

UNITED STATES PATENT AND TRADEMARK OFFICE

BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JUNE CHEN,
DAVID F. WOODWARD,
and
ALEXANDER B. KHARLAMB

Appeal 2008-1880
Application 10/153,043¹
Technology Center 1600

Decided: April 07, 2008

Before CAROL A. SPIEGEL, TONI R. SCHEINER, and
MARK NAGUMO, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge*.

DECISION ON APPEAL

¹ Application 10/153,043 ("the 043 application"), titled "Hypotensive Lipid and Timolol Compositions and Methods of Using Same," was filed 22 May 2002 and claims the benefit of the 31 May 2001 filing date of provisional application 60/294,845. The real party in interest is said to be Allergan, Inc. (Appeal Brief filed 4 December 2006 ("App. Br.") at 3).

I. Statement of the Case

June Chen, David F. Woodward, and Alexander B. Kharlamb ("Appellants") appeal under 35 U.S.C. § 134 from the 27 September 2006 rejection of claims 18-25 and 33-44, all of the pending claims. We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM. However, since our reasons for concluding that the claims are unpatentable differ substantially from those advanced by the Examiner, we denominate our affirmance as a NEW GROUND OF REJECTION pursuant to 37 C.F.R. § 41.50(b).

The subject matter on appeal relates to a composition for reducing ocular hypertension, such as occurs in glaucoma, comprising (i) a timolol component and (ii) cyclopentane N-ethyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy [1 α ,2 β ,3 α ,5 α] ("CNEH") and/or a pharmaceutically acceptable salt thereof. Claim 18 is illustrative and reads:

18. A composition comprising a blend of a timolol compound present in an amount effective to reduce ocular hypertension when applied to a hypertensive eye, and a hypotensive lipid component, different from the timolol component, present in an amount effective to reduce ocular hypertension, the hypotensive lipid being selected from the group consisting of cyclopentane N-ethyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy [1 α ,2 β ,3 α ,5 α], pharmaceutically acceptable salts thereof and mixtures thereof. [App. Br. 21.]

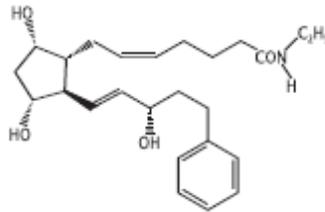
The Examiner relies on the following references² as evidence of unpatentability:

Woodard	US 5,688,819	Nov. 18, 1997
Ashton	US 6,051,576	Apr. 18, 2000

² No references to *et al.* are made in this opinion.

with reduced concentrations of each of these active materials relative to similar compositions including only the timolol component or the hypotensive component. The reduced concentrations of the active materials in the present compositions also reduce the number and/or severity of side effects, in particular side effects caused by the timolol component. [Spec. 7.]

- [5] The described compositions are said to be particularly effective in treating "patients with ocular hypotension [sic, hypertension] which effectively responds to both a reduced rate of aqueous humor production and an increase in aqueous humor outflow" (Spec. 7).
- [6] Preferably, the timolol component is an acid salt of timolol, especially timolol maleate (Spec. 7).
- [7] Preferred hypotensive lipid components include CNEH, which has the structure



(Spec. 17-18).

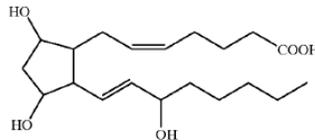
- [8] While CNEH is a prostamide which is derived from a prostaglandin, CNEH is not a prostaglandin *per se* because it lacks a prostaglandin's terminal fatty acid -COOH group.⁴

⁴ According to Webster's Ninth New Collegiate Dictionary, published by Merriam-Webster, Inc., Springfield, Massachusetts (1984), at p. 945, a prostaglandin is "any of various oxygenated unsaturated cyclic fatty acids of animals that may perform variety of hormonelike actions (as in controlling blood pressure or smooth muscle contraction)."

- [9] One exemplary composition disclosed in the 043 specification, comprises 0.001% (w/v) CNEH; 0.005% (w/v) timolol maleate; and 0.1% (w/v) polysorbate 80 in 10mM TrisHCl (Spec. 22).

B. Ashton

- [10] Ashton discloses "codrugs" formed by conjugating two or more drugs together via a labile linkage which can be cleaved at the required site in the body to regenerate the active forms of the drugs (Ashton 5:36-45).
- [11] In one embodiment, Ashton discloses a conjugated codrug comprising timolol linked to prostaglandin $\text{PGF}_{2\alpha}$ via an ester bond (Ashton 7:27-30; Example 14, 14-16).
- [12] The structure of $\text{PGF}_{2\alpha}$, as seen below, contains a terminal fatty acid -COOH group



(Ashton structure bridging 13-14).

C. Bito

- [13] Bito describes a composition comprising an effective IOP reducing amount of a mixture of an adrenergic antagonist, preferably timolol maleate, and prostaglandin or prostaglandin derivative, preferably $\text{PGF}_{2\alpha}$ or a $\text{PGF}_{2\alpha}$ derivative, in an ophthalmically compatible carrier, preferably saline-based (Bito 3:39-48; 4:57-5:29; Figs. 1 and 2).
- [14] According to Bito,

using a combination of an adrenergic blocking agent and a prostaglandin, each of them in a concentration lower than would be required if used

separately in the treatment of ocular hypertension and glaucoma, would yield a significant reduction in the occurrence of such side effects as ocular discomfort, irritative responses, conjunctival hyperemia, and cardiovascular response (Bito 3:26-34).

- [15] According to Bito, the adrenergic antagonist decreases secretion of aqueous humor and the prostaglandin increases aqueous humor outflow (Bito 3:23-26).

D. Woodward

- [16] According to Woodward, the clinical potential of prostaglandins in managing IOP conditions, e.g., glaucoma, is "greatly limited" by their associated side effects of conjunctival hyperemia and foreign-body sensation (Woodward 2:41-49).
- [17] Woodward discloses certain cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds useful as "potent ocular hypotensive agents," which in certain instances, "may be significantly more potent than their respective parent compounds and, in the case of glaucoma surprisingly, cause no or significantly lower ocular surface [conjunctival] hyperemia than the parent compound" (Woodward 3:9-19, bracketed text added).
- [18] Woodward explicitly lists and claims CNEH as a compound useful in its disclosed and/or claimed pharmaceutical compositions and treatment methods (Woodward 7:19-57, especially 44-46; claim 10).

III. Discussion

A claimed invention is not patentable if the subject matter of the invention would have been obvious to a person having ordinary skill in the art. 35 U.S.C. § 103(a); *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007);

Graham v. John Deere Co., 383 U.S. 1 (1966). Facts relevant to a determination of obviousness include (1) the scope and content of the prior art, (2) any differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) any relevant objective evidence of obviousness or nonobviousness. *KSR*, 127 S.Ct. at 1734; *Graham*, 383 U.S. at 17-18.

"[T]he suggestion to modify the art to produce the claimed invention need not be expressly stated in one or all of the references used to show obviousness. 'Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.'" *Cable Elec. Prods., Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1025 (Fed. Cir. 1985) (quoting *In re Keller*, 642 F.2d 413, 425 (CCPA 1981).

Bito describes a composition comprising an adrenergic antagonist, preferably timolol maleate, and a prostaglandin or a prostaglandin derivative, preferably PGF_{2α} or a PGF_{2α} derivative, in effective IOP reducing amounts, in an aqueous carrier solution (FF 13). Each of the adrenergic antagonist and prostaglandin/prostaglandin derivative is used in a concentration lower than would be required if used separately in the treatment of IOP and, therefore, Bito's composition produces a significant reduction in the occurrence of side effects, e.g., ocular discomfort, irritative responses, conjunctival hyperemia and cardiovascular response (FF 14). CNEH is a prostaglandin PGF_{2α} derivative (FF 7 and 12). Bito differs from the subject matter of claims 18-25 and 33-44 by failing to describe the prostaglandin derivative CNEH as being suitable for combination with timolol maleate in an aqueous carrier solution in effective IOP reducing

amounts to produce a composition for topical treatment of ocular hypertension.

According to Woodward, certain compounds, of which CNEH is explicitly identified as representative, are potent ocular hypotensive agents, which may be significantly more potent than their respective parent compounds and cause no or significantly lower conjunctival hyperemia than the parent compound (FF 17 and 18).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have substituted the $\text{PGF}_{2\alpha}$ derivative, CNEH, for its parent compound, $\text{PGF}_{2\alpha}$, in the composition of Bito since the potential clinical usefulness of $\text{PGF}_{2\alpha}$ is "greatly limited" by its associated side effects of conjunctival hyperemia and foreign-body sensation and CNEH would have been expected to cause no or significantly lower conjunctival hyperemia than its parent compound $\text{PGF}_{2\alpha}$.

Ashton's teaching of combining timolol and $\text{PGF}_{2\alpha}$ in a single composition, albeit a "co-drug," is cumulative to Bito's teaching of combining timolol maleate and $\text{PGF}_{2\alpha}$ into a single composition for topical ocular use.

Appellants argue that Ashton teaches away from the claimed invention because CNEH cannot form a codrug via an ester linkage and because a 1:1 molar ratio of timolol:CNEH would result in a subeffective dose of timolol or a potentially harmful overdose of CNEH (App. Br. 14-16). These arguments are irrelevant to Bito. Moreover, the subject matter of claims 18-25 and 33-44 simply requires the timolol component and CNEH to be combined or "blended," not conjugated to each other, let alone in a 1:1 ratio. Furthermore, Ashton fairly suggests combining timolol and $\text{PGF}_{2\alpha}$ into a single composition.

Appellants state that "Woodward discloses certain prostaglandin F_{2α} derivatives," including CNEH (App. Br. 16). Appellants argue that neither Woodward nor Ashton teaches or suggests combining CNEH with an adrenergic antagonist, such as timolol (App. Br. 16). However, the test for obviousness is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller*, 642 F.2d at 425. It is improper to criticize the teachings individually. Here, Bito teaches combining an adrenergic antagonist, e.g., timolol maleate, with a prostaglandin, e.g., PGF_{2α}, or a derivative thereof; while Woodward suggests that the PGF_{2α} derivative, CNEH, may be significantly more potent than its parent compound PGF_{2α} with no or significantly lower associated side effects, e.g., conjunctival hyperemia. Therefore, Appellants' argument is not persuasive of nonobviousness.

Appellants rely on the Declaration under 37 C.F.R. § 1.132 of June Chen, Ph.D., submitted September 9, 2005 ("Declaration") as evidence of nonobviousness, i.e., an asserted unexpectedly lower incidence of conjunctival hyperemia, over the combination of Bito, Woodward, and Ashton (App. Br. 17). According to Appellants,

the Chen Declaration makes clear that the statistically significant decrease in hyperemia seen in the study described therein is seen in comparison of a) a combination comprising 0.03% Lumigan® and 0.5% timolol maleate, and b) concurrent application of 2 separate solutions, the first containing 0.03% Lumigan®, and the other containing 0.5% timolol maleate. Thus, unlike the situation described in Bito, the decrease in hyperemia described in the Chen Declaration was seen when the concentration of each agent in the claimed composition was the same as when

applied separately. These results could not have been predicted and are truly surprising. [App. Br. 18.]

Appellants identify Lumigan® as CNEH (App. Br. 14).

- [19] Dr. Chen described a three-week study involving a "Combination Therapy" and a "Concurrent Administration" (Declaration ¶ 2).
- [20] Patients in the "Combination Therapy" were administered a single solution containing 0.03% (w/v) CNEH and 0.5% (w/v) timolol maleate once a day for three weeks (Declaration ¶ 2a).
- [21] Patients in the "Concurrent Administration" were administered a first solution containing 0.03% (w/v) CNEH once a day, "PM dosing," and a second solution containing 0.5% (w/v) timol maleate twice a day ("BID"), for three weeks (Declaration ¶ 2b).
- [22] Dr. Chen testified that the occurrence of conjunctival hyperemia was 19.3% in the "Combination Therapy" patients versus 25.6% in the "Concurrent Administration" patients (Declaration ¶ 9).
- [23] Although Dr. Chen testified to the concentration of drug solutions used and the number of times per day the drug solutions were administered, Dr. Chen did not testify as to the individual daily total drug dosages for either group of patients.

Dr. Chen did not testify as to how much of the respective solutions was administered in each dose. For example, if the 2 drops of each solution was administered to each patient in each dose, then the patients receiving the "Concurrent Administration" would have received the same total amount of CNEH but twice the total amount of timolol maleate on a daily basis as the patients receiving the "Combination Therapy." If so, then it would stand to reason that the occurrence of side effects due to timolol maleate would be

higher in the group receiving the higher daily dosage of timolol maleate than the group receiving the lower daily dosage of timolol maleate, the "Concurrent Administration" group.

Indeed, the study described by Dr. Chen might be interpreted as asking whether IOP could be effectively reduced using lower amounts of drugs in combination than typically administered individually to treat ocular hypertension and glaucoma. Such an interpretation is not inconsistent with Dr. Chen's testimony that "the Combination Administration and the Concurrent Administration had substantially similar efficacies in terms of reducing IOP" (Declaration ¶ 7) and Bito's teaching that lower amounts of drugs may be administered in combination, than administered individually, to treat ocular hypertension and glaucoma (FF 14).

Therefore, the Chen Declaration is insufficient to rebut the *prima facie* case of obviousness of the subject matter of claims 18-25 and 33-44 over the combined disclosures of Bito, Woodward, and Ashton for at least the foregoing reason. *Rohm and Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997) (nothing in the rules or in jurisprudence requires the fact finder to credit unsupported or conclusory assertions); *In re Schulze*, 346 F.2d 600, 602 (CCPA 1965) (argument in the brief does not take the place of evidence of record). Moreover, the Chen Declaration is not commensurate in scope with claims 18-24 and 33-43, which are not limited to timolol maleate as the recited "timolol component."

Based on the foregoing, the rejection of claims 18-25 and 33-44 under § 103(a) as unpatentable over the combined teachings of Bito, Woodward, and Ashton is AFFIRMED. However, since our reasons for concluding the claims are unpatentable differ substantially from those advanced by the

Examiner, we denominate our affirmance as a NEW GROUND OF REJECTION. 37 C.F.R. § 41.50(b).

IV. Order

Upon consideration of the record and for the reasons given, it is ORDERED that the decision of the Examiner to reject claims 18-25 and 33-44 under 35 U.S.C. § 103(a) as unpatentable over Ashton, Woodward, and Bito is AFFIRMED;

FURTHER ORDERED that our affirmance is a NEW GROUND OF REJECTION under 37 C.F.R. § 41.50(b); and,

FURTHER ORDERED that pursuant to 37 C.F.R. § 41.50(b), *WITHIN TWO MONTHS FROM THE DATE OF THE DECISION*, Appellants 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. . . .

Should Appellants elect to prosecute further before the Examiner pursuant to 37 C.F.R. § 41.50(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

Appeal 2008-1880
Application 10/153,043

If Appellants elect prosecution before the Examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejection, including any timely request for rehearing thereof.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(iv)(2006).

AFFIRMED; 37 C.F.R. § 41.50(b)

Appeal 2008-1880
Application 10/153,043

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Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, CA 92612-1599