potent dopamine agonist approved for the treatment of PD symptoms is the enantiomer of R(+) pramipexole. However, R(+) pramipexole lacks pharmacological dopamine activity. *Accordingly, R(+) 2-amino-4,5,6,7-tetrahydro-6-propylaminobenzathiazole and the pharmacologically acceptable salts thereof can be administered in much larger doses than S(-) pramipexole and can achieve brain levels capable of providing neuroprotection*. In accordance with one embodiment [amyotrophic lateral sclerosis] is treated by administering either R(+) or R(-) pramipexole, however the administration of R(+) 2-amino-4,5,6,7-tetrahydro-6-propylaminobenzathiazole is preferred because much higher doses can be given. As indicated in Example 1, the S(-) and R(+) isomers are approximately equipotent in reducing oxidative stress. *However the use of the R(+) isomer allows one to administer higher doses and thus achieve greater reduction in toxic oxygen free radical*.

Id. at 12 (emphases added). Bennett further teaches that:

> The use of R(+) pramipexole to treat NDD, by virtue of its being a relatively inactive stereoisomer of the dopamine agonist S(-) pramipexole (Mirapex, Pharmacia and Upjohn), solves an important problem associated with the use of S(-) pramipexole as a dopamine agonist. Dosing of Mirapex is limited by dopaminergic side effects on blood pressure and mentation. R(+)-2-amino-4,5,6,7-tetrahydro-6-propylaminobenzathiazole

> has 1% or less of the potency to produce the side effects that result from the use of S(-) pramipexole. Thus, the present invention can be administered more safely to AD patients, who are typically intolerant of even small doses of dopamine agonist medication. Also the present invention can be administered intravenously in much larger doses than S(-) pramipexole.

Id. at 13. Finally, Bennett teaches that:

> The amounts of the individual active compounds are easily determined by routine procedures known to those of ordinary skill in the art. For example, the tetrahydrobenzthiazoles of the present invention can be administered orally to humans with [neurogenerative disease] in *daily total doses between 10 mg and 500 mg*. Alternatively, the tetrahydrobenzthiazoles can be administered parenterally to humans with acute brain injury in single doses between 10 mg and 100 mg, and/or by continuous intravenous infusions between 10 mg/day and 500 mg/day.

Id. at 13–14 (emphasis added).

We quote extensively from Bennett to emphasize the point that a person of ordinary skill in the art, comprehending the teachings of Bennett would understand that, due to its much lower dopamine binding affinity, R(+) pramipexole can be safely administered at much higher dosages than S(-) pramipexole, and can therefore produce greater neuroprotective effect. We agree with the Examiner that such a skilled artisan would have therefore been motivated to treat neurodegenerative disorders with much higher dosages of R(+) pramipexole than its S(-) enantiomer, and would have had a reasonable expectation of success in so doing.

The daily dosage taught by Bennett (between 10 mg and 500 mg) falls substantially within the range recited in independent claim 12, i.e., "greater than 100 mg and up to 3,000 mg." As our reviewing court has held: "[i]n cases involving overlapping ranges, we and our predecessor court have

consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003).

Finally, Bennett teaches:

> Since approximately equivalent neuroprotective actions of pramipexole are observed in the R(+) and S(-) enantiomers, and since dopamine agonist actions reside primarily in the S(-) enantiomer, the ROS-scavenging actions likely have no relationship to dopamine agonist properties. *If this is true, then the R(+) enantiomer of pramipexole should be tolerated in much higher doses than the S(-) enantiomer used in the present study, with the potential for increased antioxidative activity in vivo*.

Bennett 24 (emphasis added).

We agree with the Examiner that these teachings of Bennett would have motivated a person of ordinary skill to explore the upper ranges of the safe daily dosage for R(+) pramipexole to maximize the beneficial neuroprotective effects of the compound while still taking advantage of the much smaller amplitude of R(+) pramipexole's affinity as a dopaminergic agonist, and that such experimentation would have been obvious. *See In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980) (holding that "discovery of an optimum value of a result effective variable ... is ordinarily within the skill of the art"). In the case of the claims on appeal, there can be little doubt that the amount of the daily dosage that can be safely employed is a result-effective variable.

We note in passing that the daily dosage amount of S(-) pramipexole need not be considered in our analysis of the claim as a necessary requirement, because the language of independent claim 12 expressly recites that the inclusion of S(-) pramipexole is optional. Therefore, the inclusion of any amount of S(-) pramipexole is neither mandatory nor limiting on the

claim. *See, e.g.*, *Cadence Pharma. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1373 (Fed. Cir. 2015).

Consequently, we do not find Appellant's argument persuasive.

Issue 2

Appellant argues that the Examiner erred by failing to consider the teachings of the combined cited prior art as a whole. App. Br. 10.

Analysis

Appellant argues that the Examiner, in finding that the references teach the claimed dose range, selects teachings from the face of the reference (in the case of Hall), or uses toxicology studies in mice to convert into purported human dose ranges (in the case of Bennett). App. Br. 10 (citing Non-Final Act. 7–8. Appellant contends that the inclusion of the claimed therapeutically-effective dosages of more than 100 mg and up to 3,000 mg of R(+) pramipexole while minimizing S(-) pramipexole to less than 0.05 mg are not arbitrary, rather, they are recited because they represent Appellant's discovery that much larger amounts of R(+) pramipexole than would have been obvious to one skilled in the art can be given as a therapeutic to a mammal, such as a human, and that the amount of S(-) pramipexole should be minimized to avoid the deleterious dopaminergic effects. *Id.* at 10–11.

Appellant points to the Declaration of Dr. John M. McCall, filed April 17, 2017 (the McCall Declaration") as opining that:

> [Appellant's] discovery that a beagle dog could tolerate doses greater than 100 mg/kg in a single dose was a key and surprising finding. Beagles are extremely sensitive to dopamine agonist

> activity; they vomit. A dose of 100 mg/kg in a dog translates, using allometric scaling, to a dose of 54 mg/kg in a human.… For a 70 kg man, this would predict a massive, but tolerable human dose on the order of 3780 mg of dexpramipexole. This was totally unexpected based on the assumed amount of dopamine agonist activity of [R(+) pramipexole] as reported in the literature.

App. Br. 11 (quoting McCall Decl. ¶ 7).

Appellant contends that the teachings of Lee and Hall must be read in context of the later discoveries of Bennett and Schneider, which teach that the understood inherent dopamine agonist activity of R(+) pramipexole limited the doses that could be administered to a human. *Id.* Appellant acknowledges that the maximum daily dose of R(+) pramipexole taught by Bennett is 500 mg and, relevantly, the maximum single unit dose of R(+) pramipexole taught by Bennett is 100 mg in a continuous IV infusion for an otherwise lethal acute brain injury. *Id.* (citing Bennett 13, 14). Appellant further argues that the maximum oral single unit dose given to a human by Bennett prior to the present invention was 30 mg of R(+) pramipexole, after a titration regimen. *Id.* (*see* Bennett 20–21, Ex. 2)

We are not persuaded. As we have explained *supra*, Bennett expressly teaches that daily doses between 10 mg and 500 mg can be administered, and this range substantially overlaps Appellant's claimed range. The specific exemplary embodiments of Bennett are not limiting upon the teachings of the reference. *See Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (holding that "all disclosures of the prior art, including unpreferred embodiments, must be considered"). And, as we have pointed out, the substantial overlap between

the daily dosages is sufficient to establish a *prima facie* conclusion of obviousness. *Peterson*, 315 F.3d at 1329.

Furthermore, although Bennett teaches a daily dosage range of between 10 mg and 500 mg, but the fact, as Appellant argues they have discovered, that humans can tolerate even higher doses, is not enough to sustain a conclusion that the claims are not *prima facie* nonobvious over the prior art. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) (holding that "[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention").

Finally we acknowledge that Bennett teaches only a daily total doses between 10 mg and 500 mg, and not as a "single unit dose," as recited in the claims on appeal. However, Appellant adduces no evidence that a person of ordinary skill in the art would have understood that a dose falling within this range could, for whatever reason, *not* be administered as a single daily dose. *See In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984) (holding that arguments and conclusions unsupported by factual evidence carry no evidentiary weight). We are consequently not persuaded by Appellant's argument in this respect.

Issue 3

Appellant argues that the Examiner erred because the phrase "a pharmaceutical composition" should be accorded patentable weight. App. Br. 11.

Analysis

Appellant argues that the terms "pharmaceutical composition" or a "single unit dose" are appropriately construed as a composition administered to a living being for treatment purposes. App. Br. 11. Appellant asserts that the Examiner incorrectly finds that the present claims read on unfinished formulations, such as those used for storage purposes and/or future use. *Id.* (citing Non-Final Act. 10). Appellant disputes the Examiner's finding, particularly with respect to those claims on appeal that are directed to a single unit dose pharmaceutical in the form of a tablet or capsule (claim 15), which is safe upon administration to a human (claim 45), is an oral dosage form (claims 46 and 47), and is comprised of pharmaceutically acceptable carriers (claims 49 and 50). *Id.* at 11–12.

Appellant notes that the Examiner has acknowledged that there is no teaching or guidance in the cited references that would motivate a skilled artisan to arrive at a pharmaceutical composition containing up to 3,000 mg of R(+) pramipexole to be administered to a human safely. App. Br. 12. According to Appellant, the fact that the pharmaceutical composition is formulated as a single unit dose for administration to a human mandates certain structural limitations; that is, the composition is small enough to be ingested, it is in a unit dosage form, and it is a medicinal preparation. *Id.* Appellant asserts that the Examiner has acknowledged that Appellant's discovery that much larger amounts of R(+) pramipexole can be given as a therapeutic to a mammal is a reason for allowing a method of administering to a human larger amounts of the R(+) enantiomer, but, Appellant contends, the Examiner does not agree to allow the composition comprising larger amounts of the R(+) enantiomer. *Id.* Appellant asserts that this is a false

distinction. *Id.* Appellant argues that the Examiner states that "the reasons for making such a formulation are numerous and not necessarily imply that such formulations will be administered as such to humans, but instead they can be formulated for storage and then when necessary divide the tablet in portions that will be required for treatment in humans." *Id.* (citing Final Office Action 13). Appellant asserts that no person of ordinary skill in the art would have been motivated to make a large dose pharmaceutical composition of greater than 100 mg of R(+) pramipexole (or 99.875% or greater pure R(+) pramipexole) because of the heretofore unforeseen utility. *Id.*

Appellant points to several U.S. district court cases in support of their contention that a pharmaceutical composition is understood by one ordinarily skilled in the art to have limitations that the composition is administered to a living being for treatment purposes, which is further emphasized by the fact that Appellant has claimed a "single unit dose" pharmaceutical composition. App. Br. 12–14. Appellant also points to the McCall Declaration, in which Dr. McCall states that "the term 'pharmaceutical composition' is understood to mean an ingestible composition provided to a patient (such as an animal or human) in an amount that provides a medicinal or therapeutic benefit to the patient (or has an acceptable benefit to side effect ratio)." *Id.* (quoting McCall Decl. ¶ 16). As such, argues Appellant, one skilled in the art at the time of the invention would not have made a pharmaceutical composition containing greater than 100 mg and up to 3,000 mg of R(+) pramipexole for human consumption. *Id.* Appellant contends that the discovery that greater than 100 mg and up to 3,000 mg of R(+) pramipexole can be formulated into a single unit dose

pharmaceutical composition that is safe and effective for administration to a subject, such as a human, is completely unexpected and surprising based upon the prior art teachings. *Id.*

We are not persuaded by Appellant's reasoning. As we have explained, Bennett expressly teaches that:

> In one embodiment a method for treating a patient having a neurodegenerative disease is provided, that simultaneously reduces the risk of dopaminergic side effects.… In one embodiment the neurodegenerative disease to be treated is selected from the group consisting of ALS, Alzheimer's disease and Parkinson's disease, and the composition is administered at a dosage of about 10 mg to about 500 mg per day of R(+) [pramipexole] or the pharmacologically acceptable salts thereof.

Bennett 13–14. Bennett, the closest prior art reference, thus expressly teaches administering a daily dose of 500 mg/day that reduces the risk of dopaminergic side effects, which substantially overlaps Appellant's claimed daily dosage range of 100 mg to 3,000 mg.

Given that the overlap of the dosage ranges between the teachings of Bennett and Appellant's claimed invention renders the claims *prima facie* obvious (*see Peterson*, 315 F.3d at 1329), we must next determine whether Appellant's discovery that the upper range of the safe dosage of R(+) pramipexole to 3,000 mg/single dosage, is sufficiently unexpected or surprising to overcome the Examiner's *prima facie* conclusion of obviousness. We conclude that it does not. As we have explained, Bennett teaches that:

> The use of R(+) pramipexole to treat NDD, by virtue of its being a relatively inactive stereoisomer of the dopamine agonist S(-) pramipexole […], solves an important problem associated with the use of S(-) pramipexole as a dopamine agonist. Dosing of

> [S(-) pramipexole] is limited by dopaminergic side effects on blood pressure and mentation. R(+)-2-amino-4,5,6,7-tetrahydro-6-propylaminobenzathiazole has 1% or less of the potency to produce the side effects that result from the use of S(-) pramipexole. Thus, the present invention can be administered more safely to AD patients, who are typically intolerant of even small doses of dopamine agonist medication. Also the present invention can be administered intravenously in much larger doses than S(-) pramipexole. Thus, it can safely be used in conditions such as stroke, where lowering of blood pressure can be detrimental.

Bennett 13.

Appellant claims no unusual or unexpected result of the 3,000 mg/day safe upper limit of R(+) pramipexole's neuroprotective effect, rather, the allegedly unexpected result is the upper safe limit itself. For the reasons we have explained *supra*, we do not find that this discovery, in itself, is enough to overcome the Examiner's conclusion that the claims are *prima facie* obvious over the prior art. *See Newell Cos. v. Kenney Mfg. Co.*, 864 F.2d 757, 769 (Fed. Cir. 1988), *cert. denied*, 493 U.S. 814 (1989) (holding that: "Although the record may establish evidence of secondary considerations which are indicia of nonobviousness, the record may also establish such a strong case of obviousness that the objective evidence of nonobviousness is not sufficient to outweigh the evidence of obviousness").

Finally, in the passages quoted above, Bennett expressly teaches the use of R(+) pramipexole as a pharmaceutical composition, as defined by Appellant. We are consequently not persuaded by Appellant's argument in this respect.

Issue 4

Appellant argues that the Examiner erred by failing to appreciate the difference between the claimed "single unit dose" and a "daily dose." App. Br. 15.

Analysis

Appellant asserts that, at the time of invention, a skilled artisan would not be motivated to administer a therapeutically effective amount of R(+) pramipexole greater than 100 mg and up to 3,000 mg as a single unit dose. App. Br. 15. Appellant argues that the cited prior art teaches an amount per day and also teaches the limitations in R(+) pramipexole dosing (whether a single dose or a daily dose) due to the understood inherent dopamine agonist activity. *Id.* Appellant argues that a single unit dose will be administered at one time point during the day, it is not a continuous intravenous administration over an extended period of time nor is it an amount delivered over multiple time points throughout the day. *Id.*

We are not persuaded by Appellant's argument. "[C]laims are interpreted in light of the specification and with the knowledge of one of ordinary skill in the art." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Appellant's Specification does not provide an express definition of the claim term "single unit dose," but discloses that:

> As used herein, the term "daily dose amount" refers to the amount of pramipexole per day that is administered or prescribed to a patient. This amount can be administered in multiple unit

> doses or in a single unit dose, in a single time during the day or at multiple times during the day.

Spec. ¶ 50. From this disclosure, we construe "single unit dosage" to mean the amount of R(+) pramipexole to be administered that is contained in a single unit dose, which is administered once or several times a day to obtain the daily dose amount. In this sense, the single unit dose is unconnected from the daily dose amount, and refers only to the means of administration. For example, a specified 400 mg daily dosage, which could be administered in multiple doses per day, could be administered as a single 200 mg pill (i.e., a single unit dose) or two 100 mg pills (i.e., a multiple unit dose) twice a day.

Furthermore, Bennett teaches that:

> In one embodiment, pramipexole, and more preferably R(+ -2-amino-4,5,6,7-tetrahydro-6-propylaminobenzathiazole is compounded with binding agents to yield tablets for oral administration, or with substances known to the art to yield a transdermal patch ("skin patch") for continuous delivery. Alternatively, pramipexole can be formulated with the necessary stabilizing agents to produce a solution that can be administered parenterally ([i.e.], intravenously, intramuscularly, subcutaneously).

Bennett cols. 8, ll. 59–67. We find that, at the very minimum, Bennett's teaching of a transdermal patch corresponds to a "single unit dose," as recited in claim 12, because all of the R(+) pramipexole to be administered in a dose can be contained within the transdermal patch.

We consequently affirm the Examiner's rejection of the claims.

DECISION

The Examiner's rejection of claims 12–15 and 44–50 under 35 U.S.C. § 103(a) is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED

Claims Rejected	35 U.S.C. §	Basis	Affirmed	Reversed
12–15, 44–50	103(a)	Lee, Hall, Bennett	12–15, 44–50	
Overall Outcome			12–15, 44–50	