App. 1

901 F.3d 803

United States Court of Appeals, Seventh Circuit.

Wendy B. DOLIN, Individually and as Independent Executor of the Estate of Stewart Dolin, Deceased, Plaintiff-Appellee,
v.
GLAXOSMITHKLINE LLC, Formerly Known as SmithKline Beecham Corp., Defendant-Appellant.

No. 17-3030
|
Argued May 30, 2018
|
Decided August 22, 2018
|
Rehearing and Rehearing En Banc Denied September 20, 2018

Appeal from the United States District Court for the For the Northern District of Illinois, Eastern Division. No. 12-CV-6403—**William T. Hart**, *Judge*.

Attorneys and Law Firms

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Before Wood, Chief Judge, and Sykes and Hamilton, Circuit Judges.

Opinion

Hamilton, Circuit Judge.

Defendant GlaxoSmithKline LLC (GSK) appeals from a jury verdict awarding $3 million to plaintiff

Wendy Dolin for the death of her husband, Stewart Dolin. Mrs. Dolin alleges that GSK's negligent omissions in the drug label for Paxil caused her husband's death. Stewart did not actually take Paxil. In 2010, a doctor prescribed Paxil, the brand-name version of paroxetine, to treat Stewart's depression and anxiety. But his prescription was filled with generic paroxetine manufactured by another company (one that is no longer a defendant). Six days later, Stewart committed suicide. Blood tests showed that paroxetine was in his system. He was 57 years old.

At the time of Stewart's death, GSK manufactured brand-name Paxil and was responsible under federal law for the content of the drug's label. When Stewart died, the labels for paroxetine and similar antidepressant drugs warned that they were associated with suicide in patients under the age of 24. The labels did not warn about any association between the drugs and an increased risk of suicide in older adults.

The current state of federal law makes it virtually impossible to sue generic drug manufacturers on a state-law theory for failure to warn. In response to this legal landscape, plaintiffs have advanced a new theory of liability and have sued brand-name manufacturers, who have more control over drug labels, for injuries caused by taking the generic drugs. Mrs. Dolin followed this recent trend here, suing GSK on the theory that it negligently failed to include warnings that paroxetine was associated with suicide in patients older than 24.

Throughout the lawsuit, GSK has maintained that it is not liable under Illinois law simply because Stewart Dolin did not consume a drug that GSK manufactured. Mrs. Dolin responds that the relevant harm was caused by the incomplete label, not the drug, and that under federal law, only GSK could change the label. GSK also argued that federal law preempted Illinois law from requiring the warning that Mrs. Dolin claims was negligently omitted because the FDA had rejected GSK's attempts to add just such a warning. The district court disagreed with GSK's various arguments, and the case proceeded to trial and a verdict for Mrs. Dolin.

In this appeal, GSK challenges the district court's conclusions about liability under Illinois law and preemption. GSK also argues that the evidence at trial did not support the jury's verdict. We agree with GSK that federal law prevented GSK from adding a warning about the alleged association between paroxetine and suicides in adults. On that basis of federal preemption, we reverse the judgment. The case must be dismissed.

I. *Legal and Factual Background*

A. *Regulation of Drug Labels*

We start with the regulatory background that explains why the parties make the arguments they do. The Food, Drug, and Cosmetic Act bars pharmaceutical companies from manufacturing new drugs unless the Food and Drug Administration approves a "new drug

application." 21 U.S.C. § 355(a). The new drug application must show that the drug is safe and effective, which requires an extensive series of clinical trials. *Guilbeau v. Pfizer, Inc.*, 880 F.3d 304, 307 (7th Cir. 2018); *see also* 21 U.S.C. §§ 355(b) & (d). The application must also include "the labeling proposed to be used for such drug." § 355(b)(1)(F); 21 C.F.R. § 314.50(c)(2)(i).

The label contains a lot more than the drug's name. It must disclose, among other things, warnings and precautions related to the drug's effects. The FDA reviews the proposed label to determine whether it is "false or misleading." 21 U.S.C. § 355(d)(7); 21 C.F.R. § 314.125(b)(6). Once the new drug application is approved, the manufacturer must distribute the drug using the FDA-approved label. Otherwise, the drug is misbranded and may not be distributed in the United States. *See* 21 U.S.C. §§ 331(a), 333(a), & 352(a), (c). In 1992, the FDA approved GSK's new drug application for paroxetine, including a label.

Plaintiff's theory of liability is based on GSK's ability to change the paroxetine label after the FDA approved it in 1992. There were two ways relevant to this lawsuit for GSK to change the label without running afoul of federal law. First, GSK could have asked the FDA for permission to change the label. 21 C.F.R. § 314.70(b)(2)(v)(A). This is the default rule for most substantive changes to drug labels. Second, in narrow circumstances GSK could unilaterally change the label under what is called the "changes being effected" or CBE regulation. The CBE regulation is an exception to

the general rule that changes require advance FDA permission. It allows manufacturers to change a label to "reflect newly acquired information" if, as relevant here, the changes "add or strengthen a . . . warning" for which there is "evidence of a causal association. . . ." 21 C.F.R. § 314.70(c)(6)(iii)(A). In other words, GSK needed FDA permission to change the paroxetine label unless three things were true: (1) GSK had newly acquired information about paroxetine (2) that showed a causal association (3) between the drug and an effect that warranted a new or stronger warning. The FDA reviews CBE submissions and can reject label changes even after the manufacturer has made them. *See* 21 C.F.R. § 314.70(c)(6), (7).

The new drug approval process is "onerous and lengthy." *Mutual Pharmaceutical Co. v. Bartlett*, 570 U.S. 472, 476, 133 S.Ct. 2466, 186 L.Ed.2d 607 (2013). Generic manufacturers can avoid much of this costly process, but they have little influence on the contents of drug labels. Under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, a manufacturer can file an "abbreviated new drug application" for approval to distribute a generic drug. *See* 21 U.S.C. § 355(j). The Supreme Court summarized the requirements for generics:

> First, the proposed generic drug must be chemically equivalent to the approved brand-name drug: It must have the same "active ingredient" or "active ingredients," "route of administration," "dosage form," and "strength"

> as its brand-name counterpart. 21 U.S.C. §§ 355(j)(2)(A)(ii) and (iii). Second, a proposed generic must be "bioequivalent" to an approved brand-name drug. § 355(j)(2)(A)(iv). That is, it must have the same "rate and extent of absorption" as the brand-name drug. § 355(j)(8)(B). Third, the generic drug manufacturer must show that "the labeling proposed for the new drug is the same as the labeling approved for the [approved brand-name] drug." § 355(j)(2)(A)(v).

Bartlett, 570 U.S. at 477, 133 S.Ct. 2466. "This allows manufacturers to develop generic drugs inexpensively, without duplicating the clinical trials already performed on the equivalent brand-name drug." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 612, 131 S.Ct. 2567, 180 L.Ed.2d 580 (2011).

In sum, "brand-name and generic drug manufacturers have different federal drug labeling duties." *Mensing*, 564 U.S. at 613, 131 S.Ct. 2567. "A brand-name manufacturer seeking new drug approval is responsible for the accuracy and adequacy of its label." *Id.*; *see also* 21 U.S.C. § 355(b)(1), (d); *Wyeth v. Levine*, 555 U.S. 555, 570–71, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009). "A manufacturer seeking generic drug approval, on the other hand, is responsible for ensuring that its warning label is the same as the brand name's." *Mensing*, 564 U.S. at 613, 131 S.Ct. 2567; *see also* 21 U.S.C. §§ 355(j)(2)(A)(v) & (j)(4)(G); 21 C.F.R. §§ 314.94(a)(8) & 314.127(a)(7). Thus, from 1992 to 2014, when GSK sold the right to distribute brand-name Paxil, GSK was responsible for the "accuracy and

adequacy" of the drug's label. To change the label, GSK needed either FDA permission or newly acquired information that supported a strengthened warning under the CBE regulation.

B. *The History of Paroxetine's Label*

Paroxetine is a selective serotonin reuptake inhibitor, one of a class of antidepressants commonly called SSRIs. For decades, the FDA has scrutinized data on the relationship between SSRIs and suicidal behavior. The FDA's analysis of that relationship is central to the preemption question in this appeal.

1. *The New Drug Application Approval*

GSK's predecessor, SmithKline Beecham Corporation, submitted a new drug application for paroxetine in 1989. Around that time, the FDA began investigating a potential relationship between suicidal behavior and SSRIs. The FDA requested GSK to submit a supplemental analysis of data related to suicide. GSK submitted the additional analysis in May 1991. In June 1991, the FDA safety reviewer for GSK's paroxetine application reported: "there is no signal in this large data base that paroxetine exposes a subset of depressed patients to additional risk for suicide, suicide attempts or suicidal ideation."

The FDA continued its investigation of the risk of suicide. In September 1991, the agency convened an independent committee of experts to review whether

SSRIs were associated with suicide. The FDA also asked the committee to evaluate data specific to paroxetine. The committee "unanimously agreed that there is no credible evidence of a causal link between the use of antidepressant drugs . . . and suicidality or violent behavior." The committee also found that paroxetine was safe and effective for treating adult depression.

In December 1992, the FDA approved the new drug application for paroxetine, which allowed GSK to market the drug as Paxil. The original label did not contain any paroxetine-specific warning about suicidality. Instead, the FDA required that the label contain the same warning as all other antidepressants at the time: "The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy."

Throughout the late 1990s and early 2000s, GSK submitted additional data on paroxetine to the FDA. The FDA continued to reject any link between paroxetine and suicidality. In January 2004, the FDA summarized its findings as follows:

> FDA has done several analyses on completed suicides for adult data sets provided to us in response to a request for patient level data sets for all relevant studies involving 20 antidepressant drugs studied in 234 randomized controlled trials with [major depressive disorder]. Based on our initial analyses of these data, we have reached a similar conclusion,

> i.e., that there does not appear to be an increased risk of completed suicide associated with assignment to either active drug or placebo in adults with [major depressive disorder].

2. *The FDA's 2004 Pediatric Suicide Warning*

Later in 2004, however, the FDA found an association between SSRIs and suicide in pediatric patients. The FDA convened an advisory committee to review data on nine antidepressant drugs, including paroxetine and other SSRIs, in pediatric patients. The committee unanimously agreed that the "data in aggregate indicate an increased risk of suicidality" in "pediatric patients." As a result, the FDA required that the labels for paroxetine and other SSRIs be changed to include a warning that antidepressants "increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders."

The FDA required that this appear as a "black-box" warning, meaning that it "should be added to the beginning" of the label "with bolded font and enclosed in a black box." The FDA also required new language in the "WARNINGS—Clinical Worsening and Suicide Risk" section of the previous label applicable to all SSRIs. The new language warned that patients "with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior . . . whether or not they are taking antidepressant

medication," and that a "causal role for antidepressants in inducing suicidality has been established in pediatric patients." The FDA did not require a warning about any association between antidepressants and suicidality in adults.

3. *GSK's 2006 Adult Suicide Warning*

After finding that SSRIs were associated with suicide in pediatric patients, the FDA began a similar analysis of suicide in adults. The FDA requested more data from manufacturers of antidepressants, including data from GSK on paroxetine. The FDA limited its data request to "completed, double-blind, randomized, placebo-controlled trials." GSK submitted data to the FDA.

At the same time, GSK conducted its own re-analysis of data on adult suicidality and paroxetine. In the re-analysis, GSK looked for an association between paroxetine use with suicidal ideation and increased suicide attempts. GSK found no statistically significant difference when looking at suicidal ideation, but it found "evidence of an increase in suicide attempts in adults with [major depressive disorder] treated with paroxetine compared with placebo." GSK submitted its findings to the FDA, explaining that its data showed a 6.7-fold increase in suicide attempts in adults treated with paroxetine compared to a placebo. GSK cautioned the FDA that "these data should be interpreted with caution" because "the absolute number and incidence of events" were "very small."

After completing the re-analysis, GSK acted unilaterally to change paroxetine labeling on April 27, 2006. It did so under the CBE regulation, i.e., without advance FDA approval. GSK removed language that described the risk of suicide in adults as "unknown" and added the following:

> In adults with [major depressive disorder] (all ages), there was a statistically significant increase in the frequency of suicidal behavior in patients treated with paroxetine compared with placebo (11/3,455 [0.32%] versus 1/1,978 [0.05%]); all of the events were suicide attempts. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These [major depressive disorder] data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

GSK also sent a letter to doctors nationwide, attaching the new paroxetine label and explaining the "important changes to the Clinical Worsening and Suicide Risk subsection of the Warnings section."

4. *FDA's Meta-Analysis & the 2007 Class-Wide Label Change*

About seven months later, in November 2006, the FDA completed a meta-analysis—that is, a statistical analysis of a large group of similar studies—to study the risk of suicide in adults who use antidepressants. The meta-analysis considered 372 placebo-controlled

clinical trials and involved nearly 100,000 adult patients, including data on paroxetine submitted by GSK. The FDA found "an elevated risk for suicidality and suicidal behavior among adults younger than 25," but concluded that the "net effect appears to be neutral on suicidal behavior but possibly protective for suicidality for adults between the ages of 25 and 64 and to reduce the risk of both suicidality and suicidal behavior in subjects aged 65 years and older."

The FDA's meta-analysis analyzed the data for each drug. For paroxetine, the FDA data showed a statistically-significant 2.76-fold increase in suicidal behavior compared with adults treated with placebo. The FDA noted this result, but concluded that "the significance of those findings must be discounted for the large number of comparisons being made."

In response to these findings, in 2007, the FDA took action that is central to GSK's preemption defense in this case. The agency ordered that all SSRI labels be updated based on the results of the meta-analysis. Critically, the FDA decided to order that warnings be uniform for all SSRIs. On May 1, 2007, the FDA directed GSK to revise the paroxetine labeling "to ensure standardized labeling pertaining to adult suicidality with all of the drugs to treat major depressive disorder." Def. Ex. 122. The SSRI labels were to warn of a suicidality risk in patients 24 years old or under, and to state that "studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults

aged 65 and older." The FDA required all SSRI labels to include this language "verbatim." This action had the effect of rejecting GSK's unilateral change to the paroxetine label in 2006 using the CBE regulation to warn of increased risk among older adults.

5. *Later Attempts to Add a Paroxetine-Specific Warning*

After the FDA ordered uniform warnings for all SSRIs, GSK asked the FDA several times for permission to maintain a paroxetine-specific suicide warning. Within a week of the FDA's announcement, GSK emailed the FDA to "clarify" whether it could retain the paroxetine-specific warning it had added in 2006 under the CBE regulation. The FDA immediately said no. It replied that GSK should "replace the previous warning section with the new language" that the FDA had circulated. Def. Ex. 124.

Four days later, on May 11, GSK more formally asked the FDA to maintain the paroxetine-specific warning. In a letter to the FDA, GSK proposed keeping the paroxetine-specific language and argued that it "would complement the class labeling" and "could help physicians." The FDA advised GSK to submit the paroxetine-specific warning as a separate CBE supplement and explained that the FDA would "be discussing all" manufacturers' "proposals during the last week of May." GSK submitted the CBE supplement that the FDA requested.

On June 21, 2007, the FDA finalized the new class-wide warnings. The FDA stressed that "it is critical that the labeling be consistent for all" SSRIs. This final version omitted GSK's paroxetine-specific warning. The next day, GSK again followed up with the FDA to clarify whether the FDA had rejected its most recent CBE supplement adding a paroxetine-specific warning. It had. The FDA responded that it was rejecting product-specific warning language:

> [T]he Agency has reviewed your proposed changes, and we do not believe that your product specific analysis should be included in class labeling revisions since the labeling is targeted at the class of drugs. If you would like to discuss this matter further, please submit a formal meeting request.

Def. Ex. 129. GSK did not pursue the matter any further.

On June 25, 2007, GSK implemented the new class-wide warning that the FDA ordered. GSK continued to assert to the FDA that "the paroxetine specific language" would "be useful for prescribers." On August 2, 2007, the FDA approved GSK's supplement—and thus the new paroxetine label—containing *only* the class-wide SSRI suicide warning. GSK continued to market paroxetine under the Paxil brand name in the United States using the FDA-approved label through 2014, when GSK sold the right to sell Paxil to another manufacturer. The paroxetine label maintains the FDA's class-wide warning today. It does not warn of

any association with an increased risk of suicide in adults older than 24.

C. *This Lawsuit*

Mrs. Dolin sued GSK in state court, alleging that paroxetine increases the risk of suicide in adults; that GSK negligently failed to update the paroxetine label to reflect that risk; and that GSK's negligence caused Stewart's death. GSK removed to the Northern District of Illinois, asserting diversity jurisdiction under 28 U.S.C. § 1332(a)(1). Mrs. Dolin is a citizen of Illinois. GSK is a limited liability company organized under Delaware law, and its sole member is GlaxoSmithKline Holdings (Americas) Inc., a Delaware corporation with its principal place of business in Delaware. The amount in controversy exceeds $75,000.[1]

Once in federal court, GSK made two arguments that are relevant to this appeal. First, GSK argued that it did not owe Stewart—who consumed paroxetine made by another company—a duty of care under Illinois law. Second, GSK argued that plaintiff's claim was preempted under *Wyeth v. Levine*, 555 U.S. 555, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009), because the FDA had rejected the paroxetine-specific warning that, according to plaintiff, Illinois law required. The district

[1] Mrs. Dolin also sued Mylan, Inc., the company that manufactured the generic paroxetine that Stewart Dolin actually took. Mylan moved to dismiss on preemption grounds under *Mensing*, 564 U.S. 604, 131 S.Ct. 2567, and *Bartlett*, 570 U.S. 472, 133 S.Ct. 2466. The district court granted Mylan's motion, and Mrs. Dolin has not appealed that decision.

court denied GSK's motions for summary judgment, and the case proceeded to trial.

GSK moved for judgment as a matter of law during and after trial. GSK argued that plaintiff had failed to provide evidence that paroxetine causes suicide and that the paroxetine labeling caused Stewart's suicide. GSK also renewed its arguments that it was not liable both because it did not owe Stewart a duty under Illinois law and because federal law preempted the failure-to-warn claim. The district court denied GSK's motions and entered final judgment in favor of Mrs. Dolin.

II. *Preemption*

The Supremacy Clause was at the core of the Framers' effort to provide a national government with the powers needed to govern the new Republic effectively. It provides: "This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. The Supremacy Clause "invalidates state laws that 'interfere with, or are contrary to,' federal law." *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985), quoting *Gibbons v. Ogden*, 22 U.S. (9 Wheat.) 1, 211, 6 L.Ed. 23 (1824). State law

includes duties imposed by court decisions applying state tort law. E.g., *Mensing*, 564 U.S. 604, 131 S.Ct. 2567 (invalidating state laws imposing duty on generic manufacturers to change drug labels).

"Preemption comes in three forms." *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 390 (7th Cir. 2010). First is express preemption, "which occurs when Congress clearly declares its intention to preempt state law." *Id.* Second is implied preemption, "which occurs when the 'structure and purpose' of federal law shows Congress's intent to preempt state law." *Id.* This case involves the third form, called conflict or impossibility preemption. Conflict preemption occurs when there is "an actual conflict between state and federal law such that it is impossible for a person to obey both." *Guilbeau v. Pfizer, Inc.*, 880 F.3d 304, 310 (7th Cir. 2018), quoting *Mason*, 596 F.3d at 390. When that is true, "federal law controls and the state-law tort claims must be dismissed." *Id.*

In *Wyeth v. Levine*, the Supreme Court addressed how conflict preemption applies to state-law claims against brand-name drug manufacturers. The Court held that state-law claims based on labeling deficiencies are not preempted if the manufacturer could have added the warning unilaterally under the CBE regulation. 555 U.S. at 573, 129 S.Ct. 1187 (finding that defendant had "failed to demonstrate that it was impossible for it to comply with both federal and state requirements" when the "CBE regulation permitted" defendant "to unilaterally strengthen its warning" on its brand-name drug). In a later case addressing how

Levine would apply to claims against manufacturers of generic drugs, the Court reiterated that the "question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *Mensing*, 564 U.S. at 620, 131 S.Ct. 2567, citing *Levine*, 555 U.S. at 573, 129 S.Ct. 1187. As a general rule, then, state law can hold a brand-name manufacturer liable for failing to use its powers under the CBE regulation to add a new warning to a drug label.

There is one final part to this standard, and it is decisive here. Recall that the FDA can reject CBE submissions and require manufacturers to revert to the prior version of the label. *Levine* acknowledged that the FDA retains this authority, and "held that there could be preemption if the manufacturer met the stringent standard of proving that there was *clear evidence* the FDA would have rejected the proposed change in the drug's label." *Mason*, 596 F.3d at 391, citing *Levine*, 555 U.S. at 571, 129 S.Ct. 1187. The evidence here meets that standard.

In sum, Dolin's state-law claim against GSK is preempted if GSK could not have added the adult-suicidality warning using the CBE regulation. *See In re Celexa & Lexapro Marketing & Sales Practices Litigation*, 779 F.3d 34, 41 (1st Cir. 2015) (finding that plaintiff must allege a label deficiency that defendant "could have corrected using the CBE regulation."). To add a warning through the CBE regulation, GSK needed newly acquired information about paroxetine that would allow it to add a warning about suicide risk in adults. And even if GSK had newly acquired

information along these lines, GSK can still succeed on its preemption defense if there is clear evidence that the FDA would have rejected the adult-suicidality warning that plaintiff argues was tortiously omitted. Based on the evidence in this case, we conclude that, as a matter of law, (1) there is clear evidence that the FDA would have rejected the warning in 2007, and (2) GSK lacked new information after 2007 that would have allowed it to add an adult-suicidality warning under the CBE regulation.[2]

A. *Standard of Review*

Before we can reach the merits of GSK's preemption defense, we must address a threshold issue. Plaintiff argues that we must review the district court's preemption finding for clear error. In the district court, both plaintiff and GSK maintained that preemption under *Levine* was a question of law. The district court initially found that *Levine* preemption was a question of fact to be submitted to the jury. GSK objected to the wording of the court's proposed jury instructions and continued to argue that the issue was a legal one. The

[2] Judge Zagel denied GSK's motion for summary judgment on the preemption defense, finding that the FDA's invitation to request a meeting after the fourth denial of a paroxetine-specific warning defeated the *Levine* preemption defense. App. 28. We respectfully disagree with our colleague's finding on this point, though our decision is based on the trial record rather than the summary judgment record. The case was later re-assigned from Judge Zagel to Judge Hart for trial.

district court ultimately omitted the instruction and did not submit the question of preemption to the jury.

Our cases have analyzed preemption under *Levine* as a legal question. In *Guilbeau*, we wrote that "preemption is a legal question for determination by the courts. . . ." 880 F.3d at 318, quoting *Watters v. Wachovia Bank, N.A.*, 550 U.S. 1, 20, 127 S.Ct. 1559, 167 L.Ed.2d 389 (2007); *see Mason*, 596 F.3d at 390, 393–96 (referring to preemption issue as "a legal one" and analyzing preemption as a matter of law). Recently, the Third Circuit determined that "the ultimate question of whether the FDA would have rejected a label change is a question of fact for the jury rather than for the court." *In re Fosamax Products Liability Litig.*, 852 F.3d 268, 282 (3d Cir. 2017). The district court in this case relied on the Third Circuit's decision when it proposed submitting the preemption defense to the jury.

The Third Circuit noted that other circuits treat the *Levine* "test" as "a legal question." *Id.* at 287 & nn.103–105 (collecting cases). To reach a contrary conclusion, the Third Circuit relied in part on *Boyle v. United Technologies Corp.*, 487 U.S. 500, 108 S.Ct. 2510, 101 L.Ed.2d 442 (1988), which addressed conflict preemption for product liability claims against manufacturers of military equipment whose products must comply with military specifications. The Court stated that "whether the facts establish the conditions for the [government specification] defense is a question for the jury." *Id.* at 514, 108 S.Ct. 2510. The Supreme Court has granted certiorari to review the Third Circuit's decision on this issue. *Merck Sharp & Dohme Corp. v.*

Albrecht, ___ U.S. ___, 138 S.Ct. 2705, ___ L.Ed.2d ___ (2018).

We need not determine in this case whether preemption under *Levine* involves a factual question for the jury. As the Third Circuit noted, "when no reasonable jury applying the clear-evidence standard" could "conclude that the FDA would have approved a label change," then "the manufacturer will be entitled to judgment as a matter of law." *In re Fosamax*, 852 F.3d at 282. That is the case here. As we explain next, given the facts in this case, no reasonable jury could find that the FDA would have approved an adult-suicidality warning for Paxil under the CBE regulation between 2007 and Stewart Dolin's suicide in 2010.

B. *Clear Evidence of Rejection?*

GSK has provided undisputed evidence that the FDA rejected any adult-suicidality warning in 2007 when the agency required all SSRIs to adopt the same class-wide warnings. By 2000, a potential association between SSRIs and suicide was a high-profile controversy at the center of the FDA's attention. As part of its response to that controversy, the agency reviewed data on suicidal behavior in patients taking paroxetine. In 2007, after completing that review, the FDA ordered GSK to remove a paroxetine-specific warning of increased suicide risk in adults from the paroxetine label. It is hard to imagine clearer evidence that, considering the data available in 2007, "the FDA would not have approved a change" to the paroxetine label at that

time. *Levine*, 555 U.S. at 571, 129 S.Ct. 1187. No reasonable jury could find otherwise.

When deciding preemption in this context, "*Levine* is our intellectual anchor." *Mason*, 596 F.3d at 392. We "look at the long and fairly extensive administrative history" for the drug in *Levine* "and compare it to the administrative history of Paxil." *Id.* In *Levine*, the Court found four key facts critical when it found no preemption: (1) there was "no evidence . . . that either the FDA or the manufacturer gave more than passing attention" to the risk at issue; (2) the manufacturer had not "supplied the FDA with an evaluation or analysis" of the risk; (3) the manufacturer never "attempted to give the kind of warning required" under state law; and (4) the FDA "had not made an affirmative decision" to reject the warning. *Id.* at 572–73, 129 S.Ct. 1187.

All four of those evidentiary gaps in *Levine* were filled here. In 2006, GSK re-analyzed the placebo-controlled data on paroxetine and found a link between paroxetine and suicide in adults. It then made a unilateral change to the label, using the CBE regulation and adding a warning "that the higher frequency" of suicidality "observed in the younger adult population . . . may extend beyond the age of 24." GSK submitted that data to the FDA. But within a year, the FDA completed its own analysis of the same data and ordered GSK to remove that warning. The FDA notified manufacturers that all SSRIs needed to contain the same warning, saying there was a risk of suicide in patients

under 24 but that "studies did not show an increase in the risk of suicidality . . . in adults beyond age 24."

After the FDA effectively told it to remove the paroxetine-specific warning, GSK followed up with four requests to re-consider and to allow that warning. Each time, the FDA told GSK not to add the paroxetine-specific warning. These requests by GSK and the responses are clearly documented. They are not subject to reasonable dispute. This is clear evidence that, as of 2007, the FDA rejected an adult-suicidality warning for paroxetine.

To avoid the consequences of this evidence, plaintiff raises two arguments. Neither argument undermines the preemptive effect of the FDA's actions or decisions. First, plaintiff argues that the FDA rejected the paroxetine-specific warning only because GSK proposed adding it to the wrong spot on the label. GSK proposed warning about the risks of paroxetine in the middle of the class-wide SSRI warning, which FDA wanted to maintain as a uniform warning for all SSRIs. Because GSK never proposed adding the warning elsewhere in the label, plaintiff argues, there is no "clear evidence" that the FDA would have rejected a proposal along those lines.

This is an unreasonable interpretation of the discussions between the FDA and GSK. When the FDA rejected GSK's paroxetine-specific warning, the relationship between suicide, age, and SSRI use was at the forefront of the agency's attention. The FDA had just completed two lengthy meta-analyses on the topic. In

its analyses, the FDA observed a statistically significant association between paroxetine and suicidal behavior in adults, but decided to discount that result in favor of uniform SSRI labeling. That labeling affirmatively stated that SSRIs' "net effect appears to be neutral on suicidal behavior but possibly protective for suicidality for adults between the ages of 25 and 64." Plaintiff asks us to believe that the FDA—after deciding against an adult-suicidality warning based on its own analysis—rejected GSK's warning only because GSK proposed putting it in the wrong place. That is unreasonable.

Second, plaintiff argues that GSK could have followed up with a formal meeting with the FDA to discuss the paroxetine-specific warning. According to plaintiff, GSK lacks clear evidence that the FDA would have rejected the warning after such a meeting. This misunderstands the preemption standard. State laws requiring a label change are preempted unless the manufacturer could unilaterally add the new warning under the CBE regulation. *Levine*, 555 U.S. at 573, 129 S.Ct. 1187; *see also Mensing*, 564 U.S. at 620, 131 S.Ct. 2567.

The Supreme Court has rejected a very similar preemption argument in *Mensing*, where the Court held that federal law preempts state laws that require generic drug manufacturers to change a drug's label. In reaching that conclusion, the Court rejected the plaintiff's argument that the generic manufacturer could have asked the FDA to change the brand-name label. 564 U.S. at 619–20, 131 S.Ct. 2567. The Court

explained: "when a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for preemption purposes." *Id.* at 623–24, 131 S.Ct. 2567. That is what plaintiff's second argument amounts to. The preemption analysis asks only whether GSK could have added the adult-suicidality warning through the CBE regulation, not whether GSK might have been able to persuade the FDA to change its mind in a formal meeting—and certainly not whether GSK could have persuaded the FDA after already asking four times to include that warning and being told no four times.[3]

C. *Newly Acquired Information?*

The FDA's rejection of the adult-suicidality warning in 2007 does not definitively answer whether GSK could have added the warning between 2007 and 2010, when Stewart Dolin took paroxetine and committed

[3] In *Mason*, we found that GSK's predecessor had not shown the clear evidence needed for *Levine* preemption for a 23-year-old's suicide that occurred in 2003. 596 F.3d at 395–96. *Mason* thus addressed a suicide by a patient who would have fallen within the scope of the 2004 and 2007 class-wide warnings for pediatric suicide risk, so it does not control the preemption question here. Plaintiff also cites *Tucker v. SmithKline Beecham Corp.*, 596 F.Supp.2d 1225, 1236 (S.D. Ind. 2008), which similarly found that GSK's predecessor had not established a preemption defense for Paxil. *Tucker* addressed a 55-year-old's suicide in 2002, and was decided before *Levine* and *Mensing*, so its analysis does not apply here, to a 2010 suicide with the direction of *Levine* and *Mensing* available to the court.

suicide. The CBE regulation allows manufacturers to add or strengthen a warning when they acquire new information about the drug that makes the warning necessary. Plaintiff has failed to offer evidence that GSK acquired new information after 2007, when the FDA rejected its proposal to add an adult-suicidality warning to the paroxetine label that would have justified a change in the label and thus undermine GSK's preemption defense.

Newly acquired information "is data, analyses, or other information not previously submitted to the Agency." 21 C.F.R. § 314.3. Newly acquired information is not limited to new data. It includes new analysis of old data. *Id*. The "rule accounts for the fact that risk information accumulates over time." *Levine*, 555 U.S. at 569, 129 S.Ct. 1187.

Plaintiff proposes two ways that GSK had newly acquired information that supported the paroxetine-specific warning. First, plaintiff argues that GSK withheld or manipulated data in its submissions to the FDA. Plaintiff argues that the complete, untainted data showed an association between paroxetine and suicide in adults, and that the FDA never considered this information.

This argument fails because the undisputed evidence shows that the FDA was aware of the nature of the data it received from GSK. Plaintiff argues that GSK improperly attributed suicides that occurred in the "wash-out" phase of drug tests as occurring on the placebo. The wash-out phase refers to the period when

patients are given placebos to wash out other drugs in their system before the study begins. By attributing negative incidents that occurred during the wash-out phase to the placebo, Paxil looks better by comparison.

We have already rejected this argument about the same Paxil/paroxetine data in *Mason*, 596 F.3d at 394. As we noted then, "each erroneous datum had a star by it which noted that part of the suicidal behavior occurred during the wash-out phase." *Id.* The FDA scientist who reviewed the data "understood that the wash-out events were included when he analyzed the data," and his analysis "found no relationship between Paxil and suicidal behavior." *Id.* And in 2002 and 2003, GSK re-analyzed the data while excluding the wash-out phase and submitted that data to the FDA. *Id.*

Plaintiff points to one other possible source of newly acquired information. She offers an article published in 2011 as evidence that GSK conducted a re-analysis in 2008 that found a statistically significant association between adult suicidality and paroxetine. Plaintiff's expert testified, however, that this was not new analysis. He testified that the article was "submitted for publication in 2008 and published in 2011," but "was based on" GSK's "2006 analysis." The article contained the same figures as GSK's 2006 analysis, which GSK submitted to the FDA. There is no basis to conclude that this was a new analysis or that it was "not previously submitted to the Agency." 21 C.F.R. § 314.3.

* * *

GSK asked the FDA for permission to modify the paroxetine label as plaintiff argues was needed. The FDA said no, repeatedly. Federal law thus preempted plaintiff's Illinois-law claim that GSK should have warned of a risk of adult suicidality on the paroxetine label in 2010. GSK added a similar warning in 2006, and the FDA ordered that GSK remove that label and replace it with a class-wide SSRI warning in 2007. As a matter of law, this is what *Levine* called "clear evidence" that the FDA would have rejected the warning that plaintiff seeks under Illinois law. After 2007, GSK lacked newly acquired information that would have allowed it to add an adult-suicidality warning under the CBE regulation.

The parties and amici have briefed extensively whether Illinois law would impose a duty on a brand-name drug manufacturer toward a patient like Stewart Dolin, who took a generic form of the drug manufactured by a different company. The Illinois courts have not yet considered the new theory of liability that plaintiff advances. Because the evidence of federal preemption is decisive, we do not offer for that question of duty a prediction of state law under *Erie Railroad Co. v. Tompkins*, 304 U.S. 64, 58 S.Ct. 817, 82 L.Ed. 1188 (1938). We also need not consider GSK's other arguments based on the trial evidence. The judgment of the district court is REVERSED.

269 F.Supp.3d 851
United States District Court,
N.D. Illinois, Eastern Division.

Wendy B. DOLIN, Individually and as Independent Executor of the Estate of Stewart Dolin, Deceased, Plaintiff,
v.
GLAXOSMITHKLINE LLC, Defendant.

No. 12 C 6403
|
Signed 09/14/2017

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William T. Hart, UNITED STATES DISTRICT JUDGE

OPINION AND ORDER

A jury returned a verdict in the amount of $3 million in damages in a wrongful death and survival action in favor of plaintiff Wendy Dolin, executor of the Estate of Stewart Dolin, deceased, and against defendant GlaxoSmithKline LLC ("GSK"). The case was initiated in the Circuit Court of Cook County, Illinois and removed to this court based on diversity of citizenship. A motion to remand to the state court was denied (Dkt. 73).[1] This court has jurisdiction pursuant to 28 U.S.C. §§ 1332 and 1441.

The case is now before the court for ruling on the defendant's reserved motions for judgment as a matter of law or for a new trial.

Suit was brought to recover damages arising out of the death of plaintiff's husband, Stewart Dolin, a 57-year old attorney who was suffering from depression. He was prescribed and taking paroxetine, an antidepressant. Paroxetine is a drug designed, labeled and

[1] SmithKlineBeecham Corporation, formerly a Pennsylvania corporation, converted into GlaxoSmithKline LLC, a limited liability membership company organized under Delaware law. The sole member is GlaxoSmithKline Holdings (Americas) Inc., a Delaware corporation, with its principal place of business in Wilmington, Delaware. Dismissed defendant Mylan Inc. is a Pennsylvania corporation with its principal place of business in Pennsylvania. Defendant H.D. Smith Wholesale Drug Co., a Delaware corporation, with its principal place of business in Illinois, was dismissed as improperly joined. The amount involved exceeded $75,000.

sold by GSK under the brand name Paxil. (The druggist who filled the prescription for paroxetine supplied a generic form of the drug produced and sold with the GSK Paxil label by Mylan Inc.) On July 15, 2010 Mr. Dolin left his office and went to a Chicago "L" train station and leapt in front of a train. Plaintiff alleges he was suffering from drug induced akathisia, a psychomotor agitation disorder.

The case went to trial on the claim that GSK negligently failed to include a warning in the label that the drug can be a cause of adult suicide despite being aware of a significant risk of suicide in adults taking the drug. It is alleged that GSK allowed an affirmative misrepresentation to exist in the label that there is no risk of suicide beyond the age of 24 years. The plaintiff also asserts that the label did not warn of akathisia's association with suicidal behavior. Plaintiff contends that GSK negligently misled the medical profession (including Mr. Dolin's physician and the Food and Drug Administration ("FDA")) by concealing and misrepresenting adult suicide risk data relating to paroxetine.

Prior Rulings

GSK moved for summary judgment three times. It first argued that because Mr. Dolin ingested a generic form of paroxetine it could not be liable for its conduct in creating and controlling the labeling used. The court disagreed. ***Dolin v. SmithKline Beecham Corp.,*** 62 F.Supp.3d 705, 713 (N.D. Ill. 2014) (Zagel, J.) (Dkt. 110)

("***Dolin I***"). GSK moved to have the ruling certified under 28 U.S.C. § 1292(b) for an interlocutory appeal. After that motion was denied GSK petitioned the United States Court of Appeals for the Seventh Circuit for a writ of mandamus to compel certification of an appeal. The petition was denied. ***In re GlaxoSmithKline LLC.***, 557 Fed.Appx. 578, 579 (7th Cir. 2014).

GSK's second and third motions for summary judgment focused on Federal preemption as described in ***Wyeth v. Levine*,** 555 U.S. 555, 581, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009). It argued that any state law claim was preempted because the FDA rejected its efforts to place certain warnings on the label. It was held that GSK failed to show that the FDA would have rejected a Paxil specific warning of the risk of adult suicide. In the third motion GSK urged that Mr. Dolin's physician was aware of the risks of adult suicide associated with the drug and that the label was adequate as a matter of law. Plaintiff's strict liability claims of design defect and failure to warn were dismissed. Negligence and consumer claims were allowed to proceed. ***Dolin v. SmithKline Beecham Corp.*,** 2016 WL 537949 (N.D. Ill. Feb. 11, 2016) (Zagel, J.) (Dkt. 348) ("***Dolin III***").

In ***Mut. Pharm. Co., Inc. v. Bartlett***, 570 U.S. 472, 133 S.Ct. 2466, 186 L.Ed.2d 607 (2013) and in ***PLIVA v. Mensing*,** 564 U.S. 604, 131 S.Ct. 2567, 180 L.Ed.2d 580 (2011) the Supreme Court held that state-law label design defect claims that turn on the adequacy of label warnings are preempted by Federal law

in the case of a generic supplier because a generic supplier has no power to change the label created by a brand-name supplier. *See* ***Bartlett*****,** 133 S.Ct. at 2473; ***PLIVA*****,** 131 S.Ct. at 2576. Accordingly, defendant Mylan Inc.'s motion to dismiss was granted. (Dkt. 110).

GSK's ***Daubert*** motions to exclude the testimony of plaintiff's expert witnesses (David Healy, M.D., David Ross, M.D., Ph.D., M.B.I. and Joseph Glenmullen, M.D.) were denied. ***Dolin v. Smithkline Beecham Corporation*****,** 2015 WL 7351678 (N.D. Ill. Nov. 20, 2015) (Zagel, J.) (***"Dolin II")***.

The parties' motions *in limine* and objections to exhibits were resolved or reserved for ruling at trial. (Dkts. 465, 475, and 499.) Based on Rule 403 of the Federal Rules of Evidence, GSK's motion *in limine* to exclude any reference before the jury to criminal convictions of GSK for promoting Paxil in patients under age 18 and publishing misleading pediatric information with respect to Paxil was granted. The evidence in the case was limited to data dealing with adult suicide issues. Plaintiff was also precluded from offering studies showing minimal efficacy of paroxetine compared with placebo.

Shortly before trial plaintiff moved to amend her complaint to limit her claims to one count of negligence and one count of negligence with intent to injure. Negligence with intent to injure was ruled not to be a plausible claim. (Dkt. 490.) The case went to trial on the negligence claim only. Under Illinois law, plaintiff's

burden of proof was to prove every essential element of her claim by a preponderance of the evidence.

The jury was instructed, in substance, as follows: GSK was responsible for the content of the paroxetine label. (21 C.F.R. § 201.80(e) and 121 Stat. 924–926.) GSK is charged both with crafting an adequate label and with ensuring that the warnings remain adequate as long as the drug is on the market. Under FDA regulations, GSK is required to revise and update its label to include a warning as soon as there is "reasonable evidence of an association of a serious hazard with the drug; a causal relationship need not have been proved" (21 C.F.R. § 314.80(e)).

The jury was also told that FDA regulations permit a drug manufacturer to change a product label to add or strengthen a warning about its product without prior FDA approval so long as it later submits the revised warning to the FDA for review and approval (21 CFR § 314.70(c)(6)(iii)(A), (C)).

In recognition of the learned intermediary doctrine, the jury was told that GSK had a duty to warn only the prescribing physician of the risks of which it knew, or in the exercise of ordinary care, should have known.

Based on the rulings in ***Mason v. SmithKline Beecham Corp.,*** 596 F.3d 387 (7th Cir. 2010) and, more recently, ***In re (Fosamax Alendronate) Sodium Prods. Liab. Litig.,*** 852 F.3d 268 (3d Cir. 2017) the affirmative defense of Federal preemption as set forth in ***Wyeth v. Levine,*** 555 U.S. 555, 129 S.Ct. 1187,

173 L.Ed.2d 51 (2009) was ruled to be a factual question for the jury. The court offered to submit the question to the jury with an appropriate burden of proof instruction. GSK took the position that preemption was a question of law for the court and declined to have its affirmative defense submitted to the jury in the form stated in the court's instructions.

Standards

Federal Rule of Civil Procedure 50(a) provides that if "a party has been fully heard on an issue during a jury trial and the court finds that a reasonable jury would not have a legally sufficient evidentiary basis to find for the party . . . the court may . . . grant a motion for judgment as a matter of law." For a renewed motion for judgment as a matter of law the standard is whether the evidence presented, combined with all reasonable inferences, is sufficient to support the verdict when viewed in the light most favorable to the nonmovant. ***Dadian v. Vill. of Wilmette*****,** 269 F.3d 831, 837 (7th Cir. 2001).

A new trial may be granted if the verdict is against the clear weight of the evidence or the trial was unfair to the moving party. ***Whitehead v. Bond***, 680 F.3d 919, 927 (7th Cir. 2012). When a motion for a new trial is based on a ruling of evidence, it must be shown that the error was such as to deny the party a fair trial. ***Perry v. Larson*****,** 794 F.2d 279, 285 (7th Cir. 1986).

The Evidence

Paroxetine hydrochloride is a psychotropic drug of the Selective Serotonin Reuptake Inhibitor class ("SSRIs"). It is used, among other purposes, to treat major depressive disorders. The action of the drug on brain neurons is thought to be responsible for antidepressant effects. Marketing of the drug began in 1992. Generic formulations have been available since 2003. The New Drug Application (NDA 20-031) was submitted in 1989 with data relating to suicides. In April 1991, the NDA was amended with a report containing data on suicides and suicide attempts. An approval letter for major depressive disorders (MDD) was issued on December 29, 1992. Paxil is not approved in the United States for any treatment in the pediatric population.

The testimony of all of the medical experts who testified reveals that it is recognized in the medical community that some patients treated with SSRIs may be more likely to attempt or commit suicide. An SSRI may activate patients with suicidal ideations or induce symptoms of emotional volatility leading them to attempt or commit suicide in order to escape intolerable feelings.

The so-called "black box" warning on the GSK label, the truth of which, in the case of Paxil, was a main focus of attention in this case (Joint Exhibit 1). Some content and the origin of the label is connected with criminal complaints against GSK by the Attorney General of New York in 2003 and later by United States

Department of Justice resulting in a $3 billion fine against GSK for, among other things, withholding paroxetine data from the Food and Drug Administration ("the FDA") and unlawfully promoting the drug for pediatric (under age 18) uses.[2] The FDA conducted a pooled statistical analyses of SSRIs, including paroxetine, finding an increase in suicide and suicide ideation in pediatric cases treated with SSRIs. It then ordered that each SSRI have a standardized "black box" warning which, in the case of Paxil, provides as follows:

Suicidality and Antidepressant Drugs

> Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of PAXIL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with

[2] Based on Rule 403 of the Fed. R. Evid., the facts and results relating to the criminal actions and the results of related class actions against GSK were excluded from the evidence heard by the jury.

> increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PAXIL is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

Another part of the GSK paroxetine/Paxil label which was a focus of attention in the evidence is the **WARNINGS** section:

WARNINGS

> **Clinical Worsening and Suicide Risk**: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain

patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality

per 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening of depression or suicidality, especially if those symptoms are severe, abrupt in onset, or were not part of the patients presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment With PAXIL, for a description of the risks of discontinuation of PAXIL).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both

psychiatric and non-psychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for PAXIL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Mr. Dolin's attending physician, Dr. Martin Sachman, an internist, testified that he relied on the 2010 Paxil label in deciding to prescribe Paxil for the depression experienced by Mr. Dolin in June of 2010. He said that the label did not warn that the drug could induce suicidal behavior in adults over 24, rather that it stated the risk of suicide did not extend beyond age 24 and that he relied on those representations. It was his testimony that had the label warned of the risk of adult suicidal behavior in persons over the age of 24, he would not have prescribed the drug for Mr. Dolin. Dr. Sachman stated that he had other drug choices available for the treatment of Mr. Dolin's depression.

Plaintiff's experts, Dr. Healy and Dr. Ross, testified in support of Dr. Sachman's interpretation that the label did not warn of adult suicide risks. There was also testimony that the label did not warn that akathisia can lead to suicide.

Notwithstanding a vigorous cross-examination relating to the medical community's knowledge of adult suicide risks, the jury was entitled to accept Dr. Sachman's testimony that he relied on the statement that the risk of adult suicide did not extend beyond the age of 24 when he prescribed paroxetine for Mr. Dolin.

It was plaintiff's position that the language in the Black Box and Warnings sections of the GSK label stating that "[s]hort-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age 24" was based on pooled analyses of 11 antidepressant drugs (SSRIs) not on Paxil data only. It was contended that the statement is not true of data relating only to paroxetine/Paxil.

Plaintiff presented testimony from three experts, two psychiatrists (Drs. David Healy and Joseph Glenmullen) and one physician-expert who has been an examiner at the FDA (Dr. David Ross). Each testified that paroxetine ingestion can cause suicidal behavior in adults. Those opinions were supported by case reports, challenge studies (a patient having an adverse effect while on the drug is given a repeat administration of the drug), clinical-controlled trial data and controlled placebo studies reported in peer-reviewed scientific publications. The testimony and data was found to be admissible under ***Daubert*** standards. ***Dolin II,*** 2015 WL 7351678, at *2–7 *accord* ***Tucker v. SmithKline Beecham Corp.,*** 701 F.Supp.2d 1040, 1056–66 (Hamilton, J.) (approving, under ***Daubert,***

the opinions of Drs. Healy and Glenmullen relating to paroxetine and suicidality).

The jury heard evidence of an analysis of placebo-controlled Paxil data, conducted by GSK, showing depressed patients of all ages given Paxil, as opposed to placebo, were 6.7 times more likely to engage in suicidal behavior and that the results were statistically significant. There was also testimony about data showing suicidal behavior in patients over 24 and under 65 as high as a 10-fold statistically significant increase in risk for that age group. The jury was also shown an analysis done by the FDA which showed a statistically significant 2.76 times increased risk for Paxil as opposed to placebo, across all psychiatric conditions among patients over 24. In addition to the placebo-controlled data, the jury saw analyses done on uncontrolled Paxil data in the 1980s (using GSK's and FDA's methodology at that time), which showed an 8.9-fold increase suicidality risk versus placebo.

It was shown that studies in support of the original new drug application included among major depressive disorder (MDD) patients 10 completed suicides. Five occurred among patients randomized to paroxetine; three randomized to tricyclic antidepressants. The remaining two completed suicides occurred in patients during the "washout" phase (a period when study patients are given no medication of any kind) before the study had actually begun. These two suicides should not have been assigned to any of the treatment groups, and there was no scientific justification for

assigning them exclusively to the group of patients randomized to placebo.

The sponsor reported completed suicide in the Paxil-treated patients as 5/2963 (0.17%) and in placebo-treated patients as 2/554 (0.36%) making it appear as if the incidence of completed suicide in Paxil-treated patients was lower. The actual incidence in placebo-treated patients was 0/554 (0.0%), far lower than the 0.17% incidence in Paxil-treated patients.

The sponsor also misattributed two suicide attempts during the washout phase to the placebo-randomized group. Suicide attempts in the Paxil-treated patients was reported as 42/2963 (1.4%) and in the placebo group as 3/554 (0.54%) with an odds ratio of 2.6. The actual data, removing the misattribution, is 42/2963 (1.4%) and 1/554 (0.18%) producing an odds ratio for Paxil compared to placebo of 7.8.

Dr. Martin Brecher, of GSK, admitted that attributing suicide or suicide attempts occurring during a wash-out phase to placebo-treated patients is improper.

Following approval of Paxil, GSK staff generated publications to show Paxil did not increase the risk of suicidal behavior in adults.

Dr. David Healy and Dr. David Ross stated, on behalf of the plaintiff, that all of the data, showing confidence intervals, odds ratio, and statistical significance figures together with suicidality incident reports,

establish an undisclosed adult suicide risk for persons over 24 years of age taking paroxetine.

Dr. David Ross is board certified in internal medicine. Also, he has a Ph.D in biochemistry and a Master's degree in biomedical informatics. He was an examiner on the staff of the FDA serving as deputy director of the Office of Drug Evaluation at the FDA's Center for Drug Evaluation and Research. He is now Director of a public health program at the U.S. Department of Veterans Affairs. His testimony described FDA procedures and the inadequacy of the Paxil label.

Dr. Ross testified that, in his opinion, paroxetine is associated with an increased risk of suicidal behavior in adults relative to placebo. He stated that the risk is higher than other antidepressants; that it is not restricted to patients less than 25 years of age; that the drug sponsor was aware, since 1989, of the increased risk and aware since 2006 that the risk was not restricted to patients less than 25 years of age; that the 2010 label falsely stated that the risk was restricted to patients less than 25 years of age, and did not provide any information on Paxil-specific related risks. He stated that GSK was not prevented from inserting adult suicide risk information in the label.

GSK submitted the testimony of a very qualified expert in statistics who discounted all past studies and incident reports that were not based on double-blind, randomized, dose controlled, timed data. Earlier studies and reports were rejected by him as essentially out of date and to be ignored in reaching any conclusions

about paroxetine or Paxil. Based on his analysis of controlled data, he was of the opinion that it does not appear that paroxetine presents a risk of adult suicide. A difficulty with his opinion is that data he rejected were used by GSK in submissions to the medical community and to the FDA.

The adequacy of warnings is a question of fact for the jury in prescription drug cases unless the warning is plain, clear and unambiguous and the issue of label adequacy can be resolved as a matter of law. ***Kelso v. Bayer Corp.,*** 398 F.3d 640, 642 (7th Cir. 2005). This is not such a case. The jury was entitled to decide the whether or not the label warnings were adequate. There was sufficient evidence for the jury to conclude that the label was inadequate and misleading.

GSK contends that there was insufficient evidence to show a causal link between paroxetine and Mr. Dolin's death. Dr. Sachman's prescription for 30 Paxil tablets (10 mg per day) was filled by Mr. Dolin on June 27, 2010. An autopsy showed that paroxetine was in Mr. Dolin's system at the time of his death on July 15, 2010. (There was no evidence that the exact number of tablets taken by him was significant).

Plaintiff presented the testimony of Dr. David Healy on the subject of the suicide risk of Paxil and the testimony of Dr. Joseph Glenmullen, a board certified psychiatrist, who is a clinical instructor at the Harvard Medical School, on the topic of Mr. Dolin's death.

Dr. David Healy, a professor of psychiatry at Bangor University, United Kingdom, an expert in

pharmacological psychiatric treatment and research, testified about mechanisms by which paroxetine induces suicidal behavior diagnosed as akathisia, emotional blunting and decompensation. It was shown that the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, DSM-5) of the American Psychiatric Association defines Medication-Induced Acute Akathisia as follows:

> Subjective complaints of restlessness, often accompanied by observed excessive movements (e.g., fidgety movements of the legs, rocking from foot to foot, pacing, inability to sit or stand still), developing within a few weeks of starting or raising the dosage of a medication (such as a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms.

Dr. Glenmullen testified that Mr. Dolin was suffering from paroxetine-induced akathisia which was the cause of his death. Dr. Glenmullen conducted a differential diagnosis of Mr. Dolin's symptoms and behavior during the last week of his life. A differential diagnosis is an accepted methodology for an expert to render an opinion about the identity of a specific ailment. ***Myers v. Illinois Cent. R. Co.,*** 629 F.3d 639, 644 (7th Cir. 2010). The expert must provide a list of potential causes and determine which should be ruled in and ruled out. Dr. Glenmullen listed 13 potential causes of Mr. Dolin's death and went through each and concluded that death resulted from drug-induced akathisia caused by the ingestion of paroxetine.

Dr. Glenmullen stated that Mr. Dolin did not form an intent to kill himself, rather his death was a drug-induced reaction, a compulsion to kill himself—an accident and not voluntary suicide.

Dr. Glenmullen pointed to facts in Mr. Dolin's medical record and his conduct shortly before and at the time of his death to support his opinion. Paroxetine was prescribed and being taken by Mr. Dolin approximately six days before his death on July 15, 2010. In addition to being treated by Dr. Sachman, Mr. Dolin was consulting two therapists. There was testimony from his long-time therapist who saw him in an emergency session the night before his death. She stated that his anxiety was higher than she had ever seen before, and unlike previous times, it did not come down at the end of the session. Also, for the first time in her 30-year career, because of her concern, she called her client, Mr. Dolin, (the next morning, the day of his death) to advise him to get a prescription for a fast-acting sedative. Mr. Dolin left his office shortly after lunch and went to an L-station. A nurse, who was on the platform and saw Mr. Dolin jump in front of the train, stated that moments before his death he was nervously pacing back and forth. A partner in his firm testified that shortly before his death Mr. Dolin was acting differently and had difficulty processing simple legal issues. The lawyer did not think his death was work-related.

GSK argued that Mr. Dolin's death was a voluntary act caused by a history of depression, the pressures of the practice of law in an international firm and

family problems. Medical record evidence was presented including that, in the past, Mr. Dolin had taken Paxil and another SSRI for depression without any adverse incident. Financial and business data were presented to show professional and practice pressures experienced by Mr. Dolin who was also grieving the loss of family members.

Dr. Anthony Rothschild, a psychiatrist on the faculty of the University of Massachusetts, testified in support of his opinion that Mr. Dolin's death was not due to drug-induced akathisia. He focused on Mr. Dolin's medical history and stated that his voluntary suicide was related to depression brought about by professional and family problems. Dr. Rothschild cited statistics showing the high level of suicides among the lawyer population.

Dr. Rothschild stated that it was his opinion that Mr. Dolin's suicide was not caused by paroxetine. His study of the drug does not show that it can cause suicide. Instead, in his opinion, Mr. Dolin's suicide was caused by his anxiety disorder, possible major depressive disorder, longstanding fears and feelings of inadequacy and inferiority despite apparent outward success. Multiple life stressors, including harsh criticism of Mr. Dolin at work by some of his colleagues, a significant decrease in his performance as group practice leader and a reduction in billable hours, were factors. A decrease in budgeted compensation, difficulties with clients and feeling disconnected from his wife were noted. Dr. Rothschild stated that Mr. Dolin was

receiving disorganized mental health treatment from health care providers who did not communicate.

Both sides presented evidence from which the jury could have found for the plaintiff or the defendant on the issue of the cause of death. There is, however, no basis to set aside a jury's finding that Mr. Dolin's death was caused by ingestion of paroxetine.

The issue of preemption was presented both factually and legally by GSK. The factual argument is premised on the claim that certain language it proposed to add to the label in 2007 was not permitted by the FDA. Plaintiff responded that the proposed language was inadequate and misleading and that GSK did not prove that the FDA would have refused to permit a warning of the risk of adult suicide. The proposed language is as follows:

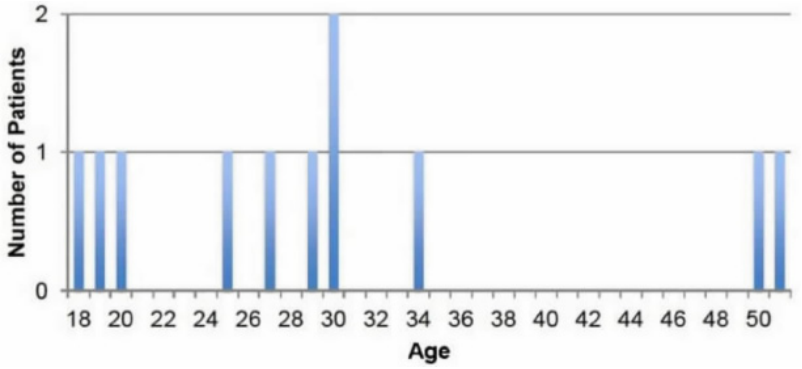
> Young adults, especially those with MDD, may be at increased risk for suicidal behavior during treatment with paroxetine. An analysis of placebo-controlled trials of adults with psychiatric disorder showed a higher frequency of suicidal behavior in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25-64 years and ≥65 years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behavior in patients treated with paroxetine compared with

> placebo (11/3,455 [0.32%] versus 1/1978 [0.05%]); all of the events were suicide attempts. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

Dr. David Ross addressed the proposed language. He stated that it was misleading with respect to the eleven patients referred to in the proposed language. The eleven paroxetine-treated patients who attempted suicide ranged in age from 18 to 51. The distribution of ages did not show any skewing towards younger or older patients. The median age was 29 years. Half the patients were younger than 29 and 50% were older. Only three were under 24. The mean age of these patients (30 years) is similar to the median age. The data do not provide a basis for concluding that the Paxil-associated increase in suicide attempt risk is restricted to any particular range of age. The sponsor chose to do that in stating that 8/11 of the patients were under 30 (not 24) or younger, implying that an increased risk of suicidal behavior was restricted to this younger group. The choice of an age cutoff of 30 was completely arbitrary. Eight of the eleven of the patients were 25 or older. The data do not support the conclusion that the increased risk associated with Paxil is restricted to any group or to those under 24 as claimed in statements made to the medical community and in a proposed

label change submitted to the FDA. The data is shown in the following Figure.

Distribution of ages of paroxetine-treated patients with suicide attempts



In Dr. Ross's opinion, the FDA would not have refused to permit GSK to warn about the risk of adult suicide in the label. He stated that GSK should have included a short statement warning of the risk of adult suicide.

Assuming, however, that the language proposed was sufficient, it does not appear that there is "clear evidence" that the FDA would have refused to permit GSK to add a warning of a risk of adult suicide. "Clear evidence" is required by ***Wyeth*** to prove preemption. The FDA informed GSK that product specific language should not be included in the class labeling revision required for the SSRI class of drugs. The FDA stated that "[i]f you would like to discuss this matter further, please submit a formal meeting request." However, GSK never requested a meeting or took any other

action to include a Paxil-specific warning outside of the class warning. There is not clear evidence that the FDA would have rejected a Paxil-specific warning outside of the class warning. *Accord* ***Forst v. SmithKline Beecham Corp.,*** 639 F.Supp.2d 948, 954 (E.D. Wis. 2009).

GSK argues that plaintiff did not prove that the paroxetine taken by Mr. Dolin was bioequivalent of Paxil. The absence of proof of a bioequivalent drug was never an issue in this case. Nevertheless there was testimony from Dr. Healy that paroxetine is Paxil. Also, a generic drug must be approved by the FDA. *See* ***Mut. Pharm. Co., Inc. v. Bartlett,*** 570 U.S. 472, 133 S.Ct. 2466, 2471, 186 L.Ed.2d 607 (2013) (a generic drug to be approved must be "chemically equivalent to the approved brand-name drug: it must have the same 'active ingredient' or 'active ingredients,' 'route of administration,' 'dosage form,' and 'strength' as its brand-name counter-part") (quoting 21 U.S.C. § 355(j)(2)–(8)).

When a fact issue has not been raised before trial, an absence of proof contention can be met, as here, with a prima facie showing of evidence, as appears in this record. There was no failure of proof that the paroxetine taken by Mr. Dolin was the bioequivalent of Paxil.

Judge Zagel rejected the legal argument that GSK cannot be held liable for negligence relating to the Paxil label. ***Dolin I,*** 62 F.Supp.3d at 713. His careful analysis of the cases will not be repeated. It is proper to observe, however, that since that ruling, the Court of Appeals for the Sixth Circuit has disagreed with this

court's interpretation of Illinois negligence law saying "we predict that the Illinois Supreme Court would not recognize brand manufacturers owed generic consumers a duty that can give rise to liability." ***In re Darvocet. Darvon, and Propoxyphene Prods. Liab. Litig.***, 756 F.3d 917, 944 (6th Cir. 2014).

The ***Darvocet*** court did not answer the points that liability in this case is based, not on the sale of the drug or drug chemistry, but on GSK's responsibility for the content of the label; that the generic supplier (Mylan) cannot be held liable for the content of the label; and that a jury has found negligence in failing to provide adequate label warning of the risk of adult suicide. Also, in this case, GSK's history of misconduct with this drug by failing to warn and providing false information to consumers and the FDA are factors which militate against providing label immunity based solely on the fact that a generic product was substituted for the prescription of Paxil because Illinois law permitted a druggist to substitute a possible lower cost identical product.

Turning next to the motion for a new trial, GSK argues that the jury instructions were improper; plaintiff's experts testified to undisclosed opinions; the court improperly limited cross-examination and the court permitted improper rebuttal testimony.

The trial of this case required the jury's attention for weeks of expert testimony relating to technical issues. The volume of testimony, exhibits and extensive arguments threatened jury overload and confusion.

The jury instructions, based on familiar Illinois negligence law, were designed to frame the issues without adding to the jury's burden. GSK's proposed additional instructions were, for the most part, unnecessary.

GSK attacks the Contentions instruction. The instruction tracked the allegations of the First Amended Complaint relating to the risk of paroxetine-induced suicide of persons over 24 years of age, inaccurate data and withheld data. GSK's additions and modifications to reflect its positions and contentions were accepted. The Contentions instruction was given together with negligence instructions. As reflected in Illinois Pattern Jury Instructions ("IPI") a plaintiff must allege facts establishing a duty of care owed by the defendant to the plaintiff, a breach of that duty, and an injury proximately caused by that breach. Illinois Pattern Instructions are presumed to accurately set forth Illinois law. ***Tragarz v. Keene Corp.,*** 980 F.2d 411, 423 (7th Cir. 1992). The jury was instructed to find that one or more of the acts claimed was "negligence" and also that the negligence was a "proximate cause" of injury.

The Causation instruction was improper according to GSK. The instruction given is the verbatim IPI instruction. IPI 15.01. The Seventh Circuit has found that the IPI instructions on proximate cause set forth Illinois law. ***Tragarz,*** 980 F.2d at 423.

GSK proposed instructions explaining distinctions between "cause-in-fact" and "legal cause" that were unnecessary and likely to cause confusion. This instruction was also said by GSK to be necessary to explain a

voluntary suicide instruction proposed. That instruction contained argument and did not explain that voluntary suicide following a tortious act only breaks a chain if it appears that the suicide could not be foreseen. This is not such a case. Moreover, Dr. Glenmullen described Mr. Dolin's death as an accident—the result of drug-induced akathisia—not voluntary suicide. Although these instructions were refused, GSK was allowed to argue that Mr. Dolin's death resulted from voluntary suicide.

The "Defendant's Duty" instruction was based on ***Wyeth*,** 555 U.S. at 570, 129 S.Ct. 1187 and FDA regulations. The last paragraph of the instruction informed the jury that it could consider to compliance with FDA regulations as a defense factor. Also, in recognition of the learned intermediary doctrine, the "Duty to Warn" instruction states that defendant had a duty to warn only the attending physician of risks.

GSK's argument that the jury was misled into believing that GSK manufactured the paroxetine ingested by Mr. Dolin is contrary to the record. The court and the parties made the distinction clear.

Other instructions proposed by GSK (Duty to Warn of Risks, How to Assess the Adequacy of the Warning, Not to Infer Fault, Liability if Dr. Sachman Knew, Spoliation, Judicial Admissions, Another Manufacturer's Product, and Preemption) were unnecessary and very argumentative. The parties were permitted full opening and final arguments which included

references to many demonstrative exhibits. GSK's defense was fully explored before the jury.

It is claimed that the court committed error by allowing plaintiff's experts to testify to opinions or matters that were not previously disclosed in discovery (i.e., Dr. Ross's testimony on the subjects of what can be included in a label, the effects of akathisia, and about documents not produced at his deposition, [but later appeared on an exhibit list]; Dr. Healy's testimony about suicide signals and GSK's failure to disclose data). Plaintiff's experts provided detailed reports and gave lengthy depositions. Defendant's experts responded in detail. The issues tried in this case have been the subject of previous litigation presented by some of the same attorneys, some of the same experts and included in many of the same documents. Surprise was not a factor in this case.

GSK states that the court improperly limited its case in the following ways: excluding two additional experts from testifying about suicide statistics; excluding the testimony of an expert on the nature of international law firms; refusing cross-examination of expert witnesses concerning fees paid to them in other cases; refusing cross-examination in order to show bias of Dr. Healy about his research and views with respect to drugs other than Paxil.

Dr. Rothschild and Dr. Gibbons testified on the subject of suicide rates. One study relating to suicide rates in the military population was excluded as being

outside the issues in this case. Additional suicide statistical studies would not have assisted the jury.

There was direct testimony from several lawyers in Mr. Dolin's law firm about structure and management. The jury would not have been helped by hearing an expert on law firm structure, procedures and stressors. The topics were extensively covered by several law firm witnesses.

Plaintiff was allowed to recall Dr. Healy in rebuttal over the objection of the defendant. His testimony was in response to testimony given by Dr. Rothschild, Dr. Gibbons and Dr. Kraus during the defense case. It was not on new topics or simply repetitious. The rebuttal was not improper.

Defendant's motion for a new trial will be denied.

IT IS THEREFORE ORDERED AS FOLLOWS:

(1) Defendant's motions for judgment as a matter of law (Dkt. 560 and 561) and its alternative motion for a new trial (Dkt. 576) are each denied.

(2) The clerk of the court will enter judgment on the jury's verdict in favor of plaintiff Wendy Dolin, individually and as Executor of the Estate of Stewart Dolin, deceased, and against defendant GlaxoSmithKline LLC in the amount of $3,000,000 together with costs of suit.

(3) Plaintiff may apply for costs of suit within 14 days. Any cost issues will be resolved in accordance with the local rules.

2016 WL 537949

Only the Westlaw citation is currently available.

United States District Court,
N.D. Illinois, Eastern Division.

Wendy B. DOLIN, Individually and as Independent Executor of the Estate of Stewart Dolin, Deceased, Plaintiff,
v.
SMITHKLINE BEECHAM CORPORATION d/b/a GlaxoSmithkline, A Pennsylvania Corporation, Defendant.

No. 12 C 6403
|
Signed 02/11/2016

Attorneys and Law Firms

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MEMORANDUM OPINION AND ORDER

James B. Zagel, United States District Judge

Plaintiff Wendy Dolin brings this action against Defendant SmithKline Beecham Corp. d/b/a Glaxo-SmithKline ("GSK"). Plaintiff's husband, Stewart Dolin ("Mr. Dolin"), was fifty-seven years old when he committed suicide in July 2010 after being prescribed and ingesting a generic form of the drug Paxil—GSK's trade name for paroxetine hydrochloride.

This matter is presently before me on two motions for summary judgment filed by GSK. GSK's first motion argues that Plaintiff's state-law claims are preempted by federal law while its other motion contends that there are no genuine issues of material fact. For the following reasons, I am denying both motions in their entirety.

GSK's argument for "implied conflict preemption" has been uniformly rejected every time it has been brought within the Seventh Circuit. *See Mason v. SmithKline Beecham Corp.*, 596 F.3d 387 (7th Cir. 2010) (failure to warn claims involving Paxil-induced suicide of a 23-year-old woman not preempted by federal law); *Forst v. Smithkline Beecham Corp.*, 639 F. Supp. 2d 948, 953 (E.D. Wis. 2009) (failure to warn claims involving the Paxil-induced suicide attempt of a 61-year-old man are not preempted by federal law); *Tucker v. SmithKline Beecham Corp.*, 596 F. Supp. 2d 1225, 1227 (S.D. Ind. 2008) (failure to warn claims involving the Paxil-induced suicide attempt of a 55-year-old Catholic priest not preempted by federal law).

The Supreme Court has held that preemption is a demanding defense which will not succeed without "clear evidence" that the FDA would not have approved an enhanced warning to the drug's label. *Wyeth v. Levine*, 555 U.S. 555, 571 (2009). To meet this demanding burden, GSK is required to produce "clear evidence" that, had it added a Paxil-specific adult suicidality warning, that change would have been rejected by the FDA or deemed a misbranding of the drug.

GSK's preemption argument rests on the premise that the FDA has considered and rejected an adult suicide warning during the relevant time period, but the record demonstrates otherwise. On June 22, 2007, the FDA extended an invitation to GSK to discuss the option of keeping the 2006 Paxil-specific adult language in its current label by requesting a formal meeting. Specifically, the FDA told GSK: "If you would like to discuss this matter further [keeping the 2006 Paxil-specific adult warning in the Paxil label], please submit a formal meeting request." GSK, however, never asked for a formal meeting, nor did it seek additional labeling regarding Paxil-specific data. Moreover, GSK never sent a separate supplement and declined the FDA's invitation for a meeting to discuss the inclusion of the 2006 Paxil-specific adult warnings.

As the record currently stands, therefore, GSK has failed to meet its demanding burden of demonstrating by clear evidence that the FDA would have rejected a Paxil-specific adult suicide warning had GSK taken the FDA up on its request to schedule a formal meeting

or submit a separate supplement to add the Paxil-specific adult suicide warnings.

GSK's other motion for summary judgment contains four distinct arguments. First, GSK argues that Plaintiff's claims fail because Mr. Dolin's prescriber, Dr. Sachman, knew that Paxil increased the risk of adult suicidal behavior prior to prescribing the drug to Mr. Dolin. Second, GSK argues that the Paxil label is adequate as a matter of law. Third, GSK argues that Plaintiff's claims based on misrepresentation and consumer fraud fail because, according to GSK, there is insufficient evidence of the element of reliance. And finally, GSK renews its previous motion for summary judgment based on the idea that GSK cannot be held liable here because Mr. Dolin ingested the generic form of Paxil and not the name-brand drug itself. None of these arguments are persuasive.

With regards to whether Dr. Sachman knew that Paxil increased the risks of adult suicidal behavior prior to prescribing the drug to Mr. Dolin and whether Dr. Sachman relied on the 2010 Paxil label in making his decision to prescribe Paxil to Mr. Dolin, the record does not support GSK's interpretation of Dr. Sachman's testimony. Considering the record in the light most favorable to the non-moving party, as I am required to do, Dr. Sachman's testimony suggests that (1) he did not know that Paxil increased the risk of suicidal behavior in adults over 24 prior to prescribing Paxil to Mr. Dolin in 2010, (2) he relied upon the 2010 Paxil label before prescribing Paxil to Mr. Dolin, (3) the 2010 Paxil label does not adequately warn about the

risk of suicidal behavior beyond age 24, and (4) had he known of the risk, he would never have prescribed Paxil to Mr. Dolin. This is enough to defeat GSK's motion for summary judgment. Ultimately, these decisions cannot be made without assessing Dr. Sachman's credibility at trial.

Similarly, I cannot conclude at this point that GSK's 2010 Paxil label is adequate as a matter of law. Plaintiff is ready to offer multiple expert opinions on this matter, including Dr. Ross and Dr. Glenmullen. The adequacy of Paxil's 2010 label will depend on this testimony, GSK's expert testimony, and the underlying statistical evidence. Reaching a decision before trial would be inappropriate.

GSK's final argument asks that I revise a previous decision of mine that was entered in a February 28, 2014 order. I assume the reader's familiarity with the facts and law set forth therein. Although I am allowed to change my previous decision on a renewed motion for summary judgment, there is nothing in the record that would justify doing so.

CONCLUSION

I am denying both of GSK's motions for summary judgment in their entirety.

United States Court of Appeals
For the Seventh Circuit
Chicago, Illinois 60604

September 20, 2018

Before

DIANE P. WOOD, *Chief Judge*

DIANE S. SYKES, *Circuit Judge*

DAVID F. HAMILTON, *Circuit Judge*

No. 17-3030

WENDY B. DOLIN, Individually and as Independent Executor of the Estate of STEWART DOLIN, Deceased,
Plaintiff-Appellee,

v.

GLAXOSMITHKLINE LLC, Formerly Known as SMITHKLINE BEECHAM CORP.
Defendant-Appellant.

Appeal from the United States District Court for the Northern District of Illinois, Eastern Division.

No. 12-CV-6403

William T. Hart, *Judge.*

ORDER

On consideration of plaintiff Wendy B. Dolin's petition for panel rehearing and en banc rehearing, filed on September 5, 2018, no judge in active service has requested a vote on the petition for rehearing en banc,

and all judges on the original panel have voted to deny the petition for panel rehearing.

Accordingly, the petition for panel rehearing and en banc rehearing filed by plaintiff Wendy B. Dolin is **DENIED**.

§314.70 Supplements and other changes to an approved application.

* * *

(c) Supplements for changes that may be made before FDA approval. An applicant shall submit a supplement at the time the applicant makes any kind of change listed below in the conditions in an approved application, unless the change is made to comply with an official compendium. A supplement under this paragraph is required to give a full explanation of the basis for the change, identify the date on which the change is made, and, if the change concerns labeling, include 12 copies of final printed labeling. The applicant shall promptly revise all promotional labeling and drug advertising to make it consistent with any change in the labeling. The supplement and its mailing cover should be plainly marked: "Special Supplement—Changes Being Effected."

(1) Adds a new specification or test method or changes in the methods, facilities (except a change to a new facility), or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, and purity which it purports or is represented to possess;

(2) Changes labeling to accomplish any of the following:

(i) To add or strengthen a contra-indication, warning, precaution, or adverse reaction;

(ii) To add or strengthen a statement about drug abuse, dependence, or over-dosage; or

(iii) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product.

(iv) To delete false, misleading, or unsupported indications for use or claims for effectiveness.

* * *

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21 CFR Ch. I (4-1-99 Edition)

§201.57 Specific requirements on content and format of labeling for human prescription drugs.

* * *

(e) *Warnings*. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectivenes for that disease or condition, and such usage is associated with serious

risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

* * *

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21 C.F.R. § 201.80

Specific requirements on content and format of labeling for human prescription drug and biological products; older drugs not described in § 201.56(b)(1).

* * *

(e) Warnings. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need

not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

(f) Precautions. Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

(1) General. This subsection of the labeling shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precautions not required under any other specific section or subsection of the labeling.

(2) Information for patients. This subsection must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling. The type size requirement for the Medication Guide set forth in § 208.20 of this chapter does not apply to the Medication Guide that is reprinted in or accompanying the prescription drug labeling unless such Medication Guide is to be detached and distributed to patients in compliance with § 208.24 of this chapter.

* * *

(g) Adverse Reactions. An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies

is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: "The most frequent adverse reaction(s) to (name of drug) is (are) (list reactions). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (list reactions), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are (list reactions)." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.126(b) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction.

* * *

DEFENDANT'S EXHIBIT 107

James E Murray/PharmRD
20-Apr-2006 17:03

US Regulatory Affairs
RTP Building 5
Rm 5.5380
919 483-5119
Pam S Barrett
PharmRD/GSK@GSK,
Rob R MacRae/
CORP/GSK@GSK,
Andrea L Parry/
CORP/GSK@GSK,
Ronald L Krail/MGMT/
PHRD/SB_PLC@GSK,
Daniel J Burch/
PharmUS/GSK@GSK,
Trevor G Gibbs/
PharmRD/GSK@GSK,
Jack G Modell/PharmRD/
GSK@GSK,
John E Kraus/PharmRD/
GSK@GSK,
Alan X Metz/PharmRD/
GSK@GSK,
Joseph P Horrigan/
PharmRD/GSK@GSK,
John T Davies/PharmRD/
GSK@GSK,
Martin M Ward/PharmRD/
GSK@GSK,
Barbara E Arning/
PharmRD/GSK@GSK,
Melissa L Ellis/PharmRD/
GSK@GSK,
Paul D Huckle/
PharmRD/GSK@GSK,

To Tosh M Butt/
PharmUS/GSK@GSK,
Peter H Lammers/
PharmUS/GSK@GSK,
David M Pemock/FPL/
Pharms/SB_PLC@GSK,
Barbara E Arning/
PharmRD/GSK@GSK,
Betty A McConnell/
PharmRD/GSK@GSK,
Christopher J Stotka/
PharmRD/GSK@GSK,
Debra H Lake/
PharmRD/GSK@GSK,
Leslie C Rogers/
PharmRD/GSK@GSK,
Maria 8 Wagner/
PharmRD/GSK@GSK,
Mary E Martinson/
PharmRD/GSK@GSK,
Olivia Pinkett1/SB-
OTHER/PHRD/SB_
PLC@GSK,
Steve F Hobbiger/DEV/
PHRD/SB_PLC@GSK,
Hugh Cowley-1/RES/
PHRD/SB_PLC@GSK.
Stan X Hull/PharmUS/
GSK@GSK,
Donna L Gutterman/
PharmUS/GSK@GSK,
Stephen 3 Hughes/
PharmRD/GSK@GSK,
Allan 2 Baxter/
PharmRD/GSK@GSK,

	Lori A Mazgay/MIS/ Pharms/SB_PLC@GSK, Mary A Rhyne/ CORP/GSK@GSK, Gaile L Renegar/ PharmRD/GSK@GSK, Colleen C Donnelly/ CORP/GSK@GSK, Leslie C Greenberg/ PharmInt/GSK@GSK, Louise A Dunn/ CORP/GSK@GSK, Denise S Benedict/ PharmRD/GSK@GSK, Todd Davey/ PharmUS/GSK@GSK, Fiona Bright-1/TRAC/ PHRD/SB_PLC@GSK, Jane M Nicholass/ PharmRD/GSK@GSK
cc	
bcc	
Subject:	Minutes of FDA/GSK TC on Paxil Proposed Labeling Change and DHCP letter on adult suicidality analysis

Attached are highlights of the April 20 teleconference with FDA regarding the recently conducted GSK analysis on suicidality in adult depression studies with paroxetine and the GSK planned revision to labeling and draft DHCP letter. FDA did not object to our plans for a labeling change and issuance of a DHCP letter.

****

Meeting Minutes FDA meeting

Thursday April 20, 2006 2:30pm to 3:00pm

GSK attendees:

For Paxil: Pam Barrett, John Kraus, Jack Modell, David Carpenter, Stephen Hughes, John Davies, Jim Murray, Barbara Arming

FDA attendees:

Tom Laughren, Paul Andreason, Renmeet Gujral, additional people from Statistics, Safety, Pregnancy and Lactation group.

Discussion with respect to Paxil adult suicidality analysis

The objective of the meeting was to get FDA's feedback on the recently submitted (April 5, 2006) results from a meta-analysis of MDD and non-MDD trials with regard to suicidality in adults, their response on suggested US label changes, a draft Dear Health Care Professional (DHCP) letter and general reactions to the communication strategy planned by GSK.

Main messages:

- FDA has not yet fully evaluate the data provided by GSK.

- However, FDA does not have objections to GSK's plan to proceed with implementing the labeling

changes under provisions of a Changes Being Effected (CBE) notification and issuance of the draft DHCP letter (with the only exception that GSK should delete any reference to FDA agreement to the DHCP letter).

- As far as FDA could judge from their review, the wording of the US label and the placement of the additional language within the warning section are acceptable.

- FDA is still performing their own analysis of the data provided by all sponsors across SSRIs and SNRIs and is not able to share their planned timeline with us at this point.

- GSK shared its communication plan with FDA, wherein – following submission of the CBE notification to FDA – GSK plans to issue the DHCP letter with the revised labeling, and then post this information on the GSK website shortly thereafter. In addition, GSK will also post results from previously submitted analyses of adult suicidality with paroxetine as well as the relevant Medical Information letter on this subject. GSK noted that they will provide a copy of the GSK DHCP letter to MEdWatch for posting on the MEdWatch website.

- GSK acknowledged that they would inform FDA upfront about the timing of the communication and would inform European regulators as well.

Jim

DEFENDANT'S EXHIBIT 114

April 27, 2006 [LOGO] GlaxoSmithKline

Thomas P. Laughren, M.D.,
Director
Division of Psychiatry Products
Center for Drug Evaluation
and Research
Office of Drug Evaluation I
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

GlaxoSmithKline
2302 Renaissance
Boulevard
P. O. Box 6154c
King of Prussia, PA
19406-2772

Tel. 610 787 7000
Fax 610 787 7777
www.gsk.com

Re: NDA 20-031; PAXIL® (paroxetine hydrochloride) Tablets
NDA 20-710; PAXIL® (paroxetine hydrochloride) Oral Suspension
NDA 20-936; PAXIL CR™ (paroxetine hydrochloride) Controlled-Release Tablets for Treatment of Depression
Supplement: Changes Being Effected
Addition of Adult Suicidality Data, Labeling

Dear Dr. Laughren:

Reference is made to our approved New Drug Applications for Paxil® (paroxetine hydrochloride) and Paxil CR™ as listed above. Reference is also made to our submission of April 5, 2006, which provided results from our internal analysis of MDD and non-MDD data on suicidality from paroxetine trials in the adult patient population. We also provided a draft revised Warnings section of the paroxetine Prescribing

Information and a draft Dear Healthcare Professional (DHCP) letter for Agency review and comment.

Additional reference is made to a teleconference between GSK and FDA on April 20, 2006, in which FDA agreed with GSK's plans to submit a Changes Being Effected labeling supplement to a change in the Warnings section of the label to describe the new information and agreed to GSK's plan to issue a DHCP letter.

Please find attached a Changes Being Effected (CBE) labeling supplement submitted under provisions of 21CFR 314.70 (6)iii). In order to allow for coordination with other regulatory authorities, we are planning to post the updated US labeling on gsk.com on Monday, May 8, 2006 together with the DHCP letter and additional information as outlined in the teleconference on April 20, 2006. This revised labeling will be implemented as soon as possible in future manufactured product.

In addition we are providing a copy of the DHCP letter, which will be mailed to US physicians starting on Friday, May 5, 2006. A pdf copy of this DHCP letter will be submitted via email to Karen A. Young on Monday May 8, 2006 for posting on FDA's MedWatch page.

We would appreciate if you could inform us about FDA's plans to publish this information on their website or communicate the data via other means to the public.

The following additional documents will be posted on gsk.com:

- Briefing Document from GSK to FDA submitted on April 5, 2006
- Relevant responses regarding suicidality from the European Article 31 Referral
- Report from the UK General Practice Research Database
- Medical Information Letter for response to Medical Inquiries

We are providing a copy of the current insert for Paxil (PX:L39, Supplement: Changes Being Effected, submitted September 6, 2005), an annotated version of the proposed Paxil insert (PX:L40) that shows revisions by underlines and deletions by strikethroughs, as well as a clean copy of the proposed labeling. We are also providing labeling for alternate image paroxetine tablets being distributed by PAR Pharmaceutical Inc., (PA:L20), which replaces the current label coded PA:L19. This submission is being provided electronically in accordance with the *Guidance for Industry, Providing Regulatory Submissions in Electronic Format- NDAs*, January 1999. Please see Guide to FDA Reviewers for detailed information about this electronic submission. The content of the labeling is also being submitted in SPL format in accordance with the *Guidance for Industry. Providing Regulatory Submissions in Electronic Format—Content of Labeling, April 2005*.

The data are being submitted to NDA 20-031 and incorporated by reference into the other referenced NDAs for paroxetine.

Should you have any questions regarding this submission or require additional information please contact me by phone at (610) 787 3069 or via secure email at Barbara.e.arning@gsk.com.

Sincerely,

/s/ [Illegible]
Barbara E. Arning, M.D.
Senior Director
US Regulatory Affairs, Psychiatry

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.

DEFENDANT'S EXHIBIT 122

[LOGO] Public Health Service

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 20-031/S-053
NDA 20-710/S-017
NDA 20-936/S-029

GlaxoSmithKline
Attention: Barbara E. Arning, M.D.
Senior Director, US Regulatory Affairs, Psychiatry
2301 Rennaissance Boulevard, P.O. Box 61540
King of Prussia, PA 19406-2772

Dear Dr. Arning:

We acknowledge receipt of your supplemental new drug applications dated April 27, 2006, and received April 28, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil (paroxetine hydrochloride) tablets (NDA 20-031), Paxil CR (paroxetine hydrochloride) controlled-release tablets (NDA 20-936), and Paxil (paroxetine hydrochloride) suspension (NDA 20-710).

These supplements, submitted under "Changes Being Effected", provide for labeling revisions to the WARNINGS and Information for Patients sections regarding

suicidality in young adults based upon your analysis of the paroxetine adult suicidality data.

We have completed our review of your supplemental applications, and they are approvable. Before these applications may be approved, you will need to make revisions to your labeling, as outline below, so as to ensure standardized labeling pertaining to adult suicidality with all of the drugs to treat major depressive disorder (MDD)

We additionally refer to the December 13, 2006 meeting of the Psychopharmacologic Drugs Advisory Committee to discuss FDA's meta-analysis of suicidality data derived from placebo-controlled trials of antidepressants in adult patients with major depressive disorder and other psychiatric disorders.

Based upon the recommendations made by the committee, we believe that additional changes are needed in antidepressant labeling and medication guides to alert practitioners, patients, family members and caregivers about an increased risk of suicidal thinking and behavior (suicidality) in young adults with MDD and other psychiatric disorders who are taking antidepressant medications. Changes are also needed to inform practitioners about an apparent favorable effect of antidepressants on suicidality in older adults and to remind them that the disorders being treated with antidepressants are themselves associated with an increased risk of suicidality.

Therefore, we are requesting revisions to your labeling and the antidepressant medication guides to

incorporate the committee's recommendations. Specifically, we are requesting the changes below in product labeling and the Medication Guide.

Revisions to Product Labeling

[These changes should be made to the box warning at the beginning of the package insert.]

DRUG NAME

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepreccants compared to placebo in adults beyond age 24: there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and

communication with the prescriber. [Insert established name] is not approved for use in pediatric patients. (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

[The following changes should be made to the current language under the **WARNINGS-Clinical Worsening and Suicide Risk** section.]

WARNINGS-Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive

disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table [add table number].

Table [add table number]	
Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Drug-Related Increases
<18	14 additional cases
18-24	5 additional cases
	Drug-Related Decreases
25-64	1 fewer ease
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness),

hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with [Insert drug name], for a description of the risks of discontinuation of [Insert established name]).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the

emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for [Insert established name] should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that [Insert established name] is not approved for use in treating bipolar depression.

> [The following changes should be made in current language under the **PRECAUTIONS-Information for Patients** section.]

PRECAUTIONS-Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with [Insert established name] and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for [Insert established name]. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking [Insert established name].

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for

the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Revisions to Medication Guide

Medication Guide
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults when the medicine is first started.**

2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is first started or when the dose is changed.

    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.

    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- other unusual changes in behavior or mood
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)

NDAs 20-031/S-053, 20-710/S-017, & 20-936/S-029
Page 6

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider

about the side effects of the medicine prescribed for you or your family member.

- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Simultaneous with this action letter, FDA has issued a Press Release as well as updated our internet site with the revised Medication Guides to alert the community to this action. Since there are so many MDD products, we feel that these actions are a better way to alert the community than individual Dear Health Care Professional (DHCP) letters for each of these products. Thus, we are not requesting individual DHCP letters.

These labeling revisions should be submitted as a formal amendment to your supplemental applications within 30 days from the date of this letter.

If you have any questions, call Renmeet Grewal, Pharm. D., Regulatory Project Manager, at (301) 796-1080 or Bill Bender, Regulatory Project Manager, at 301-796-2145.

Sincerely,

(See appended electronic signature page)

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

- -

Thomas Laughren
5/1/2007 04:49:57 PM

DEFENDANT'S EXHIBIT 128

"Crewal, Renmeet" <Rennweet.Grewal@fda.hhs.gov>

21-Jun-2007 09:11

To mary.e.martinson@gsk.com, barbara.e.arning@gsk.com, maria.8.wagner@gsk.com

cc "Bender, William" <William.Bender2@fda.hhs.gov>, "Saini, Sonny" <sonny.saini@fda.hhs.gov>, "Grewal, Renmeet" <Renmeet.Grewal@fda.hhs.gov>

Subject Wellbutrin, Paxil, Parnate Adult suicidality class labeling changes

Good Morning,

Please refer to our letter dated 5-1-07, requesting class labeling revisions for all drugs to treat major depressive disorder.

We have completed our review of all of these responses, and we believe, based upon these responses, that the labeling needs to be further edited as follows (strike through font denotes deletions to our labeling and double underline font denotes additions):

1. In Table X under **WARNINGS-Clinical Worsening and Suicide Risk**, we believe that the table descriptor under "Drug-Placebo Difference in Number of

Cases of Suicidality per 1000 Patients Treated" should be revised as follows:

- "Drug Related Increases" to "Increases Compared to Placebo"

"Drug Related Decreases" to "Decreases Compared to Placebo"

2. In the Medication Guide, we have deleted the phraseology related to "first", as denoted below, since "first" could represent a misleading concept for the patient.

- Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults ~~when the medicine is first started~~ <u>within the first few months of treatment</u>.

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is ~~first~~ started or when the dose is changed.

Additionally, some of the sponsors have inadvertently omitted the class labeling paragraph starting with "Consideration should be given . . . " under the **WARNINGS-Clinical Worsening and Suicide Risk** section, and some sponsors have incorrectly added the discontinuation language paragraph starting with "If the decision has been made . . . " to this section. Attached to this e-mail is the correct labeling, incorporating the above changes, for your product.

We have also noted that some sponsors have taken this opportunity to include other revisions to their labeling which are not applicable to the class labeling revisions requested in our 5-1-07 letter. We are requesting that these changes be submitted as a separate supplement.

In an attempt to take a final action on your supplemental applications, the Agency would like to secure labeling agreement with you via e-mail. Please be reminded that it is critical that the labeling is consistent for all of these products. As noted above, the relevant sections of the prescriber labeling as well as the entire Medication Guide are attached to this e-mail.

We request that you respond to this e-mail within a week.

If you have any questions, call William Bender, R.Ph., Senior Regulatory Project Manager at (301) 796-2145 or Renmeet Grewal, Pharm.D., Regulatory Project Manager.

Regards,
Rimmy

<<Revisions to Parnate Labeling 6-19-07.doc>> <<Revisions to Paxil Labeling 6-19-07.doc>> <<Revisions to Medication Guide 6-19-07.doc>> <<Revisions to Wellbutrin, SR, XL Labeling 6-19- 07.doc>> <<Revisions to Wellbutrin Medication Guide 6-19-07.doc>>

Renmeet Crewel, Pharm.D., LCDR USPHS
Regulatory Project Manager
Division of Psychiatry Products

Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

Revisions to Product Labeling

[These changes should be made to the box warning at the beginning of the package insert.]

Paxil

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Paxil or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening,

suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Paxil is not approved for use in pediatric patients. (See Warnings: Clinical Worsening and Suicide Risk, Precautions; Information for Patients, and Precautions: Pediatric Use)

[The following changes should be made to the current language under the **WARNINGS-Clinical Worsening and Suicide Risk section.]**

WARNINGS-Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking

and behavior (suicidality) in children,adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table [add table number].

Table [add table number]	
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No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

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The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness,

impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with Paxil, for a description of the risks of discontinuation of Paxil.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the

emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Paxil should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Paxil is not approved for use in treating bipolar depression.

[The following changes should be made in current language under the **PRECAUTIONS-Information for Patients** section.]

PRECAUTIONS-Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Paxil and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for Paxil. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Paxil.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis,

since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional. especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Revisions to Medication Guide

Medication Guide
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults ~~when the medicine is first started~~ within the first few months of treatment.**

2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is ~~first~~ started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

PLAINTIFF EXHIBIT PTX-344

US REGULATORY AFFAIRS: PSYCHIATRY/ NEUROLOGY

Monthly Highlights for June 2007

Date: 07/02/2007

KEY UPCOMING ACTION DATES for 2007

Redacted

KEY UPCOMING SUBMISSIONS for 2007

Redacted

KEY SUBMISSIONS-Status

Redacted

Redacted

PSYCHIATRY

Antidepressant Class Labeling Revisions-Suicidality

On June 21, 2007, GSK received additional changes via email from FDA for the antidepressant class label revision regarding young adult suicidality. GSK provided revised labeling incorporating the changes requested by FDA on June 28th for the 4 bupropion products; this new labeling will also be implemented for Paxil and Parnate products.

Redacted

Redacted

Paxil:

On June 21, 2007 FDA responded to our CBE submission for Paxil, Paxil CR and Paroxetine (submitted on May 23, 2007). They requested additional changes in the wording of the class labeling (from all sponsors and other GSK drugs as well) and asked for response via email within one week. GSK's request of maintaining the Paxil specific language within the class labeling was not addressed. FDA requested that those additions or changes should be addressed with a separate

supplement. In addition FDA confirmed that we would have to ask for a meeting to discuss the option of including Paxil specific language in the label. The teams will coordinate efforts and will respond via email next week and will send word versions via emails for approval.

Redacted

Redacted

Due Diligence Activities

Redacted

DEFENDANT'S EXHIBIT 129

"Crewal, Renmeet" <Rennweet.Grewal@fda.hhs.gov>

22-Jun-2007 11:56

To barbara.e.arning@gsk.com

cc "Bender, William" <William.Bender2@fda.hhs.gov>, "Saini, Sonny" <sonny.saini@fda.hhs.gov>

Subject Adult suicidality email

Hi Barbara,

I received your voicemail as well as email earlier this morning.

As for your first question, the Agency has reviewed your proposed changes, and we do not believe that your product specific analysis should be included in the class labeling revisions since the labeling is targeted at the class of drugs. If you would like to discuss this matter further, please submit a formal meeting request.

As for your second Question, please respond by email that you accept the changes arid also send in a word version of the labeling via email. We will then send an approval letter since you have accepted the changes.

Thanks
Rimmy

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21 C.F.R. § 314.70

§ 314.70 Supplements and other changes to an approved application.

Effective: June 30, 2006 – September 21, 2008

* * *

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).

* * *

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

* * *

(iii) Changes in the labeling, except for changes to the information required in § 201.57(a) of this chapter (which must be made pursuant to paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

* * *

(7) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

* * *

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21 C.F.R. § 314.70

§ 314.70 Supplements and other changes to an approved NDA.

Effective: September 22, 2008 – Present

* * *

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).

* * *

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved NDA may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

* * *

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be

made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

> (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

* * *

(7) If the agency disapproves the supplemental NDA, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

* * *