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Appellants submit this appeal involving claims to formulations of atazanavir and cobicistat. Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

1 Appellants identify the Real Party in Interest as Bristol-Myers Squibb Company. App. Br. 1.
STATEMENT OF THE CASE

“[S]ignificant reductions in death rates among AIDS patients have been recently documented as a consequence of the widespread application of combination therapy.” Spec. 2:9–11. “Because all HIV drugs must be taken as part of a combination regimen, there must be new and better ways to ensure that the patient actually takes each medication as prescribed.” Id. at 5:2–4. “[W]hat is now needed in the art are new, easily administered combination formulations containing potent antiretroviral drugs which are useful in the treatment against HIV . . . [, are] physically stable and have low degradant levels, and [] provide efficacious dosing of important HIV medications.” Id. at 5:10–14.

“In particular, stable, easily administered fixed dose combinations (FDCs) containing atazanavir and cobicistat are desired.” Spec. 5:16–17. “[A]tazanavir, has now established itself as a first-line antiretroviral in the treatment of HIV.” Id. at 2:21–22. “Like other protease inhibitors, [atazanavir] is used only in combination with other HIV medications.” Id. at 3:6–7. Cobicistat “has significant ability to inhibit liver enzymes that metabolize other medications used to treat HIV . . . It also inhibits intestinal transport proteins, increasing the overall absorption of several HIV medications, including atazanavir.” Id. at 4:9–12. Cobicistat 150 mg tablets (TYBOST™) are indicated as a boosting agent for atazanavir 300 mg once daily. Id. at 4:20–24.

Claims 2–13, 24–34, 36–38 and 43–47 are on appeal, and can be found in the Claims Appendix of the Appeal Brief. Independent claims 25

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4 Claims 1, 21–23, and 39–42 are cancelled. Claims 14–20 and 35 are withdrawn.
and 26 are representative of the different claim groups and are reproduced below:

25. A tableted composition comprising atazanavir, cobicistat and a pharmaceutically acceptable carrier, said composition providing a blood concentration profile of atazanavir in healthy subjects as measured by AUC(0–T) that is from about 80% to 125% of 34848 ng·h/mL.

26. A tableted composition comprising atazanavir, cobicistat and a pharmaceutically acceptable carrier, said composition being in the form of a bilayer tablet and comprising less than or equal to about 4.0% of total cobicistat impurities.


Obviousness over Nikfar, Tybost, and Kottala

Examiner found Nifkar teaches a bilayer tablet containing atazanavir and cobicistat. Ans. 4. Examiner found Tybost teaches an effective combination of 300 mg of atazanavir and 150 mg of cobicistat. Id. at 6. As to the blood profile limitations of claims 24 and 25, and the stability limitations of claims 26 and 30, Examiner found these properties are necessarily present in the combined teaching of the prior art. See id. at 7–8.

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Appellants contend that the cited references do not establish a reasonable likelihood of success. App. Br. 7–8. In particular, Appellants argue that Nikfar “equate[s] monolithic tablets and multi-layer tablets without indicating any impact on the bioavailability of the atazanavir caused by the presence of cobicistat or the control of impurities and degradation products.” Id. Appellants argue that the secondary references “fail to compensate for the shortcomings of the primary reference, Nikfar.” Id. at 9.

The issue is whether the preponderance of the evidence of record supports Examiner’s conclusion that the combination of references renders a bilayer composition containing atazanavir and cobicistat obvious.

Findings of Fact

We agree with and adopt the findings concerning the scope and content of the prior art as well as the conclusion as set forth in the Examiner’s Answer and the Final Office Action. The findings of fact reproduced below are referenced to highlight certain pertinent evidence.

FF1. Nikfar teaches compressed tablets containing atazanavir sulfate and an acidifying agent, optionally with another anti-HrV active agent. Nikfar, Abstr. The other active agent may include cobicistat. Id. at 13:28–29; see also p. 21, claims 1, 7.

FF2. Nikfar teaches “[w]hen another agent having anti-HIV activity is included in the compressed tablet, it may be included within the same phase as the atazanavir sulfate or its formulation, i.e., as a monolithic tablet, or it may be included within another phase, i.e., a multi-layer tablet.” Nikfar 19:4–20:2. “When included in a multi-layer tablet, the
atazanavir sulfate is in one layer and the other agent (or agents) are in another layer, e.g., bilayer.” *Id.* at 20:4–5.

FF3. Tybost teaches cobicistat (150 mg) is a pharmaco-enhancer co-administered with atazanavir (300 mg), taken orally, once daily with food. Tybost 9–10.

FF4. Tybost teaches “cobicistat under ambient conditions undergoes moisture and temperature induced phase transition from a foam into a rubber-like material. To increase physical stability of cobicistat it is adsorbed on silicon dioxide.” Tybost 11.

FF5. Tybost teaches “[t]he choice of dosage form for the cobicistat drug product was also determined by the physical and chemical stability of the active ingredient, degradation pathways of the active ingredient, size of the unit dose, manufacturability, and biopharmaceutical performance of the active substance.” Tybost 12–13. Tybost teaches “[t]he formulation was further adjusted for a dry granulation process,” wherein “[b]oth tablet formulations (dry granulation formulation and Phase 1/2 formulation) were confirmed to be bioequivalent.” Tybost 13.

*Principles of Law*

“[P]roper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.” *PAR Pharm., Inc. v. TWI*
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Pharm., Inc., 773 F.3d 1186, 1196 (Fed. Cir. 2014). “The reasonable expectation of success requirement for obviousness does not necessitate an absolute certainty for success.” Id. at 1198.

Analysis

Examiner found that the prior art teaches “a tablet, in the form of a bilayer, is a suitable arrangement of [atazanavir and cobicistat] along with a carrier for the treatment of HIV. Moreover, the art suggests the same dosage as claimed.” Ans. 8; see also FFs1–3. Examiner acknowledged “that the prior art does not teach the claimed blood profile” of claims 24 and 25. Ans. 9. However, Examiner concluded “[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. The fact that Appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability . . .” Id. As to claims 26 and 30, reciting an upper limit of cobicistat impurities and degradants, Examiner found “Nikfar already teaches the claimed composition comprising atazanivir and cobicistat and Tybost is applied for its teachings of a more stable form of the latter drug.” Id. at 11; see FF 4, 5. Examiner concluded “it would have been obvious to use the more stable form of cobicistat in the bilayer tablet of Nikfar and since Tybost teaches that no degradation is present, the skilled artisan would have had a reasonable expectation of success that the bilayer tablet would also be stable and show no degradation.” Ans. 11.

Appellants contend “the references, when viewed as a whole without the benefit of knowing what Appellant’s invention is, fail to provide the motivation to combine them in the manner suggested by the Patent Office
with a reasonable likelihood of success.” App. Br. 9. Moreover, Appellants contend the “specification and drawings demonstrate the effectiveness the multilayer tablet had on the bioavailability and control of impurities and degradants.” Id. at 9–10.

In particular, Appellants contend that the Specification demonstrates a bilayer tablet maintains cobicistat impurities of less than 2% at 12 months. App. Br. 8, citing Fig. 6. In contrast, a monolithic tablet, in which cobicistat and atazanavir are mixed, is characterized by cobicistat impurities of 3.5% at 8 weeks. Id. Appellants contend “[t]his result could not have been predicted by the disclosure of Nikfar.” Id.

As to the secondary references, Appellants contend that Kottala and Tybost do not “disclose tableted compositions comprising atazanavir and cobicistat . . . could be prepared with sufficient bioavailability to approximate the bioavailability of atazanavir and cobicistat when administered separately; and . . . [at the same time] control the impurities and degradation of cobicistat in the tableted composition by utilizing a multi-layer tablet rather than a monolithic tablet.” App. Br. 9.

We are not persuaded. The prior art suggests to a person of ordinary skill in the art to make a bilayer tablet containing atazanavir in one layer and cobicistat in another layer for combination therapy of HIV. That the prior art also suggests a monolithic tablet as an alternative, and that the monolithic tablet is insufficient to provide a suitable drug product, does not negate the reasonable expectation of success, as “obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art.” Allergan, Inc. v. Sandoz Inc., 726 F.3d 1286, 1292 (Fed. Cir. 2013).
Here, Examiner established a reasonable expectation of success based on Nikfar’s teachings of a bilayer tablet and Tybost’s teachings regarding co-administration of atazanavir and stabilized cobicistat. Appellants have not provided any evidence that a person of ordinary skill in the art would have expected a bilayer tablet of atazanavir and cobicistat to suffer from reduced bioavailability and stability. See PAR Pharm., 773 F.3d at 1196 (“The presence or absence of a reasonable expectation of success is [] a question of fact”). Rather, as cited by the Examiner, Tybost teaches toward effective co-administration of the compounds and stable formulations of cobicistat. See id. Therefore, we agree with Examiner’s conclusion that a person of ordinary skill in the art would have had a reasonable expectation of success in preparing a bilayer tablet for co-administering atazanavir and cobicistat.

The independent claims include further limitations regarding a blood concentration profile of atazanavir (claims 24 and 25), total cobicistat impurities (claim 26), and presence of cobicistat degradants (claim 30). App. Br. 2–3. Appellants contend “[t]he claims on appeal do not stand or fall together.” App. Br. 2. However, Appellants do not present separate arguments for the independent claims as compared to the prior art. Separately arguing a claim requires “more substantive arguments in an appeal brief than a mere recitation of the claim elements and a naked assertion that the corresponding elements were not found in the prior art.” In re Lovin, 652 F.3d 1349, 1357 (Fed. Cir. 2011). Accordingly we consider the claims together.

Appellants contend “the Patent Office has not provided any reason, apart from its own statement to the contrary, to question the inventiveness of
the claims which recite blood concentration levels and limitations on the presence of impurities and degradants.” App. Br. 9. In response, Examiner argues that these are latent properties in the formulation and do not support patentability. See Ans. 9.

We agree with the Examiner. As discussed above, the bilayer formulation would have been obvious to a person of ordinary skill in the art. “[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations.” Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1354 (Fed. Cir. 2012). Likewise, as applied to the claim limitations of impurities and degradants, we conclude that these limitations add nothing of patentable consequence, as “[t]o hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property.” Id.

Having considered all of Appellant’s arguments and having found them to be unpersuasive, we affirm Examiner’s rejections of claims 24, 25, 26, and 30 for the reasons of record. Claims 2–13, 27–29, 31–34, 36–38, and 43–47 fall with claims 24, 25, 26, and 30.

SUMMARY

We affirm the rejection under 35 U.S.C. § 103(a) over Nikfar, Tybost, and Kottala.

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

AFFIRMED