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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JAN-OLOF KARLSSON and ROLF ANDERSSON

Appeal 2019-001376
Application 13/379,468
Technology Center 1600

Before ERIC B. GRIMES, DEBORAH KATZ, and
MICHAEL A. VALEK, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge.*

DECISION ON APPEAL

Appellant[1] submits this appeal under 35 U.S.C. § 134(a) involving claims to a method of reducing uptake of manganese to the brain of a patient. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies PledPharma AB as the real party in interest. Appeal Br. 1.

STATEMENT OF THE CASE

The Specification states as follows:

> The present invention relates to pharmaceutical compositions and therapeutic methods employing a combination of a manganese complex of a dipyridoxyl compound, for example, MnDPDP (Manganese N,N'-bis-(pyridoxal-5-phosphate)-ethylenediamine-N,N'-diacetic acid) or other manganese complexes of Formula I . . . as a first component, and a non-manganese-containing compound of Formula I . . . for example DPDP, as a second component, as therapeutic agents.

Spec. ¶ 1.[2] According to the Specification, this combination exhibits "surprising advantages" as it "can increase the amount of excreted manganese, reduce the amount of free manganese in the patient, and/or increase the amount of therapeutic metabolite produced in vivo, as compared with the effects obtained by administration of the first manganese complex compound only, in the absence of the second non-manganese-containing component." *Id.* ¶ 16.

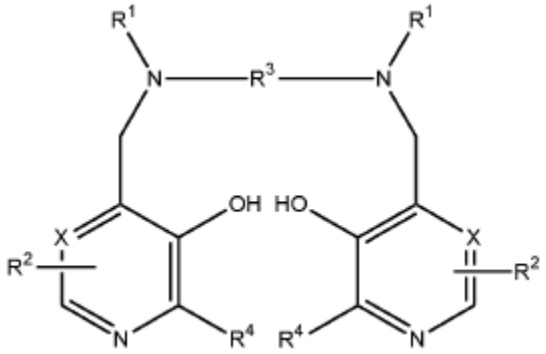
Claims 2, 4, 5, 8–11, 14–16, 25, 26, 29, 30, 34–37, and 46–52 are on appeal and can be found in the Claims Appendix of the Appeal Brief. Claim 11 is representative of the claims on appeal. It reads as follows:

> 11. A method of reducing uptake of manganese to the brain of a patient when a pathological condition in a patient caused by superoxide radicals is treated by administration of a manganese complex of a compound of Formula I in an amount effective to treat the pathological condition, the method comprising administering, as a second component, a compound of Formula I or a non-manganese metal complex of a

[2] Herein, we use the same acronyms "MnDPDP" and "DPDP" to refer to manganese N,N'-bis-(pyridoxal-5-phosphate)-ethylenediamine-N,N'-diacetic acid and N,N'-bis-(pyridoxal-5-phosphate)-ethylenediamine-N,N'-diacetic acid respectively.

compound of Formula I in an amount effective to reduce uptake of manganese to the brain of the patient as compared with administration of the manganese complex in the absence of the second component, wherein the second component is administered in an amount of about 1 to 20 μmol/kg body weight, wherein the manganese complex and the second component are included in a manganese complex:second component molar ratio in the range of about 1:1 to 1:10, and wherein the administration of the manganese complex and/or the administration of the second component are optionally together with one or more physiologically acceptable carriers and/or excipients,

Formula I



wherein
X represents CH,
each R^1 represents $–CH_2COR^5$;
R^5 represents hydroxyl;
each R^2 independently represents ZYR^6 wherein Z represents a bond, CH_2 or $–CH_2O–$;
Y represents a bond or an oxygen atom;
R^6 is a hydrogen atom, $COOR^8$, alkyl, alkenyl, cycloalkyl, aryl or aralkyl group optionally substituted by one or more groups selected from $COOR^8$, $CONR^8_2$, NR^8_2, OR^8, $=NR^8$, =O, $OP(O)(OR^8)R^7$ and OSO_3M;
R^7 is hydroxyl, optionally hydroxylated, optionally alkoxylated alkyl or aminoalkyl group;
R^8 is a hydrogen atom or an optionally hydroxylated, optionally alkoxylated alkyl group; provided that each ZYR^6 includes a $–CH_2O–$ linkage to the respective pyridine ring;

> M is a hydrogen atom or one equivalent of a physiologically tolerable cation;
> R^3 represents ethylene; and
> each R^4 independently represents hydrogen or C_{1-3} alkyl.

Appeal Br. 56–57.

Appellant seeks review of Examiner's rejection of claims 2, 4, 5, 8–11, 14–16, 25, 26, 29, 30, 34–37, and 46–52 under 35 U.S.C. § 103 as unpatentable over Towart[3] in view of Crossgrove[4] and Vander Elst.[5] Appeal Br. 9.

The issue is: Does the preponderance of evidence of record support Examiner's conclusion that the cited prior art renders obvious the claimed methods of reducing uptake of manganese to the brain?

Analysis

Examiner finds Towart teaches that "MnDPDP and DPDP have protective effects against doxorubicin-induced cardiotoxicity at doses" within the range recited in Appellant's claims. Non-Final Act. 5. While acknowledging that Towart does not teach administering both DPDP and MnDPDP in combination, Examiner determines it is "'*prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.'" *Id.* (quoting MPEP § 2144.06). In addition, Examiner finds "Crossgrove establishes that chelation therapy was a known

[3] US 6,147,094, issued Nov. 14, 2000 ("Towart").
[4] Janelle Crossgrove et al., *Manganese Toxicity Upon Overexposure*, NMR Biomed., Vol. 17, 544–553 (2004) ("Crossgrove").
[5] Luce Vander Elst et al., *Spectroscopic and Metabolic Effects of $MnCl_2$ and MnDPDP on the Isolated and Perfused Rat Heart*, Investigative Radiology, Vol. 32 (10) 581–588 (1997) ("Vander Elst").

method for reducing Mn neurotoxicity and increas[ing] Mn excretion" and that Vander Elst teaches that "the effects of MnDPDP are blocked by an excess of strong chelators, such as DPDP." *Id.* at 6–7. Based on those findings, Examiner concludes it would have been "obvious for a person of ordinary skill in the art to . . . administer DPDP in combination with MnDPDP to reduce Mn neurotoxicity in the brain in a method of reducing the cardiotoxicity of an anti-tumor agent" and that the claimed effect of "'reducing uptake of manganese to the brain of a patient' will naturally flow from the teachings of (or method made obvious by) the prior art." *Id.* at 7–8.

Appellant argues that Towart does not teach "a method using both a manganese complex of Formula I in an amount effective to treat a pathological condition, and, as a second component, a compound of Formula I or a non-manganese metal complex of a compound of Formula I" within the recited molar ratio. Appeal Br. 15–16. Appellant urges that it would not have been obvious to combine MnDPDP and DPDP, as articulated by Examiner, because "the *in vivo* effects of mixtures of two or more compounds are not always predicable." *Id.* at 17 (citing Declaration of Robertson Towart dated June 17, 2015 ("Towart Decl.") ¶ 8). According to Appellant, Towart's examples show that MnDPDP and DPDP "possess a bell-shaped dose-response curve, i.e., the protective effect gradually disappears at higher dose-levels" and therefore "there is no expectation that adding the effect of DPDP to the effect of MnDPDP results in a better effect than that of MnDPDP alone." *Id.* at 18–19 (quoting Declaration of Jan-Olof Karlsson dated Feb. 8, 2014 ("Karlsson Decl.") ¶¶ 13–15). Moreover, Appellant cites evidence that "DPDP itself is more toxic than MnDPDP" and "one skilled in the art would have avoided its use, especially in place of the

less toxic, more effective, MnDPDP, and thus, using the two compounds in combination was by no means obvious." *Id.* at 20–22 (citing Towart Decl. ¶¶ 6, 12).

Appellant further contends that Crossgrove "does not teach that chelation therapy 'was a known method for reducing Mn neurotoxicity' as asserted by the Examiner, but rather . . . Crossgrove teaches there is no cure for Mn neurotoxicity" and questions "the efficacy of chelate treatment." Appeal Br. 23. In addition, Appellant argues that Crossgrove's teachings are "directed to alleviating Mn neurotoxicity," as opposed to "'preventing manganese neurotoxicity from occurring upon administration of MnDPDP, i.e., protecting a patient from manganese-toxicity, as described in this patent application.'" *Id.* at 24 (quoting Declaration of Dr. Michael Aschner dated Sept. 9, 2014 ("Aschner Decl.") ¶ 6). Moreover, even if one were to consider chelation therapy to prevent manganese neurotoxicity, Appellant urges "one skilled in the art would not look to use DPDP in chelation therapy as manganese readily dissociates from DPDP in vivo, which causes the manganese poisoning by MnDPDP in the first place." *Id.* at 24–25.

Finally, Appellant contends the teachings in Vander Elst relate to an "ex vivo rat heart perfused with an artificial buffer," which cannot be compared to the recited in vivo method of reducing manganese uptake to the brain because, inter alia, the "ex vivo release of Mn^{2+} from DPDP" is much lower than the in vivo release rate and the "ex vivo rat heart" model in Vander Elst "does not contain Zn^{2+}." *See* Appeal Br. 25–29 (quoting Declaration of Robert H. Muller dated Sept. 30, 2014 ("Muller Decl.") ¶¶ 4–6). In particular, Appellant points to "Example 4 in the specification which shows that the DPDP appears to chelate with zinc, not manganese" and that

"the excess DPDP (or other second component in the method of claim 11), up to about 10:1 molar ratio" for the claimed method "is surprisingly low." *Id.* at 33. According to Appellant, these results, as well as the other examples in the Specification, undermine the theory behind Examiner's rejection. *See id.* at 33–37.

Upon considering the evidence cited by Examiner, and the evidence presented by Appellant, we are persuaded by Appellant's arguments and determine that the preponderance of the evidence of record does not support Examiner's conclusion of obviousness. In particular, Appellant presents persuasive argument, backed by substantial declarant evidence, to explain why it would have not been obvious to administer MnDPDP and DPDP in combination over the teachings in the cited prior art. *See* Appeal Br. 17–22 (citing Towart Decl. and Karlsson Decl.). Thus, while Examiner is correct that "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose," Appellant has rebutted that showing with evidence to the contrary. *See* Non-Final Act. 5; Ans. 15 (quoting MPEP 2144.06).

We are likewise persuaded by Appellant's arguments and evidence distinguishing Crossgrove and Vander Elst. Specification Examples 1–3 show that the combination of MnDPDP and DPDP within the claimed dosage and molar ranges results in increased manganese excretion in the urine and lower amounts of manganese in the brain as compared to administration of MnDPDP alone. Spec. ¶¶ 43–52. Example 4 supports Appellant's argument that this results from "unpredictable pharmacokinetic effects," i.e., the binding of Zn^{2+} by DPDP to stabilize the release of

manganese from MnDPDP under in vivo conditions. *See* Appeal Br. 35; Spec. ¶ 55. Neither Vander Elst, nor Crossgrove, support that one of skill in the art would have reasonably expected such results. Examiner finds the results in the Specification are "not commensurate in scope with the instant claims" because they show results for only "[a] single dose and ratio." Ans. 45. But Appellant does not rely on those results to distinguish the recited molar ratio range over an overlapping range taught in the prior art because, as Appellant points out, none of the cited references teach the combination of a compound of Formula I and a manganese complex of Formula I in any amount. *See* Appeal Br. 35 ("The Examples are not provided to show the criticality of a claimed range over a prior art disclosed range. As the combination of Towart, Crossgrove and Vander Elst does not disclose or suggest a therapeutic method using a combination of MnDPDP and DPDP . . . ."). Here, Appellant's data, and supporting declarations, sufficiently demonstrate that the combination of components, as recited in claim 11, provides unexpected results as compared to the teachings in the cited combination of references.

For these reasons, we determine that the preponderance of the evidence does not support Examiner's obviousness rejection of claim 11. Examiner's rejection of the other independent claims, i.e., claims 9 and 51, is premised on the same findings as claim 11. *See* Non-Final Act. 9–11. Accordingly, we reverse the rejection of claims 9 and 51, as well as dependent claims 2, 4, 5, 8, 10, 14–16, 25, 26, 29, 30, 34–37, 46–50, and 52, for the same reasons.

DECISION SUMMARY

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
2, 4, 5, 8–11, 14–16, 25, 26, 29, 30, 34–37, 46–52	103	Towart, Crossgrove, Vander Elst		2, 4, 5, 8–11, 14–16, 25, 26, 29, 30, 34–37, 46–52

REVERSED