United States Court of Appeals for the Federal Circuit

05-1044

ELI LILLY AND COMPANY,

Plaintiff-Appellee,

and

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
and INTERNEURON PHARMACEUTICALS, INC.,

Involuntary Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellant.

DECIDED: July 13, 2005

Before MAYER, LOURIE, and BRYSON, Circuit Judges.

Opinion for the court filed by Circuit Judge BRYSON. Circuit Judge MAYER dissents.

BRYSON, Circuit Judge.

Teva Pharmaceuticals USA, Inc., seeks review of a decision by the United States District Court for the Southern District of Indiana, in which the court found that Teva infringed U.S. Patent No. 4,971,998 ("the '998 patent") and that the patent was not

invalid. Eli Lilly & Co. v. Teva Pharms. USA, Inc., IP 02-0512-C-B/S (S.D. Ind. July 29, 2004). We affirm.

I

The '998 patent covers a method of treating premenstrual syndrome ("PMS") by administering fluoxetine, a drug belonging to a class of compounds known as Selective Serotonin Re-Uptake Inhibitors ("SSRIs"). SSRIs increase the amount of the neurotransmitter serotonin in the synaptic gaps of neurons by inhibiting the reuptake of serotonin. Reuptake is the process by which serotonin is removed from the receiving neuron and returned to the neuron from which it was sent. Fluoxetine causes the serotonin from the receiving neuron to remain in the synaptic gap for longer than it normally would, thereby increasing the chance that the serotonin will be recognized by the receptors of the receiving neuron.

The symptoms of PMS typically occur during the two weeks before the beginning of a woman's menstrual period. That two-week period is commonly known as the luteal period. Drugs relating to PMS treatment typically fall into one of two categories with respect to dosing: (1) dosing limited to the luteal period only; or (2) continuous dosing, which extends indefinitely beyond the luteal period.

The '998 patent is entitled "Methods for Treating the Premenstrual or Late Luteal Phase Syndrome." Claim 2 of the '998 patent is the only claim in suit. It reads:

> A method of treating disturbances of mood, disturbances of appetite, or both, associated with pre-menstrual syndrome, comprising administering to a woman prior to the onset of her menstrual period, a composition consisting essentially of approximately 5 mg to approximately 120 mg of fluoxetine.

Eli Lilly and Company is the secondary licensee of the '998 patent, which is assigned to Massachusetts Institute of Technology ("MIT") and licensed to Interneuron

Pharmaceuticals. Lilly received approval from the Food and Drug Administration ("FDA") to market fluoxetine under the tradename Sarafem for the treatment of Premenstrual Dysphoric Disorder, a particularly severe form of PMS. In connection with its request for FDA approval, Lilly listed the '998 patent in the FDA's Orange Book as covering Sarafem and its use. When Teva filed an Abbreviated New Drug Application with the FDA seeking approval for the generic version of Sarafem to be administered by continuous dosing, Lilly filed suit against Teva for infringement of the '998 patent. Lilly joined MIT and Interneuron Pharmaceuticals as involuntary plaintiffs. In response, Teva raised the defenses of noninfringement and patent invalidity.

On July 21, 2003, the district court issued a claim construction order. Thereafter, Teva stipulated to infringement of claim 2 for purposes of a trial on the issue of validity. Following a bench trial, the district court found that the '998 patent is not invalid for either anticipation or obviousness. The court then entered a final judgment that the '998 patent was not invalid and was infringed. Teva appeals, contending that the district court erred as a matter of law in its claim construction and committed legal and factual errors on the issue of obviousness.

II

Teva challenges the district court's construction of the claim limitation requiring the composition to be administered "prior to the onset of [a woman's] menstrual period." The district court construed that phrase to mean treatments administered "prior to the onset of a woman's menstrual period, including those that go on continuously thereafter." Teva argues that the district court erred by construing the claim to include dosing regimens "that go on continuously thereafter." Instead, Teva contends, the

district court should have construed the term to refer to dosing "limited to administration during part or all of the 14 days prior to her menstrual period and up to 3 days after," i.e., dosing limited essentially to the luteal phase only.

We disagree with Teva's proposed claim construction. The district court's interpretation is consistent with both the claim and the specification, which do not limit the dosing to the luteal phase. The claim language does not provide that dosing should take place within a certain time frame. Rather, the claim simply states that the recited composition should be administered "prior to the onset of [the woman's] menstrual period." '998 patent, col. 7, line 10. The specification also does not suggest a discrete time period for dosing, but states only that dosing should begin "prior to the expected onset of [a woman's] menstrual period." Id., col. 5, ll. 14-15; see id., col. 6, ll. 51-52 (providing, as an example, the administration of fluoxetine "starting two weeks prior to the expected onset of a subject's menstrual period").

In support of its argument that the dosing period is limited to the luteal phase. Teva relies on language from the specification stating that the dosing period for fluoxetine "will generally begin 1 to 14 days prior to menstruation and may continue for several days (e.g., 3 days) after onset of menstruation." Id., col. 2, ll. 47-49; see id., col. 5, ll. 17-19. That statement, however, is preceded by the statement that "[t]he length of time during which [fluoxetine] will be given varies on an individual basis." Id., col. 2, ll. 45-46; see id., col. 5, ll. 15-16. Hence, the specification is not as restrictive as Teva suggests and does not support limiting the dosing scheme to exclude any regimen that includes administration of the drug outside the luteal phrase.

Teva argues that the prosecution history supports construing the claim to permit dosing only during the luteal phase. Teva points to the prosecution history of a parent patent application, U.S. Patent Serial No. 111,771 ("the '771 application"), and asserts that the applicants added a luteal phase dosing limitation to the claims in that application in order to overcome a rejection. Teva's argument lacks merit because the prosecution history merely reflects the applicant's statement that dosing should occur "prior to and during the late luteal phase." That characterization of the timing requirement indicates that dosing should take place during the luteal phase, but it does not suggest that administration of the drug must terminate at any time. Hence, the prosecution history does not carry the weight Teva attributes to it.

Finally, Teva argues that the district court's claim construction is incorrect because in the case of continuous dosing no monthly treatment regime can be said to "begin prior to the onset of [a woman's] menstrual period." The claim language is broad, and we agree with the district court that it does not exclude a regime of continuous dosing. The language of the claim would plainly cover a treatment regime that began, for example, 20 days before the onset of the woman's menstrual period and continued for eight days after the end of the period, with a two-day hiatus before the beginning of the next treatment cycle. That being so, it would be highly artificial to hold that the claim would cease to apply if the treatment regime were extended to include administration of the composition during the two-day hiatus period. Although it is awkward to characterize a continuous treatment regime as having a beginning point each month, the claim by its terms merely requires that the treatment occur "prior to" the onset of menses, and that plainly occurs in the case of continuous treatment. We

therefore affirm the district court's construction of the disputed claim term, at least insofar as it applies to a regime of continuous coverage. Teva does not contest a finding of literal infringement under the district court's claim construction. Accordingly, we affirm the judgment of infringement.

III

Teva challenges the district court's conclusion that the '998 patent is not invalid for obviousness. Teva's argument is based on three main assertions: (1) there was evidence of contemporaneous invention; (2) two prior art publications would have motivated persons of ordinary skill in the art to use fluoxetine to treat PMS; and (3) a person of ordinary skill in the art would have had a reasonable expectation of success in using fluoxetine to treat PMS. Teva also argues that the district court applied the wrong legal standard in its obviousness analysis.

Teva contends that the district court confused the standard for obviousness under section 103 with the standard for anticipation under section 102. Teva points to the court's statements that "one would not find a single reference[ ] suggesting the use of fluoxetine to treat PMS" and that, prior to the '998 patent application, "no one suggested the use of fluoxetine or fenfluramine . . . to treat PMS." In context, however, those statements appear to be simply an explanation of the reasons the district court found that Teva had failed to prove by clear and convincing evidence that the '998 patent is invalid. In setting forth the legal standard for obviousness, the district court made clear that a single anticipating reference is not necessary and correctly stated that a "motivation to combine references and the reasonable expectation of success must be

found in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved."

Teva argues that the evidence showed contemporaneous invention. Teva relies on a study by Dr. Wilma Harrison, entitled "Treatment of Premenstrual Exacerbation of Chronic Mild Depression with Fluoxetine: A Pilot Study," and a study by Dr. Andrea Stone, entitled "Assessment of Fluoxetine in the Treatment of Premenstrual Syndrome." Both studies proposed the use of fluoxetine to treat PMS. The Harrison proposal was dated about four months after the filing date of the '998 patent, and the Stone proposal was dated about nine months after the filing date. The district court found those studies to be "irrelevant to a § 103 obviousness analysis" based on its finding that Dr. Harrison and Dr. Stone were not persons of ordinary skill in the art. The court ruled that the theoretical person of ordinary skill in the art is a "physician who both treats patients [with PMS] and is familiar with the relevant literature," and that research clinicians, such as Dr. Harrison and Dr. Stone, fall outside of that category because they are persons of "extraordinary" skill in the art. Teva argues that the district court's determination regarding the level of skill of a person of ordinary skill in the art is incorrect and that the district court's error requires reversal because the two clinical studies render the '998 patent obvious.

Even if the district court was incorrect in stating that research clinicians were not persons of ordinary skill in the art, any error in that regard was harmless, because notwithstanding its statement about the level of skill in the art, the district court went on to consider the Harrison and Stone studies in its obviousness analysis and found that they did not render the asserted claim invalid. Thus, the court explained that "[e]ven if

we were to consider [both studies], it supports only an 'obvious to try' theory," not a finding of obviousness. The district court based its conclusion in part on its finding that at the time Dr. Harrison and Dr. Stone proposed fluoxetine for treating PMS, they had already considered or were also simultaneously considering other drugs for treating PMS. The district court also relied on (1) the testimony of Dr. Richard Wurtman, one of the inventors of the '998 patent, who testified that at the time he conducted his case study of fluoxetine, he did not know what to expect; and (2) the testimony of Dr. Jean Endicott, one of Lilly's expert witnesses, who testified that she had undertaken similar studies that did not meet with success. Teva does not challenge the findings underlying the district court's conclusion that the studies only make fluoxetine "obvious to try." Because we conclude that the district court did not clearly err in making those findings, we reject Teva's argument on this issue.

Teva next argues that the '998 patent is rendered obvious in view of an article by Dr. Andrea Rapkin, entitled "Whole-Blood Serotonin in Premenstrual Syndrome," 70 Obstetrics & Gynecology 533 (1987), and an article by Dr. Barbara Parry, entitled "Therapeutic Effect of Sleep Deprivation in Patients With Premenstrual Syndrome," 144 Am. J. Psychiatry 6 (1987).

The Rapkin article compared blood serotonin levels in women with PMS to blood serotonin levels in asymptomatic women. Dr. Rapkin found a lower level of serotonin in patients with PMS. Teva argues that the district court failed to give sufficient weight to the teachings of the Rapkin article because the court found it was not prior art, since it was published less than one year before the filing date of the '998 patent. Prior art for purposes of determining obviousness includes all publications predating the invention,

which in this case is the filing date of the '998 patent. See Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1480 (Fed. Cir. 1997). Accordingly, the district court erred in finding that the Rapkin article did not qualify as prior art. That error is harmless, however, because notwithstanding its legal error the court considered the substance of the Rapkin article in its obviousness analysis. After considering the article, the court found that, at most, it merely "invited those of ordinary skill in the art to explore further the relationship of serotonin to PMS." The court observed that the Rapkin article did not suggest to a person of ordinary skill in the art that fluoxetine should be used to treat PMS. Instead, the Rapkin article pointed to tryptophan and trazodone as possible treating agents, not fluoxetine. Furthermore, the court found that the article "showed that women with PMS had lower serotonin levels throughout the menstrual cycle, as compared with women who did not have PMS." The court also found, based on evidence at trial, that fluoxetine decreases whole blood serotonin levels. Accordingly, the court concluded that the Rapkin article taught away from the use of fluoxetine to treat PMS, because one skilled in the art at the time "would want to increase whole blood serotonin levels," while fluoxetine "does the opposite; it decreases, not increases, whole blood serotonin." Therefore, the court concluded, "one skilled in the art who was relying on Rapkin's data would not have been motivated to use fluoxetine to treat PMS."

The court's findings with regard to the Rapkin article are not clearly erroneous, particularly in light of the absence of any suggestion in the article to use fluoxetine in PMS treatments and the seemingly contrary indication suggested by the data regarding the effect of fluoxetine on serotonin blood levels. We therefore reject Teva's argument

that the district court erred in concluding that the '998 patent would not have been obvious in light of the Rapkin article.

The Parry article reported results showing positive, albeit temporary, effects of total or partial sleep deprivation on PMS. The district court found that the Parry article was not prior art because it was not published more than a year before the effective date of the '998 patent. Teva argues that the district court's failure to consider the Parry article constituted clear error because the article was relevant to the issue of obviousness. We agree with Teva that, as in the case of the Rapkin article, the district court erred by finding that the Parry article did not qualify as prior art. Once again, however, that error is not fatal to the district court's decision. The district court recognized that the article demonstrated that Dr. Parry was "motivated to test the effect of sleep deprivation . . . on PMS because '[p]remenstrual syndrome and affective disorders may be related illnesses.'" The court made that statement in a footnote to a paragraph in which the court found that "[a]s of October 1987, those skilled in the art were just beginning to discover the relationship between affective disorders and PMS." Teva does not challenge that finding, but merely asserts that the possible link between PMS and affective disorders, which was the subject of the Parry article, demonstrates that "[a] person of ordinary skill in the art would likewise be motivated to use [fluoxetine] to treat PMS" because "fluoxetine was known to be effective in the treatment of major depressive disorder." Teva has pointed to no evidence supporting its assertion, however. Nor has it shown that the district court committed error in finding that the Parry article demonstrates only a motivation to try treatments used for affective

disorders on PMS patients. Accordingly, Teva has failed to show that the district court clearly erred in finding that the Parry article fails to render the '998 patent obvious.

Finally, Teva argues that the district court committed clear error in finding that a person of ordinary skill in the art would not have had a reasonable expectation of success in using fluoxetine to treat PMS. Teva maintains that a person of ordinary skill in the art would have found the method of the '998 patent to be obvious because the claimed method treats particular symptoms of PMS (i.e., "disturbances of mood," "disturbances of appetite," or both) as opposed to treating PMS as a whole, and because a person of ordinary skill in the art would have known that fluoxetine has already been demonstrated to be effective for treating depression. Teva relies too heavily on the distinction between treating PMS as a whole and treating its symptoms. Relying on expert testimony by Teva's expert, Dr. Laura Miller, the district court found that even if a person of ordinary skill in the art as of the filing date of the '998 patent sought to treat depression alone as a symptom, such a person would have viewed anti-depressants as unsatisfactory to treat PMS-related depression because of the negative side effects and perceived stigma associated with antidepressants. The district court's reliance on Dr. Miller's testimony and the conclusion it reached based on that testimony did not constitute clear error. Accordingly, we affirm the district court's determination that the '998 was not invalid on the basis of obviousness.

MAYER, Circuit Judge, dissents.