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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte YAN YANG, RAJIV JANJIKHEL, NIRANJAN RAO,
ANTONIA PERICLOU, WATTANAPORN ABRAMOWITZ,
MAHENDRA G. DEDHIYA, ERHARD SEILLER,
and BERNHARD HAUPTMEIER

Appeal 2011-004737
Application 11/304,976
Technology Center 1600

Before RICHARD M. LEBOVITZ, MELANIE L. McCOLLUM, and
JACQUELINE WRIGHT BONILLA, *Administrative Patent Judges*.

BONILLA, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims directed to methods of treating Alzheimer's disease by orally administering an immediate release dosage form of memantine. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm, but designate the affirmance as a new ground of rejection under 37 C.F.R. § 41.50(b).

STATEMENT OF THE CASE

The Specification describes an immediate release dosage form of memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist (Spec. 4, 8). The Specification states that “[t]here is a need for dose-proportional memantine formulations which are readily achieved with immediate release formulations” (*id.* at 3). The Summary of the Invention discloses that memantine “can be formulated into an immediate release dosage form with dose-proportional bioavailability and advantageous stability profiles where dosage forms preferably disintegrate rapidly” (*id.* at 4). In one embodiment, a dosage form “immediately releases the active agent, for example memantine or neramexane, at a rate of about 80% or more within the first 60 minutes following entry of the dosage form into a use environment” (*id.*).

Claims 19-32 are on appeal, with claims 19 and 27 being independent. Claim 19 is representative and reads as follows (emphasis added)

19. A method of treating dementia of the Alzheimer’s type of a patient in need thereof wherein the patient is orally administered *an immediate release solid dosage form consisting essentially of about 2% w/w to about 20% w/w memantine or a salt thereof*, wherein the solid dosage form exhibits dose-proportionality and provides an in vivo plasma profile comprising a mean T_{max} of about 3 or more hours; a mean C_{max} of less than about 60 ng/ml; and a mean AUC₀₋₂₄ of more than about 350 ng h/ml wherein memantine or salt thereof is released by the solid dosage form at a rate of more than about 80% within about the first 60 minutes after administration to the patient in need thereof.

Claim 27 is directed to a similar method involving similar plasma profiles, but recites “an immediate release solid dosage form *consisting essentially of about 10mg memantine or a salt thereof and about 10% w/w to about 95% w/w microcrystalline cellulose*” (emphasis added).

The Examiner has rejected claims 19-32 under 35 U.S.C. § 103(a) as obvious over Galer et al.¹ in view of Shapiro,² as evidenced by Ntawukulilyayo et al.³

Findings of Fact (“FF”)

1. Galer describes using pharmaceutical compositions comprising a GABA analog and an NMDA receptor antagonist for the treatment of CNS disorders, such as Alzheimer’s disease (Galer 5, 11).
2. Galer states that memantine is a well-known NMDA receptor antagonist (*id.* at 2) and is “useful for potentiating the CNS disorder-treating activity of the GABA analog” (*id.* at 11; *see also id.* at 28-29, claims 1, 6).
3. Galer teaches that in certain embodiments “the pharmaceutical compositions may provide for the immediate release of the GABA analog and the NMDA receptor antagonist” (*id.* at 15; *see also id.* at 34, claim 32 (reciting “at least one nontoxic antagonist for the NMDA receptor in an immediate release form”)).
4. Shapiro discloses that the treatment of Alzheimer’s disease may be improved by use of a carbonyl trapping agent in combination with “known medicaments,” such as “memantine, dosage range from 10 mg daily to 400 mg daily” (Shapiro abstract; Example 2, col. 30, ll. 28-32; col. 35, ll. 29-30).

¹ Galer et al., WO 03/061656 A1, published Jul. 31, 2003.

² Shapiro, US 5,668,117, issued Sept. 16, 1997.

³ Ntawukulilyayo et al., *Microcrystalline cellulose-sucrose esters as tablet matrix forming agents*, 121 INTERNATIONAL JOURNAL OF PHARMACEUTICS 205-210 (1995).

5. Ntawukulilyayo describes a “tablet matrix system containing microcrystalline cellulose and sucrose esters” (Ntawukulilyayo, abstract). “Theophylline monohydrate and ibuprofen were chosen as model drugs” in the study (*id.*).

6. Ntawukulilyayo describes tablets where the “amount of drug was kept constant at 100 mg per tablet, while the amount of magnesium stearate was 8 mg per tablet and the total tablet weight was set at 500 mg” (*id.* at 206, 2nd col.). Such tablets include 20% w/w (100 mg/500 mg x 100) of the drug.

7. In certain embodiments, Ntawukulilyayo’s “tablets were compressed directly using microcrystalline cellulose and 5% (w /w) sucrose esters [] and their dissolution profile in water compared with a reference tablet containing no sucrose ester” (*id.* at 207, 2nd col.). Both types of tablets demonstrated an immediate release profile in water, where more than 80% of the drug was released within the first 60 minutes (*id.* at 1st col., Fig. 1).

Analysis

The Examiner finds that Galer and Shapiro each teaches methods of treating Alzheimer’s disease using a composition comprising an immediate release formulation of memantine, and that Shapiro describes using the claimed amounts of memantine (Ans. 4). The Examiner also finds that Ntawukulilyayo describes immediate release formulations for drugs generally, including formulations comprising the amount of microcrystalline cellulose recited in claim 27, where the formulations exhibit release profiles as recited in the independent claims (*id.*). Appellants do not dispute these findings (App. Br. 10-13; *see also* FF 1-7).

Instead, as an initial matter, Appellants argue that the “consisting essentially of” language in the independent claims excludes the addition of a second pharmaceutical active ingredient in the recited solid dosage form (App. Br. 10). Appellants correctly point out that Galer and Shapiro each describe pharmaceutical compositions comprising memantine and another active ingredient, such as a GABA analog in Galer (FF 1-3), or a carbonyl trapping agent in Shapiro (FF 4). In other words, according to Appellants, these references do not teach or suggest an immediate release composition containing memantine as the only active ingredient.

As noted by Appellants (App. Br. 10), the transitional claim phrase “consisting essentially of” indicates that “the invention necessarily includes the listed ingredients,” but also that the claim is “open to unlisted ingredients that do not materially affect the basic and novel properties of the invention.” *PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998). As further noted by Appellants (*id.*), the MPEP states that “[f]or the purposes of ... applying prior art ..., absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, ‘consisting essentially of’ will be construed as equivalent to ‘comprising’” (MPEP 2111.03; *see also PPG*, 156 F.3d at 1355 (stating that “PPG could have defined the scope of the phrase ‘consisting essentially of’ for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention.”)).

In this regard, Appellants argue that “[i]t is clear from the specification and the claims that the basic and novel characteristics are oral

dosage forms with amounts of memantine and pharmacokinetic profiles that will be safe and effective for the treatment of Alzheimer's disease" (App. Br. 11). Appellants then assert that the Specification only describes "monotherapy treatment with memantine and pharmacokinetic profiles based on administering only memantine" (*id.*). Because the Specification is silent regarding the combination of memantine with another active ingredient, according to Appellants, "it is clear from the specification that dosage forms 'consisting essentially of' memantine or salt thereof *exclude* other pharmaceutically active agents" (*id.*).

The Specification and claims, including the Specification's discussion of prior art, however, indicate that the basic and novel characteristic of the claimed invention is not the use of memantine to treat Alzheimer's disease. For example, the Specification mentions using memantine for the treatment of CNS diseases generally, such as Alzheimer's disease, in the context of discussing what was known in the art (*see, e.g., id.* at 8 (stating "[m]emantine has been approved in the United States for the treatment of Alzheimer's Disease"); *see also id.* at 21).

On the other hand, the Specification discusses prior art dosage forms of memantine that comprises an instant release component and an extended release component and/or exhibit a non-dose proportional release profile (Spec. 2-3). In this context, the Specification states that "[t]here is a need for dose-proportional memantine formulations which are readily achieved with immediate release formulations" (*id.* at 3). Consistently, the rest of the Specification describes immediate release dosage formulations exhibiting "dose-proportional bioavailability and advantageous stability profiles where

dosage forms preferably disintegrate rapidly” (*id.* at 4). The “Summary of the Invention” repeatedly characterizes the “present invention” as an “immediate dosage form” of either the claimed memantine, or another 1-aminocyclohexane, neramexane (*id.* at 4-5). Thus, the basic and novel characteristic of the claimed invention is the use of an immediate release dosage form of memantine exhibiting a certain dose-proportional release profile.

Appellants imply that the addition of a second pharmaceutical active ingredient materially changes the basic and novel characteristics of a method involving the claimed immediate release dosage form (App. Br. 11; Reply Br. 2). In this case, where the Specification clarifies the basic and novel characteristic of the claimed method, Appellants have “the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant’s invention.” MPEP 2111.03; *see also In re De Lajarte*, 337 F.2d 870, 830-31 (CCPA 1964). In other words, Appellants have the burden to show that including a second active ingredient, such as a GABA analog or carbonyl trapping agent (as described in Galer and Shapiro, respectively), impacts the immediate release profile of a solid formulation with the claimed release characteristics containing only memantine as the active agent. For example, Appellants could have (but have not) provided evidence that a composition comprising an immediate release memantine component (as described in the Specification, and suggested by Galer and Shapiro, in view of *Ntawukulilyayo*) *and* a second active ingredient (such as disclosed in Galer

and Shapiro) would fail to exhibit the dose-proportionality and plasma profiles recited in the claims.

Instead, Appellants state that the “treatment of a patient with a single pharmaceutical agent is significantly different than treatment with more than one pharmaceutical agent. The effects of multiple drugs administered to a patient and drug-drug interactions make combination therapy materially different than any methods that use a single active agent” (App. Br. 11; *see also* Reply Br. 2). Such statements assert that the treatment of Alzheimer’s disease differs depending on whether one drug or two is administered. These statements do not discuss, or provide evidence as to, what happens to memantine release profiles when one includes another drug in a dosage form. In addition, such statements do not suggest or establish that including a second active ingredient impacts the immediate release profile of a first drug in a relative dosage form. In the absence of any evidence germane to a change in the basic and novel characteristic at issue, i.e., the immediate release profile of memantine or its salt, Appellants do not meet their burden, as required in the present case. *In re De Lajarte*, 337 F.2d at 830-31.

Appellants additionally argue that even if the “consisting essentially of” language permits including a second active ingredient, the cited references fail to render the claims obvious (App. Br. 12-13). Appellants argue that “[n]one of the cited references discloses or suggests *any* specific compositions comprising memantine” (*id.* at 12). Specifically, according to Appellants, the references “do not indicate which parameters are critical, provide any direction as to which of the many possible choices would lead to

the claimed invention, or provide a reasonable expectation that the claimed invention would be successful” (*id.* at 12-13; Reply Br. 3-4).

We conclude, however, that the Examiner establishes a *prima facie* case of obviousness. Galer and Shapiro both teach using a composition comprising an immediate release form of memantine to treat Alzheimer’s disease (FF 1-4). In addition, Ntawukulilyayo describes how to make immediate release formulations having a relevant release profile (i.e., that release drug at a rate of more than about 80% within the first 60 minutes), where the drug corresponds to 20% of the formulation (FF 6). Shapiro further describes using a dosage range of memantine “from 10 mg daily” (FF 4). Appellants do not submit evidence or argument that persuades us that the Examiner has failed to establish obviousness by a preponderance of the evidence when we consider the “totality of the record.” *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). For example, Appellants do not explain how/if an immediate release formulation of memantine (combined with a second drug, for example), prepared in view of the teachings of Ntawukulilyayo, would fail to generate a dosage form exhibiting the drug release profile recited in the claims.

Thus, we affirm the Examiner’s conclusion of obviousness regarding claims 19 and 27. Because Appellants do not provide any additional arguments in relation to dependent claims 20-26 and 28-32 (App. Br. 13), we likewise affirm the obviousness rejection regarding these claims as well. 37 C.F.R. § 41.37(c)(1)(vii).

Because our reasoning in relation to the transitional phrase “consisting essentially of” differs in certain respects from that of the Examiner (Ans. 5

(construing “consisting essentially of” as “comprising”)), however, we designate our affirmance as a new ground of rejection.

SUMMARY

We affirm the rejection of claims 19-27 as obvious over Galer in view of Shapiro, as evidenced by Ntawukulilyayo. Because our reasoning differs from, or at least expands upon, the Examiner’s reasoning, however, we designate the affirmance as a new ground of rejection.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b). 37 CFR § 41.50(b) provides that “[a] new ground of rejection ... shall not be considered final for judicial review.”

37 CFR § 41.50(b) also provides that the Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

(1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner

(2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record

AFFIRMED; 37 C.F.R. § 41.50(b)

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