

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte JAN BUCH

Appeal No. 2006-1304
Application No. 10/214,058

HEARD April 6, 2006

Before SCHEINER, ADAMS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a pharmaceutical composition comprising atorvastatin and amlodipine. The examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 134. Because we conclude that the prior art would have led those skilled in the art to combine atorvastatin and amlodipine in a single composition, we affirm the rejections with respect to all claims except claim 144.

Background

“The conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate is an early and rate-limiting step in the cholesterol biosynthetic pathway. This step is catalyzed by the enzyme HMG-CoA reductase. Statins inhibit HMG-CoA

reductase from catalyzing this conversion. As such, statins are collectively potent lipid lowering agents.” Specification, page 1. The hemicalcium salt of one such statin, or “[a]torvastatin calcium, disclosed in U.S. Patent 5,273,995 . . . is currently sold as Lipitor®.” Id.

“Amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers. As such, amlodipine [and] amlodipine besylate . . . have utility as antihypertensive agents and as antiischemic agents. Amlodipine and its pharmaceutically acceptable acid addition salts are also disclosed in U.S. Patent No. 5,155,120 as having utility in the treatment of congestive heart failure. Amlodipine besylate is currently sold as Norvasc®.” Id., page 2.

“Jukema et al., Circulation, 1995 (Suppl. 1), 1-197, disclose that there is evidence that calcium channel blockers act synergistically in combination with lipid lowering agents (e.g., HMG-CoA reductase inhibitors), specifically pravastatin. Orekhov et al., Cardiovascular Drugs and Therapy, 1997, 11, 350 disclose the use of amlodipine in combination with lovastatin for the treatment of atherosclerosis.” Id., page 5.

Discussion

1. Claim construction

Claims 1-3 and 118-147 are pending and on appeal. The claims subject to each rejection will stand or fall together because Appellant has not argued any of the claims separately. See 37 CFR § 41.37(c)(1)(vii). Claim 1 is representative and reads as follows:

1. A single pharmaceutical composition comprising:
 - a. an amount of amlodipine or a pharmaceutically acceptable acid addition salt thereof;

- b. an amount of atorvastatin or a pharmaceutically acceptable salt thereof;
and
- c. a pharmaceutically acceptable carrier or diluent.

Thus, claim 1 is directed to composition comprising amlodipine (or a salt thereof), atorvastatin (or a salt thereof), and a pharmaceutically acceptable carrier.

2. Obviousness in view of Roth, Lazar, and Jukema

The examiner rejected claims 1, 3, 118-120, 124, 125, and 128-141 under 35 U.S.C. § 103 on the basis that the claimed subject matter would have been obvious in view of Roth,¹ Lazar,² and Jukema.³ The examiner relies on Roth and Lazar for their respective teachings of atorvastatin and amlodipine. See the Examiner's Answer, pages 4-5. The examiner relies on Jukema as evidence that a person of ordinary skill in the art would have been led to combine the known compounds and thereby create the composition defined by claim 1. See *id.*, pages 6-8.

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). "[I]dentification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant." In re Kotzab, 217

¹ Roth, U.S. Patent 5,273,995, issued December 28, 1993.

² Lazar et al., U.S. Patent 5,155,120, issued October 13, 1992.

³ Jukema et al., "Evidence for a synergistic effect of calcium channel blockers with lipid-lowering therapy in retarding progression of coronary atherosclerosis in symptomatic patients with normal to moderately raised cholesterol levels," Arteriosclerosis, Thrombosis, and Vascular Biology, Vol. 16, pp. 425-430 (1996).

F.3d 1365, 1370, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000). A finding of motivation to combine must be supported by a preponderance of the evidence. See In re Kahn, 441 F.3d 977, 989, 78 USPQ2d 1329, 1337 (Fed. Cir. 2006).

In this case, the claims require the combination, in a single pharmaceutical composition, of amlodipine and atorvastatin. Appellant does not dispute that Roth discloses atorvastatin or that Lazar discloses amlodipine. See the Appeal Brief, page 5 (“Appellant recognizes that the two specified agents were known per se.”).

The central issue in this appeal is whether those skilled in the art, without the benefit of the present disclosure, would have been led to combine the known compounds in the manner claimed. We conclude that Jukema’s teachings, as read by those of ordinary skill in the art, would have led the skilled artisan to make the claimed composition. See In re Hedges, 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed. Cir. 1986) (When determining obviousness, “the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill.”).

Jukema provides a retrospective analysis of a study that had been “designed to determine the effect of lipid-lowering therapy with pravastatin.” Abstract. Jukema analyzes the results found in patients who had been given pravastatin as part of the previous study and who also had been taking any of several calcium channel blockers (CCBs) at the same time. See the abstract (“To assess whether the two therapies may have an additive or synergistic beneficial effect on human atherosclerosis, we reviewed in this regard the data of the angiographic Regression Growth Evaluation Statin Study (REGRESS) trial.”).

Jukema discloses that, out of the 885 patients in the REGRESS trial (page 426, under “Results”), 536 were taking CCBs (*id.*, under “Calcium Channel Blocker Comedication Results.”). That is, roughly 60% of the patients in both the placebo and pravastatin groups were also taking a CCB.

Jukema discloses that “with respect to MOD [minimum obstruction diameter; see page 426, left-hand column], patients in the pravastatin group had on average 0.05 mm . . . less progression if cotreated with CCBs compared to no CCB cotreatment. . . . With respect to new lesion formation, in the pravastatin group, there were 50% . . . fewer patients with new lesions if cotreated with CCBs compared with no CCB cotreatment.” Page 427, paragraph bridging the columns.

Jukema also separately analyzes the data relating to patients taking a dihydropyridine CCB (nifedipine, amlodipine, or “another dihydropyridine CCB”) and those taking a nondihydropyridine CCB (diltiazem or verapamil) (page 426, under “Calcium Channel Blocker Comedication Results.”). Jukema reports that a “beneficial effect of CCB treatment together with pravastatin therapy was evident” for both types of CCBs “regarding the effect on MOD and percent of patients with new lesions. . . . No beneficial effect was found for either type of CCB treatment on 2-year event-free survival. If there was any effect on event-free survival, it was in favor of no CCB treatment; however, this was not statistically significant.” Page 428, paragraph bridging the columns.⁴

⁴ Jukema also notes that “any trend to more clinical events in the CCB groups can be largely explained by the higher number of unscheduled CABG [coronary artery bypass graft surgery; page 426, left-hand column] procedures in the nondihydropyridine CCB group.” Page 428, right-hand column.

Jukema prefaces its conclusions with two caveats: “Whether all CCBs or only some of these drugs are capable of extending the antiatherosclerotic effect of pravastatin is not yet known,” and “[t]he REGRESS trial was not designed to study the effect of CCB administration. In this regard, it is a retrospective analysis and therefore no definite conclusions can be drawn concerning the beneficial effect of adding a CCB to lipid-lowering therapy.” Page 429, right-hand column.

Jukema concludes that, “[r]ecognizing these limitations, it may be stated that this is the first report to provide substantial evidence that CCBs may have a beneficial effect on the evolution of coronary atherosclerosis in patients treated with lipid-lowering therapy. Our results appear to warrant a prospective randomized trial to determine in a more definitive manner the merits of this combination in the prevention of progression of coronary atherosclerosis.” Id.

We recognize that Jukema attaches some conditions to the conclusions it draws from the data of the REGRESS study. Research papers published in peer-reviewed scientific journals are often cautious about drawing conclusions that go beyond the specific data presented. See, e.g., Bakker-Arkema:⁵

Atorvastatin . . . appears to be unique in the magnitude of the associated decrease in VLDL-C. . . . This well-tolerated drug, therefore, may provide single-agent therapy for some of the most difficult problems faced in clinical lipidemiology. . . . Specific explanations for the differences in efficacy are under study. However, at this time, atorvastatin appears to offer greater efficacy in the reduction of triglycerides, LDL, and VLDL levels than other reductase inhibitors with similar safety profiles.

⁵ Bakker-Arkema et al., “Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia,” Journal of the American Medical Association, Vol. 275, pp. 128-133 (1996).

Page 133, right-hand column. Notwithstanding that Jukema shows the professional caution expected in such publications, we agree with the examiner that the reference would have suggested, to those skilled in the art, the combination of atorvastatin with amlodipine. Several factors support this conclusion.

First, Jukema would have suggested amlodipine to those skilled in the art because Jukema's study involved only four named calcium-channel blockers: nifedipine, amlodipine, diltiazem, and verapamil. Thus, those skilled in the art would have recognized that Jukema's conclusion that "the addition of CCBs to 3-hydroxy-3-methyl-glutaryl-coenzyme[A] reductase inhibitor therapy (pravastatin) acts synergistically in retarding the progression of established coronary atherosclerosis" (abstract), applies equally to each of the four named CCBs. Cf. In re Petering, 301 F.2d 676, 681-82, 133 USPQ 275, 280 (CCPA 1962) (disclosure of a small genus is equivalent to disclosure of each member of the genus).

Second, Jukema would have reasonably suggested to those skilled in the art the substitution of atorvastatin for Jukema's pravastatin, because those skilled in the art appear to have considered all statins to be roughly equivalent. The instant specification itself supports this conclusion, in its statement that "[s]tatins inhibit HMG-CoA reductase from catalyzing this conversion. As such, statins are collectively potent lipid lowering agents." Page 1 (emphasis added). The specification provides evidence that, at the time the application was filed, statins were considered as a group to have similar lipid-lowering effects.

This interpretation is confirmed by the Orekhov abstract.⁶ The Orekhov abstract states that “[i]n the frame of the Regression Growth Evaluation Statin Study (REGRESS) trial synergistic anti-atherogenic effect of lipid antagonists has recently been shown.” The researchers “tried to elucidate the mechanism of more pronounced effect of statin-calcium antagonist combination on atherosclerotic lesion.” Even though they were building on the REGRESS trial, however, the authors did not use the pravastatin that had been used in that trial; instead, they used another statin (lovastatin). The Orekhov abstract therefore provides evidence that those skilled in the art considered pravastatin and lovastatin to be equivalents. In addition to the instant specification’s statement that all statins are HMG-CoA reductase inhibitors and lipid-lowering agents, the abstract provides further evidence that those skilled in the art considered statins to be equivalents for purposes of lipid-lowering therapy.

Finally, Jukema 1995⁷ provides further evidence that those skilled in the art would have interpreted Jukema’s results to be significant, notwithstanding the caveats attached to the Jukema paper. Jukema 1995 presents the results of a review of the REGRESS trial data and reports that in patients taking pravastatin “less progression . . .

⁶ Orekhov et al., “Anti-atherogenic effect of calcium antagonist plus statin combination,” Cardiovascular Drugs and Therapy, Vol. 11, pp. 350 (1997). The Orekhov abstract is cited in the specification (page 5) and was submitted in the Information Disclosure Statement filed January 15, 2003. We note that this reference, an abstract, was published before the effective filing date of the present application, in contrast to the full-text Orekhov paper (Orekhov et al., “Antiatherosclerotic and antiatherogenic effects of a calcium antagonist plus statin combination: amlodipine and lovastatin,” Int’l Journal of Cardiology, Vol. 62 (Suppl. 2), pp. S67-S77 (Dec. 31, 1997)). See the Supplement to Appeal Brief, filed January 11, 2005, page 3.

⁷ Jukema et al., “Evidence for a synergistic effect of calcium channel blockers with lipid lowering therapy in retarding progression of coronary atherosclerosis in symptomatic patients,” Circulation, Suppl. 1, pp. I-197 (1995). Jukema 1995 appears to be an abstract of a presentation at a meeting (the top of the page bears the heading “Abstracts from the 68th Scientific Sessions”) that summarizes the results presented in the Jukema paper, published in 1996. Jukema 1995 was cited in the specification (page 5) and made of record in the IDS filed January 15, 2003.

and less new lesion formation . . . was observed if co-treated with CCBs as compared to PRAV [pravastatin] alone. . . . This is the first report which shows that CCBs act synergistically [sic] with lipid lowering therapy to retard the progression of coronary atherosclerosis.”

We therefore conclude that a person of ordinary skill in the art would have been led by Jukema to combine atorvastatin and amlodipine to make a pharmaceutical composition for treating coronary atherosclerosis. The skilled artisan would have been motivated to make the combination by Jukema’s positive results in combining CCBs and pravastatin, the limited genus of specific CCBs disclosed by Jukema, and the recognition by those in the art that statins as a group are HMG-CoA reductase inhibitors and potent lipid lowering agents.

Appellant argues that “Jukema actually teaches away from the specific claimed combination,” because “patients receiving the combination of a CCB with pravastatin experienced more adverse ‘clinical events’ as compared to patients that received pravastatin alone.” Appeal Brief, pages 10 and 11.

We do not find this argument persuasive. Jukema acknowledges the increased “clinical events” experienced by patients receiving CCBs but attaches no significance to that finding. See page 428, right-hand column (“not statistically significant”). Jukema also explains that the result is largely due to an increase in unscheduled coronary bypass operations in patients taking non-dihydropyridine CCBs; that is, the group of CCBs that does not include amlodipine. See id. Thus, if the number of clinical events would have had any effect, it would have been to steer those skilled in the art toward dihydropyridine CCBs such as amlodipine. Finally, Jukema states that the “apparent

paradox” of reduction of clinical progression without reduction of clinical events may be influenced by the “remarkable low incidence of events” in the study population, and expresses an expectation that a beneficial effect on clinical events would be observed with longer follow-up. See page 429, left-hand column.

Appellant also argues that those skilled in the art would recognize that Jukema’s retrospective analysis precluded drawing any definitive conclusions. See the Appeal Brief, pages 11-13. Appellant argues that the tentative nature of Jukema’s conclusions would support at best an “obvious to try” rationale, not prima facie obviousness under 35 U.S.C. § 103. Id., pages 14-15.

We have considered the full disclosure of Jukema, as it would have been viewed by a person of ordinary skill in the art at the time the present application was filed. In our view, the reference would have led those skilled in the art to make the claimed combination with a reasonable expectation of success, for the reasons discussed in detail above. “Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success.” In re O’Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Jukema provides the required reasonable expectation of success.

Appellant also argues that Jukema would not have suggested the claimed composition because “there is no mention or suggestion of atorvastatin at all,” and “only a small percentage of [the CCBs] (6.5%) was amlodipine.” Thus, the argument goes, “there is nothing in Jukema that would have motivated one to select a specific CCB (amlodipine – used in only 6.5% of the patients) and a specific statin (atorvastatin – not mentioned or suggested at all).” Appeal Brief, page 13.

This argument is not persuasive, because it fails to address the teachings of Jukema in combination with those of Roth and Lazar. See In re Rosselet, 347 F.2d 847, 851, 146 USPQ 183, 186 (CCPA 1965) (“[T]he test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them.”) (emphasis omitted). In view of the small number of specific CCBs disclosed by Jukema and the apparent equivalence of statins, the prior art as a whole supports the examiner’s conclusion that the claimed composition would have been prima facie obvious to a person of ordinary skill in the art.

Finally, Appellant argues that the Orekhov paper⁸ provides evidence that contradicts the reasoning underlying the examiner’s rejection. See the Appeal Brief, pages 15-22.

We decline to consider the evidence provided by the Orekhov paper because that evidence was not available to those skilled in the art at the time this application was filed. The determination of obviousness or nonobviousness must be based upon what was known in the art at the time the invention was made. See 35 U.S.C. § 103: “A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art” (emphasis added).

⁸ Orekhov et al, “Antiatherosclerotic and antiatherogenic effects of a calcium antagonist plus statin combination: amlodipine and lovastatin,” Int’l Journal of Cardiology, Vol. 62 (Suppl. 2), pp. S67-S77 (Dec. 31, 1997).

The Orekhov “paper did not publish until a few months after Appellant’s filing date.” Supplement to Appeal Brief, filed January 11, 2005, page 3. Appellant asserts that the paper “show[s] the general knowledge that a person of skill in the art would have at Appellant’s filing date,” *id.*, but Appellant has presented no evidence or reasoned explanation of how a paper that was published December 31, 1997 shows the general knowledge of those in the art as of August 29, 1997, the apparent effective filing date of the present application. Because the Orekhov paper was not known to those of ordinary skill in the art as of this application’s effective filing date, it cannot be relied on as evidence of whether the claimed composition would or would not have been obvious at that time.

We have considered the other arguments presented in the Appeal Brief and Reply Brief. They are adequately addressed above. The rejection of claim 1 under 35 U.S.C. § 103 is affirmed. Claims 3, 118-120, 124, 125, and 128-141 fall with claim 1.

3. Other obviousness rejections

The examiner rejected the rest of the pending claims under 35 U.S.C. § 103, as follows:⁹

- claims 2, 121-123, 126, 127, 142, 143, and 145-147, as obvious in view of Roth, Lazar, Jukema, and Davison;¹⁰ and
- claim 144, as obvious in view of Roth, Lazar, Jukema, and Wright.¹¹

⁹ In addition, the examiner rejected claim 1 as obvious in view of Jukema and Bakker-Arkema. We need not reach this rejection, since we have already concluded that claim 1 is unpatentable over the other references cited by the examiner.

¹⁰ Davison et al., U.S. Patent 4,879,303, issued November 7, 1989.

¹¹ Wright et al., U.S. Patent 5,208,037, issued May 4, 1993.

Although Appellant did not separately argue these rejections, we must still consider whether the examiner has made out a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993): “[T]he examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of going forward with evidence or argument shift to the applicant.”); In re McDaniel, 293 F.3d 1379, 1384, 63 USPQ2d 1462, 1465-66 (Fed. Cir. 2002) (An applicant has a “right under the statute to have each contested ground of rejection by an examiner reviewed and measured against the scope of at least one claim within the group of claims subject to that ground of rejection.”).

Claim 2 is directed to the “composition of claim 1 comprising amlodipine besylate.” Davison teaches that “the besylate salt of amlodipine shows a unique combination of good solubility, good stability, non-hygroscopicity and good processability which makes it outstandingly suitable for the preparation of pharmaceutical formulations of amlodipine.” Column 4, lines 21-26. We agree with the examiner that Davison’s teaching, in combination with those of Roth, Lazar, and Jukema, would have rendered the composition of claim 2 prima facie obvious. Claims 121-123, 126, 127, 142, 143, and 145-147 fall with claim 2.

Claim 144 depends on claims 1 and 139. As a result of those dependencies, claim 144 is directed to a composition comprising amlodipine and atorvastatin (claim 1), in controlled release form (claim 144), in the form of an aqueous suspension and further comprising a sweetener, a flavoring agent, a coloring agent, an emulsifier, and a suspending agent (claim 139). The examiner cited Wright to meet the further limitations of claim 144, asserting that Wright teaches a controlled release dosage formulation of

amlodipine. Examiner's Answer, page 12. The examiner's rejection does not address any of the limitations present in claim 144 by virtue of its dependence on claim 139; specifically, that the composition be in the form of an aqueous suspension comprising a sweetener, a flavoring agent, a coloring agent, an emulsifier, and a suspending agent. Because the examiner has not adequately explained why a composition meeting all the limitations of claim 144 would have been obvious to those skilled in the art, we reverse the rejection of claim 144.

Summary

The prior art relied on by the examiner would have suggested the composition defined by claims 1 and 2 to a person of ordinary skill in the art at the time the application was filed. We therefore affirm the rejection of claims 1-3, 118-143, and 145-147 under 35 U.S.C. § 103. The examiner's rejection of claim 144, however, does not adequately state a prima facie case of obviousness with respect to the claimed composition; we therefore reverse the rejection of claim 144.

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

AFFIRMED IN PART

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| Toni R. Scheiner |) | |
| Administrative Patent Judge |) | |
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