United States Court of Appeals for the Federal Circuit

PROMETHEUS LABORATORIES, INC.,
Plaintiff-Appellant

v.

ROXANE LABORATORIES, INC., CIPLA, LTD.,
Defendants-Appellees

2014-1634, 2014-1635

Appeals from the United States District Court for the District of New Jersey in Nos. 2:11-cv-00230-FSH-MAH, 2:11-cv-01241-FSH-MAH, Judge Faith S. Hochberg.

Decided: November 10, 2015

NEAL KUMAR KATYAL, Hogan Lovells US LLP, Washington, DC, argued for plaintiff-appellant. Also represented by JACLYN DILAURO, MATTHEW A. SHAPIRO; THOMAS SCHMIDT, New York, NY.

HENRY C. DINGER, Goodwin Procter LLP, Boston, MA, argued for defendants-appellees. Also represented by KEITH A. ZULLOW, MARTA E. GROSS, MICHAEL B. COTTLER, TIMOTHY J. DOYLE, New York, NY; WILLIAM M. JAY, Washington, DC.

Before DYK, TARANTO, and HUGHES, *Circuit Judges.*

DYK, *Circuit Judge.*

Prometheus Laboratories, Inc. ("Prometheus") appeals a judgment of the U.S. District Court for the District of New Jersey holding the amended claims of U.S. Patent No. 6,284,770 ("the '770 patent") invalid. The district court found the claims would have been obvious over the prior art or, in the alternative, invalid on grounds of obviousness-type double patenting over U.S. Patent No. 5,360,800 ("the '800 patent"). We affirm the district court's decision because the claims of the '770 patent are invalid as obvious over the '800 patent and other prior art, and do not reach the issue of double patenting.

BACKGROUND

Irritable bowel syndrome ("IBS") is a condition defined and diagnosed by its constellation of symptoms. Patients may suffer from diarrhea-predominant IBS ("IBS-D"), constipation-predominant IBS ("IBS-C"), or, less often, mixed IBS ("IBS-M") or alternating IBS ("IBS-A"). A patient's symptoms define the type of IBS with which a patient is diagnosed.

In this case, Prometheus, the owner of the '770 patent, sued Roxane Laboratories, Inc. ("Roxane") and Cipla, Ltd. ("Cipla") (together "defendants"), alleging infringement of claims 5, 6, 10, 13, and 14 of the '770 patent. As described below, the '770 patent claims a method of treatment for IBS-D utilizing alosetron (known by the brand name Lotronex). The question is whether these claims of the '770 patent would have been obvious over various prior art references or are invalid for obviousness-type double patenting over the prior '800 patent.

Prometheus also owns the '800 patent, which also covers the use of alosetron for treatment of IBS. The '800

patent issued on November 1, 1994, and has now expired.[1] The '800 patent is prior art to the '770 patent asserted here. Claim 17 of the '800 patent is directed to "[a] method of treating a condition [such as IBS] which is ameliorated by antagonism of 5-HT_3 receptors which comprises administering to a patient an effective amount of [alosetron]." '800 patent col. 38 ll. 7–12. Claim 27 of the '800 patent covers "[a] method according to claim 17 for the treatment of irritable bowel syndrome." *Id.* at col. 38 ll. 50–51.

The '770 patent, entitled "Medicaments for the Treatment of Non-Constipated Female Irritable Bowel Syndrome," is also directed to a method of treating IBS patients using alosetron. The '770 patent has a priority date of October 7, 1997. After the '770 patent issued, Prometheus initiated an ex parte reexamination of the '770 patent, and a reexamination certificate was issued on October 19, 2010. During reexamination, Prometheus amended claim 5 to add new claim limitations (those new limitations are underlined below) and added, *inter alia*, claims 10 and 13.

Reexamined claims 5, 10, and 13 provide:

> 5. A method for treating a diarrhea-predominant female IBS patient, <u>while excluding those with predominant constipation, said method comprising:</u>
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> <u>assessing whether said diarrhea-predominant female IBS patient has experienced symptoms for at least six months; and</u>

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[1] Prometheus acquired the '770 and '800 patents, along with other rights relating to the Lotronex franchise, from Glaxo Group Ltd. in 2007.

> administering an effective amount of alosetron or a pharmaceutically acceptable derivative thereof to said patient who has experienced symptoms for at least six months, wherein said effective amount is dependent on the condition of the patient and is at the discretion of the attendant physician.
>
> 10. The method for treating according to claim 5, further comprising assessing whether said female IBS patient has experienced at least moderate pain prior to administration of alosetron.
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> 13. A method for treating a diarrhea-predominant female IBS patient, while excluding those with predominant constipation, said method comprising:
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> assessing whether said diarrhea-predominant female IBS patient has experienced symptoms for at least six months;
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> assessing whether said nonconstipated female IBS patient experiences at least moderate baseline pain from IBS; and
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> administering an effective amount of alosetron or a pharmaceutically acceptable derivative thereof to said patient who has experienced symptoms for at least six months and who experiences at least moderate baseline pain from IBS, wherein said effective amount is dependent on the condition of the patient and is at the discretion of the attendant physician.

Ex Parte Reexamination Certificate, '770 patent. Claims 6 and 14, which depend from claims 5 and 13, respectively, limit alosetron to its hydrochloride salt form. *Id.*

Some background information on the history of Lotronex is helpful to understanding the issues here. Shortly before the issuance of the '770 patent, Lotronex was

approved by the FDA as a treatment for IBS and was launched in 2000. That same year, the drug had to be taken off the market because of serious side effects, including death. The drug was re-launched in 2002, with a new, more restrictive label, new warnings about side effects, and a risk management program. After reintroduction, the label specified that Lotronex is indicated only for women with severe IBS-D who have, *inter alia*, chronic symptoms generally lasting six months or longer, and should not be used on patients with constipation—indications that correspond to the limitations of the amended '770 patent claims. The label also included so-called "black box" warnings regarding the potential for serious side effects and repeated that Lotronex should only be prescribed to women with severe diarrhea-predominant IBS who have not responded adequately to conventional therapy.

Following reintroduction, the number of severe incidents associated with Lotronex dropped, but the rate of adverse events did not change. The district court found that "[l]imiting the patient population to women with severe IBS-D did not change the risk profile for Lotronex. Even when limited to that cohort of the patient population, Lotronex's incidence of complications did not decrease." J.A. 12. The district court also found that the decrease in the number of severe incidents is less likely due to the more restrictive label, and:

> more likely attributable to other changes in how Lotronex is prescribed. For example, Lotronex can only be prescribed pursuant to a REMS (Risk Evaluation and Mitigation Strategies), which requires patients and doctors to complete a form that highlights the risks; Lotronex's label now has "black box" warnings about the drug's potential side effects and instructs doctors that it should only be prescribed to patients with severe IBS-D who have not responded to conventional therapy;

> and its prior removal from the market caused doctors to be more vigilant with respect to complications. These cautionary steps are not claimed in the '770 patent.

J.A. 13 (citations omitted).

In 2009, Roxane filed an Abbreviated New Drug Application ("ANDA") with the Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of Lotronex prior to the expiration of the '770 patent. In 2010, following the relisting in the Orange Book of the '770 patent after its reexamination, Roxane submitted to the FDA a paragraph IV certification that the patent was non-infringed or invalid.

In 2011, Prometheus filed suit against defendants alleging infringement of reexamined claims 5, 6, 10, 13, and 14 of the '770 patent based on the filing of the ANDA, an artificial act of infringement. *See* 35 U.S.C. § 271(e)(2). Prometheus alleged, *inter alia*, that Roxane's label would encourage doctors to prescribe alosetron in a manner that infringes the claims. Cipla, a defendant-appellee, manufactures the active pharmaceutical ingredient, alosetron hydrochloride, used in Roxane's ANDA products.

After a bench trial, the district court held that the asserted claims of the '770 patent would have been obvious when considering the prior art and secondary considerations of nonobviousness. The district court found that "the elements of the '770 patent were present in the prior art, and the differences between the prior art and the claims of the '770 patent are insubstantial . . . [as] some of the prior art is virtually identical to the claimed inventions." J.A. 44. The district court also found that the asserted claims of the '770 patent would have been obvious in light of secondary considerations. The district court found that it was not unexpected for alosetron to exhibit greater efficacy in IBS-D patients, who have exhibited symptoms for greater than six months, and who have experienced at

least moderate pain. The district court held that the limited evidence at trial did not establish that there is an unexpected result of greater efficacy in women. The district court concluded that, "[a]t best, the claims at issue are a combination of known elements, combined in a known way, to produce expected results." J.A. 47. As noted above, the district court found that the clinical improvement of reintroduced Lotronex was due to factors other than the '770 patent. Moreover, the district court found that any commercial success of reintroduced Lotronex could not be attributed to the method claimed in the '770 patent, but rather was due to Prometheus' marketing and sales practices. Finally, the district court found that the method claimed in the '770 patent did not satisfy a long-felt but unmet need. Thus, "[a]fter considering the knowledge of one of ordinary skill in the art, the scope and content of the prior art compared to the claimed invention, and the objective considerations of nonobviousness," the district court held that "the claims of '770 patent, considered as a whole, are obvious." J.A. 44. In the alternative, the district court held that the claims were invalid for obviousness-type double patenting in light of the claims of the '800 patent.[2] Given its invalidity rulings, the district court did not reach the issue of infringement.

Prometheus appeals. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1). "On appeal from a bench trial, this court reviews the district court's conclusions of law de novo and findings of fact for clear error." *MeadWestVaco*

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[2] The parties stipulated below that if the district court found independent claim 5 of the '770 patent invalid due to, *inter alia*, obviousness or obviousness-type double patenting, then dependent claims 6, 11, and 12 would be invalid for the same reason. The same stipulation was entered with respect to independent claim 13 and dependent claims 14, 15, and 16.

Corp. v. Rexam Beauty & Closures, Inc., 731 F.3d 1258, 1266 (Fed. Cir. 2013). Both obviousness and double patenting are questions of law based on underlying facts. *Power Integrations v. Fairchild Semiconductor Int'l, Inc.*, 711 F.3d 1348, 1355–56 (Fed. Cir. 2013) (obviousness); *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1372 (Fed. Cir. 2014) (double patenting).

DISCUSSION

We conclude that the asserted claims of the '770 patent are invalid as obvious under 35 U.S.C. § 103. A patent would have been obvious "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." *Id.* Obviousness is based on underlying factual findings, including: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the claims and the prior art; and (4) secondary considerations of nonobviousness, such as commercial success, long-felt but unmet needs, failure of others, and unexpected results. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007); *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

The primary prior art reference relied on by the district court was the '800 patent. In addition to the '800 patent, the district court relied on a number of research publications that predated the October 7, 1997, priority date of the '770 patent as prior art references.

The district court determined, and the parties agreed, that the relevant person of ordinary skill in the art is a gastroenterologist with three years of experience. The district court also found, and Prometheus and defendants agreed, that the claims of the '770 patent recite a species of the genus method claimed in the '800 prior art patent.

The '800 patent claims the use of alosetron to treat patients suffering from IBS. The '770 patent claims treating a subset of those IBS patients—those who (1) are women (2) with IBS-D (3) who have experienced symptoms for at least six months and (4) who have had moderate pain. While the parties dispute whether the claims of the '770 patent operate as exclusions defining patient categories that should not be treated with alosetron, we need not decide this question. Even treating the limitations of the '770 claims as exclusions, we conclude that before October 7, 1997, it would have been obvious to a person of ordinary skill to treat those sub-species claimed here.

To be sure, "[i]t is well-settled that a narrow species can be non-obvious and patent eligible despite a patent on its genus." *AbbVie*, 764 F.3d at 1379. An "earlier disclosure of a genus does not necessarily prevent patenting a species member of the genus." *Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed. Cir. 2003).

The genus-species distinction may have particular relevance in the field of personalized medicine, where, for example, a particular treatment may be effective with respect to one subset of patients and ineffective (and even harmful) to another subset of patients. *See, e.g.*, Margaret A. Hamburg & Francis S. Collins, *The Path to Personalized Medicine*, 363 New Eng. J. Med. 301, 301 (2010). Singling out a particular subset of patients for treatment (for example, patients with a particular gene) may reflect a new and useful invention that is patent eligible despite the existence of prior art or a prior art patent disclosing the treatment method to patients generally. An obviousness rejection likely would not be appropriate where the new patient subset displayed unexpected results.

But that is not the situation here. In this case, the district court's factual findings make clear that, at the time of the '770 patent, it would have been obvious for a

person skilled in the art to have separately treated the limited subset claimed in the '770 patent with alosetron, and that any unexpected results were attributable to factors exogenous to the '770 patent.

The first limitation of asserted claim 5 of the '770 patent pertains to treating women. Prometheus argues that the district court erred in framing its inquiry as whether alosetron was administered to women with IBS-D in the prior art, rather than as whether it was obvious to focus on treating women rather than men. It is not disputed that it was well known in 1997 that a majority of IBS patients were women. As the district court found, it was well known that "approximately 75% to 80% of IBS-D patients . . . have always been[] women."[3] J.A. 9. For example, the 1992 Thompson article reported that female IBS patients predominate in Western countries. Even if the claims should be read as focusing treatment on women, as Prometheus urges, the district court found the prior art taught precisely that. The Hysu study (1995) taught that females taking alosetron "had higher concentrations of alosetron in their blood and total amount of the drug absorbed compared to [males taking alosetron]" and the district court found that "[t]his could reasonably suggest that women would have a greater response to the drug than men." J.A. 25. At the time of the '770 patent's priority date, it would have been obvious to a person having ordinary skill in the art to treat women as a separate group of IBS patients.

The next claim limitation in asserted claim 5 of the '770 patent pertains to only treating patients suffering from IBS-D. The district court concluded that several pre-

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[3] The district court also found that "the limited evidence at trial . . . did not actually show that there is a greater efficacy [of alosetron] in women compared to men." J.A. 40.

1997 publications taught that "alosetron and other 5-HT_3 antagonists slow colonic transit" and "taught that alosetron would be beneficial to prescribe to those with IBS-D and potentially harmful to those with IBS-C." J.A. 30. For instance, the district court found that the Talley study (1992) "taught that 5-HT_3 antagonists slowed colonic transit and would be helpful in treating IBS-D and harmful in treating IBS-C." J.A. 30. The district court found that the Sanger study (1996) taught that "5-HT_3 antagonists have the potential to treat diarrhea and recommends that they only be used with severe patients because of the potential to cause constipation." J.A. 22.

Prometheus' basic objection is that the district court simply relied on studies suggesting that the class of 5-HT_3 antagonist drugs, of which alosetron is a part, should be used to treat IBS-D and not IBS-C. While those studies were not focused on alosetron, but the class of drugs, there is ample testimony that a person of ordinary skill would have understood the studies as equally applicable to alosetron. *See, e.g.*, J.A. 1747–51, 1760. We do not think the district court clearly erred in concluding that the lessons drawn with regard to a class of drugs (5-HT_3 antagonists) are applicable to a species (alosetron) within that class.

Prometheus submits that the district court relied on references in which alosetron was administered to healthy volunteers instead of IBS patients, and that studies that did test alosetron in IBS patients suggested only that alosetron would be helpful in treating IBS generally. But the district court did not extrapolate those study results on its own; rather, this conclusion was informed by expert testimony. *E.g.*, J.A. 1763. And the studies cited by Prometheus specifically state that alosetron delays colonic transfer. J.A. 866, 868. We see no clear error in the district court's conclusion that it would have been obvious to a person of ordinary skill in the art reading the claims of

the '800 patent and the prior art to limit treatment to patients suffering from IBS-D.

As to the claim limitation requiring symptoms for "at least six months" before administering alosetron, J.A. 71, it was common practice at the time of the '800 patent to determine whether a patient had suffered symptoms for longer than six months. Dr. Lucak, Prometheus' own expert, testified that the benefit of the six-month limitation was having "a greater confidence in the diagnosis." J.A. 1372. Pre-October 1997 studies suggest using a six-month standard for the diagnosis of IBS. The so-called Manning criteria (named after a 1978 study) call for symptoms lasting at least 6 months. The Kruis study (1984) "specifically teaches using the existence of symptoms for over two years as a basis for increasing the confidence in a diagnosis of IBS." J.A. 20. The Francis paper (February 1997) "discloses the use of a 6-month duration criterion to reduce the margin of error" in diagnosing IBS. J.A. 21. In fact, the district court found that "most IBS-D patients will have symptoms for more than 6 months" and "it has always been true that waiting a longer period of time to observe a patient's symptoms decreases the likelihood of a false positive." J.A. 9. In 1997, it would have been obvious for a person having skill in the art to treat patients displaying IBS symptoms for more than six months as a separate group. Although Prometheus argues that three months was the diagnostic standard in 1997, the district court's finding as to the six-month standard is amply supported by the record and is not clearly erroneous.

Regarding the limitation directed to at least moderate pain, at the time the '800 patent issued, it was well-known to evaluate patients for pain in order to diagnose

IBS. The Rome criteria[4] for diagnosing IBS are standard criteria used to diagnose IBS and inquire into pain and its severity. Pain is in fact a main symptom of IBS (along with diarrhea and constipation). The Manning study (1978) states that "[a]bdominal pain, constipation, and diarrhoea are the main symptoms [of IBS]." J.A. 822. The Kruis study (1984) defines IBS as "a cluster of chronic symptoms that include abdominal pain." J.A. 815. The Steadman study (1992) states that "[c]linically, patients with IBS experience fluctuations in bowel habit, abdominal pain, and other symptoms." J.A. 839. And the Talley study (1992) states that "[p]atients with irritable bowel syndrome typically have a chronic but erratic disturbance of defecation and associated abdominal pain." J.A. 855. In the Manning study, all but one of the thirty-two patients diagnosed with IBS had pain. In the Kruis study, 96% of patients diagnosed with IBS had abdominal pain.

Prometheus concedes that doctors commonly assess IBS patients for pain, and does not dispute that it would have been obvious to use alosetron to treat pain. Instead, Prometheus argues that it would not have been obvious to administer alosetron only to patients suffering from at least moderate pain. But as the district court noted, Prometheus' own expert, Dr. Lembo, testified that because a candidate for Lotronex was a patient with severe IBS, "it's pretty obvious that [a physician] will assess for at least moderate pain." J.A. 1303. The expert testimony also shows that a person of ordinary skill would have adopted a conservative approach in treating IBS patients, and avoided drug intervention for a patient with mild symptoms. The district court did not err in finding that it would have been obvious for a person having skill in the

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[4] According to the district court, the Rome criteria are described in the Thompson reference (1992).

art to single out IBS patients displaying at least moderate pain.

Relevant here is our decision in *AbbVie*. There, a prior art genus patent claimed a method of co-administering two drugs to treat rheumatoid arthritis. *AbbVie*, 764 F.3d. at 1378–79. The later patent contained a species claim limiting the prior art genus to a more specific patient group: individuals with "active disease." *AbbVie,* 764 F.3d at 1378–79. Borrowing from "the law of obviousness generally," we noted that "if the later expiring patent is merely an obvious variation of an invention disclosed and claimed in the reference patent, the later expiring patent is invalid." *Id.* at 1378–79 (quotation marks and citation omitted). This case is analogous. Here, it would have been obvious for a person having ordinary skill in the art reading the '800 patent to treat female patients with IBS-D who had symptoms for at least six months and who had experienced at least moderate pain. As discussed above, these limitations are directed to a known type of IBS, to treating the gender that predominantly experiences IBS, to treating patients with a characteristic that is always or almost always evaluated in establishing IBS, and to assessing symptoms for a duration of time that was common in diagnosing patients with IBS.

While this case, unlike *AbbVie*, involves a few different variables, the district court found that it would have been obvious to combine the teachings of the prior art in the form of the '770 patent. The record contains abundant evidence that there was a limited number of known parameters and it would have been obvious to combine the teachings as to each parameter.

Finally, the district court carefully considered secondary considerations of nonobviousness as required by our precedent, *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012), and found that the secondary considerations

did not support a conclusion of nonobviousness. Prometheus first argued that the reintroduced Lotronex's commercial success can be attributed directly to the '770 patent, noting that from 2003 to 2007, net sales of Lotronex increased each year and the original patent owner was able to sell the Lotronex franchise to Prometheus for $120 million. The district court recognized that sales revenue of Lotronex increased from the time of its reintroduction into the market in 2002 until 2012, but observed that "by 2011, there were just over 42,000 prescriptions of Lotronex written per year for about 10,000 patients. This was only about 2,100 more prescriptions compared to its peak year of sales with [the original patent owner]." J.A. 14. The district court determined that the '770 patent was not responsible for the commercial success of reintroduced Lotronex, but instead that the evidence showed "the growth in revenue [since Lotronex's reintroduction into the market] is due to Prometheus's actions in marketing, increasing the price of Lotronex, and introducing a series of rebates to stimulate sales of the drug, rather than from the treatment method claimed in the '770 patent." J.A. 15. The district court was not persuaded by Prometheus' evidence relating the commercial success of Lotronex to the '770 patent, because Prometheus did not submit an analysis that would show the commercial success for the '770 patent on its own merits, "control[ling] for other variables and separat[ing] the treatment instructions from the drug compound and the method in the '800 patent that already existed, nor any analysis to control for other changing variables, such as marketing campaigns, new drug warnings, pricing changes, *etc.*" J.A. 41.

Prometheus argues that the district court erred by placing the burden of proof on Prometheus to demonstrate the nexus between Lotronex's commercial success and the '770 patent. The party challenging the validity of a patent always has the burden of persuading the trial court of

invalidity. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242–43 (2011). However, "once a challenger has presented a prima facie case of invalidity, the patentee has the burden of going forward with rebuttal evidence. But, all that means is that even though a patentee never *must* submit evidence to support a conclusion by a judge or jury that a patent remains valid, once a challenger introduces evidence that might lead to a conclusion of invalidity—what we call a prima facie case—the patentee would be well advised to introduce evidence sufficient to rebut that of the challenger." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007) (quotation marks and citations omitted).

We do not find that the district court improperly shifted the burden of proof as to commercial success. Although the district court described and rejected Prometheus' attempts to "prove commercial success of Lotronex and that [Lotronex] fulfilled a long-felt but unmet need," J.A. 41, we understand those statements to be in reference to Prometheus' burden of production. We have found that similar imperfect language is not grounds for reversal. *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 991 (Fed. Cir. 2006) (citation and quotation marks omitted) (affirming the district court's holding of invalidity despite the court's statement that "[t]here is no indication that the [motivation to combine] was non-obvious," because the district court's opinion as a whole indicated it "correctly allocated the burden of proof"). The district court opinion clearly states the correct standard in finding the claims of the '770 obvious by clear and convincing evidence. J.A. 44.

Prometheus next argued that the '770 patent met a long-felt but unmet need and created an unexpected result by improving the safety and risk-benefit profiles of alosetron. The district court rejected these contentions. The district court was not persuaded that any long-felt need was satisfied by the instructions claimed in the '770

patent "as distinguished from . . . the drug itself, which is covered by the '800 patent." J.A. 41. It found that "it is clear that many of the benefits touted by Prometheus were attributable to the compound itself rather than the '770 patent's method of treatment." J.A. 16. The district court further found that "any praise or reduction in the severity of side effects is more likely attributable to elements from the '800 patent, the new safety precautions, heightened awareness, and warnings issued after Lotronex's reintroduction." J.A. 44. We find no clear error in the district court's factual conclusions in this respect.

We affirm the district court's holding that the challenged claims of the '770 patent would have been obvious over the '800 patent and other prior art.

AFFIRMED

COSTS

Costs to appellees.