

Detailed Factual and Legal Basis for BARR's Paragraph IV Certification

I. Introduction

This document is the detailed factual and legal basis for the assertion of BARR LABORATORIES, INC. ("BARR") that, in its opinion and to the best of its knowledge, U.S. Patent No. 6,514,531 B1 ("the '531 patent") is invalid, unenforceable or will not be infringed by the manufacture, importation, use or sale of the drug products described in BARR's ANDA. The right to raise additional defenses is specifically reserved.

II. Background Information

A. AMBIEN CR[®]

According to the FDA-approved label, the compound zolpidem tartrate is the active ingredient in the drug product AMBIEN CR[®]. AMBIEN CR[®] is available as a coated two-layer tablet: one layer that releases its drug content immediately and another layer that allows a slower release of additional drug content. AMBIEN CR[®] tablets contain either 6.25 or 12.5 mg of zolpidem tartrate. AMBIEN CR[®] is approved for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset).

B. The ANDA Formulation

The products that are the subject of BARR's ANDA No. 78-672 ("BARR's ANDA products") are a generic version of AMBIEN CR[®]. BARR's ANDA products comprise 6.25 mg or 12.5 mg zolpidem tartrate and various excipients. BARR's ANDA products will be marketed for the currently approved indication for AMBIEN CR[®], the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset).

III. Factual and Legal Basis For BARR's Certification

A. No Infringement of Claims 1-47 of the '531 Patent

1. No Literal Infringement

Each of claims 1-47 of the '531 patent requires that the controlled release dosage form has a "biphasic in vitro profile of dissolution when measured in a type II dissolution apparatus according to the U.S. Pharmacopoeia in 0.01M hydrochloric acid buffer at 37 °C., where the first phase is an immediate release phase having a maximum duration of 30 minutes and . . . wherein 40 to 70% of the total amount of zolpidem is released during the immediate release phase." BARR's ANDA products do not have a "biphasic in vitro profile of dissolution when measured in a type II dissolution apparatus according to the U.S. Pharmacopoeia in 0.01M hydrochloric acid buffer at 37 °C., where the first phase is an immediate release phase having a maximum duration of 30 minutes and . . . wherein 40 to 70% of the total amount of zolpidem is released during the immediate release phase."

As such, BARR's ANDA products are missing at least one element of each of claims 1-47 of the '531 patent. Accordingly, the manufacture, use, sale, offer for sale or importation of BARR's ANDA products would not literally infringe any of claims 1-47 of the '531 patent.

a. No Infringement Under the Doctrine of Equivalents

BARR's ANDA products will not infringe any of claims 1-47 of the '531 patent under the doctrine of equivalents because the patentees are estopped from expanding the claims to cover BARR's ANDA products under the doctrine of prosecution history estoppel. Based on claim amendments made during prosecution of the '531 patent to particularly specify the dissolution profile of the claimed composition, SANOFI cannot now expand the scope of the claims to encompass surrendered subject matter.

Accordingly, the manufacture, use, sale, offer for sale or importation of BARR's ANDA products would not infringe any of claims 1-47 of the '531 patent under the doctrine of equivalents.

B. Invalidity of the Claims of the '531 Patent Under 35 U.S.C. § 103

1. At Least Claims 1, 6-8, 11, 12, 18, 20, 28, 29, 32, 33 and 34 are Prima Facie Obvious Over the Prior Art

At least claims 1, 6, 7, 12 and 32 are invalid under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 4,986,987 ("the '987 patent") in view of Wheatley, D., "Prescribing Short-Acting Hypnosedatives: Current Recommendations from a Safety Perspective," *Drug Safety* 7(2): 106-115 (1992) ("Wheatley"); (b) at least claim 8 is invalid under 35 U.S.C. § 103(a) as obvious over the '987 patent in view of Wheatley and further in view of GB Patent Number 2 245 492 published January 8, 1992 ("the '492 patent"); (c) at least claims 11 and 20 are invalid under 35 U.S.C. § 103(a) as obvious over the '987 patent in view of Wheatley and REMINGTON'S PHARMACEUTICAL SCIENCES, 18TH ED. (1990) ("REMINGTON'S"); (d) at least claims 18 and 28 are invalid under 35 U.S.C. § 103(a) as obvious over the '987 patent in view of Wheatley and further in view of AMBIEN[®]; and (e) at least claims 29 and 34 are invalid under 35 U.S.C. § 103(a) as obvious over the '987 patent in view of Wheatley, AMBIEN[®] and REMINGTON'S.

2. The Objective Evidence of Nonobviousness is Insufficient to Rebut the Prima Facie Case of Obviousness

SANOFI cannot rebut the *prima facie* case of obviousness recited herein.

Even assuming *arguendo* that AMBIEN CR[®] is encompassed by the claims of the '531 patent, SANOFI will be unable to show commercial success because AMBIEN CR[®] has not been on the market for sufficient time to determine whether it is a "commercial success." In addition, the active ingredient in AMBIEN CR[®], zolpidem, is claimed in U.S. Patent No. 4,382,938 ("the '938 patent"), assigned to SANOFI-AVENTIS. Owing to a five year patent term extension, the '938 patent expired on October 21, 2006, barring competitors from making, selling, using, offering for sale or importing zolpidem until October 21, 2006, without obtaining a license from SANOFI. Because evidence of commercial success is insufficient to rebut a *prima facie* case of

obviousness where market entry by competitors is barred through patent or statutory exclusion rights, any inference of non-obviousness from evidence of commercial success would be weak.

Further, there is no evidence of unexpected results associated with any of the dosage forms claimed in any of claims 1, 6-8, 11, 12, 18, 20, 28, 29, 32, 33 and 34 sufficient to rebut the *prima facie* case of obviousness recited herein.

Finally, SANOFI has not provided any public information about any licensing agreements involving the '531 patent that may be used as evidence of secondary indicia of the nonobviousness of claims 1, 6-8, 11, 12, 18, 20, 28, 29, 32, 33 and 34 sufficient to rebut the *prima facie* case of obviousness recited herein.

Accordingly, at least claims 1, 6-8, 11, 12, 18, 20, 28, 29, 32, 33 and 34 are invalid under 35 U.S.C. § 103(a) as obvious over the prior art.