

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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*Ex parte* JEAN-LOUIS JUNIEN, ALAN EDGAR,  
and EVELYNE CHAPUT

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Appeal 2008-0971  
Application 10/636,670  
Technology Center 1600

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Decided: August 8, 2008

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Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and JEFFREY  
N. FREDMAN, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 2-9 and  
11-21. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

According to the Specification, the “present invention relates to the use of a PPAR $\alpha$  agonist to treat patients suffering from weight gain associated with a PPAR $\gamma$  agonist treatment” (Spec. 1: 4-5). It is stated that “it has been observed that rosiglitazone [a PPAR $\gamma$  agonist] markedly increased body weight gain . . . . This side effect renders rosiglitazone monotherapy an undesirable prophylactic measure in the treatment of” non-insulin dependent diabetes (Spec. 2: 18-21). The Specification states that co-administration of a PPAR $\alpha$  agonist, such as fenofibrate, with a PPAR $\gamma$  agonist, such as rosiglitazone, decreased weight gain associated with the latter (*id.* at 4:11-21; at 5: 3-5).

Claims 2-9 and 11-21 stand rejected under 35 U.S.C. § 103(a) as obvious over Paterniti (WO 98/05331, published Feb. 12, 1998) and the PDR (*Physician’s Desk Reference*, 56<sup>th</sup> ed. 2002, pages 1493-94, 2652-53)<sup>1</sup> (Ans.<sup>2</sup> 3).

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<sup>1</sup> Appellants complain that a “full copy” of the “label” for Avandia and Lipid “as recited in the PDR” were not provided by the Examiner (Reply Br. 8-9). We agree with Appellants’ that it is the Examiner’s burden to establish prima facie obviousness, which includes providing full copies of the cited prior art. In this case, it appears that the Examiner only provided copies of the relevant pages of the PDR cited in the Answer, but not the complete PDR description (“label”) of the cited drug. Nonetheless, the PDR is widely available to those interested in its content. That said, had there been additional information dispositive to the outcome of this Appeal in the portion of the PDR not provided by the Examiner, we expect that such information would have been put forward in the record. Nevertheless, to be complete, we have included a full copy of the PDR sections relating to Avandia and Lipid with this Decision.

<sup>2</sup> “Ans.” is the Examiner’s Answer mailed Jan. 9, 2007.

We select claims 16 and 20, which read as follows, to focus our analysis:

16. A method of decreasing body weight gain in a subject treated with a thiazolidinedione, where said body weight gain is associated with the thiazolidinedione treatment, which method comprises co-administering to the subject an effective dosage of a fibrate and an effective dosage of said thiazolidinedione, wherein

said effective dose of said thiazolidinedione is an amount sufficient to induce said body weight gain, and

said effective dosage of said fibrate is an amount sufficient to decrease said body weight gain associated with the thiazolidinedione treatment.

20. A pharmaceutical composition comprising

a fibrate, a thiazolidinedione and a pharmaceutically acceptable carrier,

wherein the effective dosage of the thiazolidinedione is in the range of about 0.5 to about 3 mg per day, and the fibrate is present in an amount sufficient to decrease body weight gain associated with the dosage of thiazolidinedione.

#### FINDINGS OF FACT

##### *Scope and content of the prior art*

In making an obvious determination, the Examiner must first identify the scope and content of the prior art and then ascertain the differences between the prior art and the claimed invention. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Thus, we first turn to the prior art. The following numbered findings of fact (“FF”) summarize the prior art relied upon by the Examiner in setting forth the basis of the rejection (Ans. 3-6):

##### The Paterniti WO application

1. Paterniti teaches compositions “useful for treating, curing, reducing, or preventing one or more clinical symptoms of or associated with Type 2

diabetes and cardiovascular disease with diabetic or pre-diabetic conditions” (Paterniti, at 3, ll. 18-22).

2. The compositions comprise “suboptimal doses of a PPAR $\gamma$  agonist (e.g., thiazolidinedione) and a PPAR $\alpha$  agonist (e.g., a fibrate)” (*id.* at 4, ll. 21-23).

3. “Such combination therapy thus allows one to use lower doses of a PPAR $\gamma$  agonist and a PPAR $\alpha$  agonist to avoid or reduce their respective toxicity to patients without compromising their antidiabetic and cardio-protective effects” (*id.* at 4, ll. 25-28; *see also id.* at 28, ll. 3-10).

4. The combination is described by Paterniti as useful for “reducing body weight” (*id.* at 5, l. 8).

5. Paterniti states that a “preferred PPAR $\gamma$  agonist is a thiazolidinedione compound” and lists rosiglitazone (“BRL 49653”) as an example (*id.* at 8, ll. 3-6).

6. A “preferred” PPAR $\alpha$  agonist is described as a “fibrate compound”, with gemfibrozil and fenofibrate as examples (*id.*, at 8, l. 28 to 9, l. 1).

7. In the examples, the PPAR $\gamma$  agonist rosiglitazone (“BRL 49653”) was administered to diabetic mice at 0.4 mg/kg/day (*id.* at 14, ll. 16-20).

8. The PPAR $\alpha$  agonist gemfibrozil was administered at 50 mg/kg/day in the same example (*id.*); fenofibric acid at 40 mg/kg/day (*id.* at 14, ll. 25-27).

9. Paterniti states that the “exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient’s condition” (*id.* at 37, ll. 6-8). “Determination of the effective amounts is well within the capability of those skilled in the art” (*id.* at 39, ll. 14-17; *see Ans.* 8).

10. Paterniti teaches that its compositions can also be used for animals (“veterinary medicine”) (*id.* at 37, ll. 22-23).

The PDR

11. According to the PDR: “Dose-related weight gain was seen with *Avandia* [rosiglitazone] alone and in combination with other hypoglycemic agents (Table 6)” (PDR, at 1493, col. 1).
12. “The usual starting dose of *Avandia* is 4 mg . . . daily” (*id.* at 1494, col. 3).
13. The recommended dose of Lopid [gemfibrozil, a fibrate] for adults is 1200 mg (*id.* at 2653).

*Level of ordinary skill in the art*

When making an obviousness determination, the level of ordinary skill must be considered. *Graham*, 383 U.S. at 17.

14. Therapeutic dosages of a thiazolidinedione and fibrate could routinely be determined by one of ordinary skill in the art (*see* FF8).

*Differences between the prior art and the claimed invention*

Once the scope and content of the prior art has been determined, the next step is to identify the differences between the prior art and the claimed invention. *Graham*, 383 U.S. at 17. The following numbered findings of fact are pertinent to this issue:

Claim 16

15. Claim 16 is directed to a “method of decreasing body weight gain in a subject treated with a thiazolidinedione.”
16. The method involves “co-administering” effective dosages of a fibrate and thiazolidinedione.

17. The effective dosage of the thiazolidinedione is recited to be “an amount sufficient to induce said body weight gain.”

18. The effective dosage of the fibrate is recited to be “an amount sufficient to decrease said body weight gain associated with the thiazolidinedione treatment.” We do not interpret this limitation to require recognition that fibrate alone achieves the desired weight loss required by claim 16.

19. Paterniti teaches co-administering a fibrate and thiazolidinedione (FF2-3) as recited in claim 16 (*see* FF16).

20. Paterniti does not describe weight gain associated with thiazolidinedione administration as stated in claim 16 (FF17), but the PDR states that “weight gain” is associated with rosiglitazone (FF11) which is a thiazolidinedione.

21. Paterniti does not state that the effective dosage of fibrate is sufficient to decrease body weight gain associated thiazolidinedione treatment as claimed (FF18), but Paterniti states that the combination of drugs, including a fibrate and thiazolidinedione, is effective for reducing body weight (FF4).

#### Claim 20

22. Claim 20 is drawn to pharmaceutical composition comprising a fibrate and a thiazolidinedione.

23. The fibrate “is present in an amount sufficient to decrease said body weight gain associated with the dosage of thiazolidinedione.”

24. The thiazolidinedione “is in the range of about 0.5 to about 3 mg per day” and are “associated with” body weight gain.

25. Paterniti does not state that the effective dosage of fibrate is sufficient to decrease body weight gain associated thiazolidinedione as claimed (FF23), but Paterniti states that combination of drugs, including a fibrate and thiazolidinedione, is effective for reducing body weight (FF4).

26. Paterniti does not describe weight gain associated with thiazolidinedione administration as stated in claim 20 (FF25) or the specifically claimed dosage, but the PDR states that “weight gain” is associated with rosiglitazone treatment (FF11) and the claimed amounts overlap with those that are disclosed or suggested in the prior (*see* Ans. 4, 8, 10).

*Reason to combine the prior art*

Once the differences between the prior art and the claimed invention have been ascertained, the next step is to identify a reason why persons of ordinary skill in the art would have been prompted to combine the prior art to have made the claimed invention. *KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The following findings are relevant to this determination:

27. The dosage of rosiglitazone described in Paterniti and the PDR would have been reasonably expected to produce weight gain in view of the PDR’s explicit teaching that therapeutic amounts of it are associated with weight gain (FF11) – thus meeting the limitations of claims 16 and 20 (*see* FF17, 24).

28. Paterniti does not disclose that fibrate reduces weight gain associated with a thiazolidinedione (FF21, 25), but in view of 1) Paterniti’s teaching that the combination of a thiazolidinedione and fibrate reduce body weight (FF4); and 2) the knowledge that rosiglitazone produces weight gain (FF11), that Examiner had reasonable basis to believe that the disclosed or suggested fibrate dosage would have reduced the gain in weight associated with rosiglitazone as recited in claims 16 and 20.

29. With regard to the specific dosage of rosiglitazone as recited in claim 20 (FF24), such dosage overlaps with the effective amounts disclosed in Paterniti (*see* FF7) and are close to the disclosed in the PDR (compare 3 mg to 4 mg) (*see* FF12).

30. Persons of ordinary skill in the art would have had reason to decrease the dosage of rosiglitazone described in the PDR (i.e., from 4 mg to “about 3 mg” as in claim 20) in view of Paterniti’s teaching that lower doses should be administered when used in combination with a fibrate and that such lower amounts are effective (FF2-3).

31. Optimization and selection of effective dosages of a thiazolidinedione and fibrate would have been within the level of ordinary skill in the art (FF 14).

#### ANALYSIS

During patent examination, the Examiner bears the initial burden of establishing a prima facie case of obviousness. *In re Kumar*, 418 F.3d 1361, 1366 (Fed. Cir. 2005). In setting forth a case of obviousness, “it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” *KSR Int’l v. Teleflex Inc.*, 127 S. Ct. at 1741.

After reviewing the scope and content of the prior art and the reason for combining it, we conclude that sufficient evidence has been provided to establish prima facie obviousness of claims 16 and 20. We agree with the Examiner’s findings that the combination of a fibrate and a thiazolidinedione

for weight loss is taught by Paterniti (FF2, 4, 7, 8). To the extent that the dosages described in Paterniti do not meet the claim limitations, persons of ordinary skill in the art would have had reason to optimize them based on Paterniti's teachings about the desire to administer low dosages (FF30-31). Thus, we turn to Appellants' rebuttal arguments.

Appellants argue that Paterniti does not disclose that body weight gain is associated with thiazolidinedione administration (App. Br.<sup>3</sup> 10, 17; Reply Br. 5-6). This argument is not persuasive. As found by the Examiner, the PDR explicitly teaches that the thiazolidinedione rosiglitazone is associated with weight gain (FF11). Appellants have not otherwise distinguished the claimed amount of rosiglitazone (i.e., "an amount sufficient to induce said body weight gain") from that disclosed in the prior art nor have they provided arguments that the specific amount recited in claim 20 would not have been obvious from Paterniti's teaching that reduced amounts are desirable (FF30).

Appellants also argue that the Paterniti "stated that this treatment [with rosiglitazone] did not induce changes in body weight as recited at page 19, lines 24-29" (Reply Br. 4) and in fact "**teaches away**" from this effect (App. Br. 11). They quote from Paterniti's statement that administration of rosiglitazone "for 7 days did not change body or liver weights" (Paterniti, at 19, ll. 24-29). This argument is not convincing. In the following line, Paterniti states: "epididymal fat pad weights, however, increased in a dose-dependent fashion, an observation which is consistent with previous described effects of thiazolidinediones . . . and adipose tissue mass" (*id.* at

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<sup>3</sup> "App. Br." is the "Appeal Brief in Response to Notification of Non-compliant Appeal Brief", date stamped April 2, 2007.

19, l. 29 to 20, l. 4). Thus, it would have been reasonably expected that a longer period of administration would lead to body weight gain, consistent with the PDR teachings. Moreover, the PDR's teaching that weight gain is associated with administration of the commercially available thiazolidinedione rosiglitazone is admitted in the Specification to have been known (Spec. 2: 18-21). Thus, when viewed in the context of the prior art as a whole, we do not agree that Paterniti teaches away from the claimed invention (*see* Reply Br. 11). ("Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of applicant's invention." *Syntex (USA) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (citations deleted)). Paterniti explicitly teaches the claimed combination (FF2-6) and explicitly teaches that the combination is useful for reducing body weight as in claims 16 and 20.

On page 21 of the Appeal Brief, Appellants state:

Administration of the thiazolidinedione PPAR $\gamma$  activator rosiglitazone can be accompanied by the side effect of weight gain. However, such a side effect will of course only arise when the amount of rosiglitazone taken is actually sufficient to induce body weight gain.

This statement appears to be inconsistent with Appellants' earlier position that rosiglitazone is not associated with weight gain (*see e.g.*, App. Br. 10-12). Nonetheless, as acknowledged by Appellants, rosiglitazone is associated with a dose-related gain in weight (FF11); thus, lower doses might result in less weight gained, but it would still be reasonably expected that some gain of weight would be observed.

In the Answer, the Examiner states that "weight loss" is recognized "as a possible side effect" of Lopid administration (Ans. 4). Appellants

argue that a “causal relationship between Lopid [a fibrate] and weight loss **has not been established**” (App. Br. 13; Reply Br. 9). We have considered this argument but do not find it persuasive.

Claims 16 and 20 state that the claimed fibrate is in an amount “to decrease body weight gain associated with” thiazolidinedione administration as recited in the claims. We do not interpret this claim limitation to require recognition that the fibrate alone achieves the desired result of weight loss (FF18). In our opinion, the claim limitation is met if the effective amount of fibrate disclosed or suggested by Paterniti and the PDR would achieve the stated mechanism of decreasing weight gain caused by a thiazolidinedione. For this reason, it is not pertinent whether the prior art teaches that Lopid is associated with weight gain. The relevant question is whether the prior art suggests a dose of it which “decrease body weight gain associate with” thiazolidinedione administration.

In view of: 1) Paterniti’s teaching that the combination of a thiazolidinedione and fibrate reduces body weight (FF4); and 2) the knowledge that a thiazolidinedione produces weight gain (FF11), the Examiner had reasonable basis to believe that the fibrate dosages disclosed or suggested in the prior art meet the claimed limitation (“an amount sufficient to decrease said body weight gain associated with” thiazolidinedione administration) (*see* FF28). Appellants have not provided adequate arguments to rebut this reasonable belief.

Appellants also argue that Paterniti “recites a laundry list of therapeutic compounds ... This document is something of a ‘shopping list’ as regards the combination of active substances (thiazolidinedione and fibrate)” (App. Br. 11). We agree with the Examiner that Paterniti “is not a

shopping list” (Ans. 8). Paterniti expressly teach an example of a thiazolidinedione and fibrate (FF2, 5-8) – as required by claims 16 and 20. Thus, “pharmaceutical formulations comprising thiazolidinedione and fibrate are clearly disclosed by Paterniti” (Ans. 8).

It is argued in the Appeal Brief that the Paterniti “does not teach or suggest any specific dose ranges of either thiazolidinedione or fibrate being administered to a human” (App. Br. 20, 23). This argument is not convincing. The claims are not limited to human administration. Thus, Paterniti’s teaching regarding amounts administered to animals (FF7, 8, 10) are pertinent to the claims. As well, Paterniti teaches that its compositions can also be used for animals (FF10).

Furthermore, amounts administered to humans are taught in the PDR. Appellants have not provided evidence that the claimed dosages, including 0.5 to about 3 mg per day as in claims 20, 18, and 19, would not have been reasonably suggested by the prior art. In particular, persons of ordinary skill in the art would have had reason to decrease the dosage described in the PDR (i.e., from 4 mg to “about 3 mg” as in claim 20) in view of Paterniti’s teaching that lower doses should be administered when used in combination with a fibrate and that such lower amounts are effective (FF2-3).

Appellants’ argument that “the Examiner has not addressed adequately supported the selection and combination of” Paterniti and the PDR “to render Appellants’ claimed invention obvious” (App. Br. 15) is without merit. Paterniti teaches the claimed combination (FF2, 5-8), states that the selection of effective doses of each compound would be routine (FF9), and the PDR is evidence that effective dosages were known (Ans. 9).

For the foregoing reasons, we affirm the rejection of claims 16 and 20.

Claims 2, 3, 11, and 12

Appellants argue that there is no teaching or suggestion in Paterniti of the specific fibrates recited in the dependent claims, nor of fenofibrate as recited in claims 3 and 12 (App. Br. 26, 28). This argument does not convince us that the Examiner erred. Paterniti specifically teaches fenofibrate as a preferred fibrate (see FF6, 8).

Claims 4, 13

Appellants contend that the Paterniti does not “teach or suggest” a fibrate “in the range of about 10 to about 3000 mg per day” as recited in claims 4 and 13 (App. Br. 26, 28). This argument is not persuasive. The Examiner cited the PDR for teaching a dosage of 1200 mg per day of a fibrate (FF13) which falls within the claimed range.

Claims 5, 6, 14, and 15

Appellants argue that there is no teaching or suggestion in Paterniti of a fibrate with rosiglitazone (App. Br. 26-27, 28-29). We do not agree. This combination is explicitly suggested by Paterniti (FF5-8) and, as discussed above, the claimed effective amounts of each are suggested in the prior art.

Claim 7

Appellants argue that there is no teaching or suggestion in Paterniti of thiazolidinedione “in the range of 0.1 to about 100 mg per day” as in claim 7 (App. Br. 27). This argument has no merit. The Examiner cited the PDR

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for teaching a dosage of 4 mg per day of a thiazolidinedione which falls within the claimed range (FF12).

Claim 8 and 9

Appellants argue that there is no teaching or suggestion in Paterniti of administering thiazolidinedione and fibrate “simultaneously or sequentially” as claimed (App. Br. 27).

The Examiner fully addressed these limitations in the Answer (*see* Ans. 8). Appellants do not point to any deficiency in the Examiner’s findings.

Claims 17 and 21

Appellants argue that there is no teaching or suggestion of a fibrate “in the range of about 50 to about 300 mg per day” as recited in claims 17 and 21 (App. Br. 29, 30). This argument does not convince us that the Examiner erred. Paterniti teaches states that, when co-administered, the fibrates can be administered at dosages lower than those typically used (FF3). Therapeutic dosages of a fibrate could routinely be determined by one of ordinary skill in the art (FF8, 14).

## CONCLUSION

In summary, we affirm the rejection of claims 2-9 and 11-21 as obvious over Paterniti and the PDR.

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TIME PERIOD

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

AFFIRMED

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