In the Superior Court of Pennsylvania

No. 459 EDA 2014

APRIL CZIMMER

v.

JANSSEN PHARMACEUTICALS, INC.,

Appellant.

BRIEF FOR PLAINTIFFS/APPELLEES

On Appeal from the Judgment of the Court of Common Pleas of Philadelphia County, Pennsylvania Entered January 2, 2014 at May Term 2011, No. 3459

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I. COUNTERSTATEMENT OF THE SCOPE AND STANDARDS OF REVIEW

As the Supreme Court of Pennsylvania explained in *Birth Center* v. *St. Paul Cos.*, 787 A.2d 376, 383 (Pa. 2001), when conducting appellate review of a trial court's ruling on a motion for judgment notwithstanding the verdict, "[w]e view the evidence in the light most favorable to the verdict winner and give him or her the benefit of every reasonable inference arising therefrom while rejecting all unfavorable testimony and inferences."

Earlier, in *Moure* v. *Raeuchle*, 604 A.2d 1003 (Pa. 1992), the Supreme Court explained:

> [T]he evidence must be considered in the light most favorable to the verdict winner, and he must be given the benefit of every reasonable inference of fact arising therefrom, and any conflict in the evidence must be resolved in his favor. Moreover, [a] judgment n.o.v. should only be entered in a clear case and any doubts must be resolved in favor of the verdict winner. Further, a judge's appraisement of evidence is not to be based on how he would have voted had he been a member of the jury, but on the facts as they come through the sieve of the jury's deliberations.

Id. at 1007; *see also Quinby* v. *Plumsteadville Family Practice, Inc.*, 907 A.2d 1061, 1074 (Pa. 2006) (same).

This Court is familiar with the very heavy burden a party bears in order to obtain j.n.o.v.:

> A JNOV can be entered upon two bases: (1) where the movant is entitled to judgment as a matter of law; and/or, (2) the evidence was such that no two reasonable minds could disagree that the verdict should have been rendered for the movant. When reviewing a trial court's denial of a motion for JNOV, we must consider all of the evidence admitted to decide if there was sufficient competent evidence to sustain the verdict. In so doing, we must also view this evidence in the light most favorable to the verdict winner, giving the victorious party the benefit of every reasonable inference arising from the evidence and rejecting all unfavorable testimony and inference. Concerning any questions of law, our scope of review is plenary. Concerning questions of credibility and weight accorded the evidence at trial, we will not substitute our judgment for that of the finder of fact. If any basis exists upon which the jury could have properly made its award, then we must affirm the trial court's denial of the motion for JNOV. A JNOV should be entered only in a clear case.

American Future Systems, Inc. v. *Better Business Bureau*, 872 A.2d 1202, 1215 (Pa. Super. Ct. 2005) (citation omitted), *aff'd*, 923 A.2d 389 (Pa. 2007).

With regard to Janssen's appeal from the trial court's denial of a new trial, in *Harman ex rel. Harman* v. *Borah*, 756 A.2d 1116 (Pa. 2000), the Supreme Court of Pennsylvania explained: "[a]lthough all new trial orders are subject to appellate review, it is well–established law that, absent a clear abuse of discretion by the trial court, appellate courts must not

interfere with the trial court's authority to grant or deny a new trial." *Id.* at 1121–22.

Moreover, in *Harman*, Pennsylvania's highest court proceeded to observe:

> The harmless error doctrine underlies every decision to grant or deny a new trial. A new trial is not warranted merely because some irregularity occurred during the trial or another trial judge would have ruled differently; the moving party must demonstrate to the trial court that he or she has suffered prejudice from the mistake.

Id. at 1122.

Lastly on the issue of a new trial, in *Buckley* v. *Exodus Transit & Storage Corp.*, 744 A.2d 298 (Pa. Super. Ct. 1999), this Court explained:

> Our review of the trial court's denial of a new trial is limited to determining whether the trial court acted capriciously, abused its discretion, or committed an error of law that controlled the outcome of the case. In making this determination, we must consider whether, viewing the evidence in the light most favorable to the verdict winner, a new trial would produce a different verdict. Consequently, if there is any support in the record for the trial court's decision to deny a new trial, that decision must be affirmed.

Id. at 305 (internal citations omitted).

II. COUNTERSTATEMENT OF THE CASE

A. Relevant Factual History

The evidence at trial established that, in early December 2006, plaintiff April Czimmer became pregnant with her son, Blake Czimmer. R.723a (Tr. 10/21/13 a.m. at 91). During the first trimester of her pregnancy, Ms. Czimmer ingested Topamax, a prescription medication manufactured and marketed by defendant Janssen, in order to treat her migraines. *Id.* Lisa Basye, a physician's assistant at the Virginia clinic where Ms. Czimmer was treating, prescribed Topamax beginning in August 2006 and continuing through February 2007. R.717a, 721a (*Id.* at 74, 78); R.1512a–15a (Plt. Exh. 1267 at 33, 37).

On September 24, 2007, Blake was born with a severe, complete unilateral cleft lip and palate. R.725a–26a (Tr. 10/21/13 a.m. at 103–04); R.1454a (Plt. Exh. 1266 at 38–39). Since his birth, Blake has undergone four surgeries to repair his oral clefts and associated injuries. R.1459a–60a (Plt. Exh. 1266 at 72). According to Blake's craniofacial surgeon, Dr. Kant Lin, Blake will require extensive future surgeries and treatment for his physical and emotional injuries. R.1460a–65a (*Id.* at 92–109, 250).

The evidence introduced at trial further established that Ms. Basye was never aware that Topamax, a pregnancy category C medication in 2006 and 2007, was a teratogen in humans, or that it could cause, or increase the risk of, cleft lip and cleft palate. R.1517a–18a (Plt. Exh. 1267 at 49–53). In fact, in 2006 and 2007, during the time Ms. Czimmer ingested Topamax while pregnant with Blake, the label for Topamax (on which Ms. Basye relied) stated, "[t]here are no studies using TOPAMAX® in pregnant women [and] TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus." R.3895a, 3907a (Plt. Exhs. 1210, 1211). The label also stated that "cases of hypospadias [a deformation in the underside of a male infant's penis] have been reported in male infants exposed in utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established." *Id.*

At trial Ms. Basye testified, via deposition, that if she been warned that Topamax was a teratogen in humans, or that it could cause, or increase the risk of, cleft lip and cleft palate — information which plaintiff's labeling and safety surveillance expert, Peggy Pence, Ph.D., testified Janssen knew well before 2006, but which was not communicated to prescribing

healthcare providers (R.593a–94a, 596a–97a (Tr. 10/16/13 a.m. at 92–93, 95–96))— she would not have prescribed Topamax to Ms. Czimmer. R.1517a–18a (Plt. Exh. 1267 at 49–53).

Evidence of general causation between Topamax and cleft lip and/or palate was presented to the jury by plaintiff's experts, Dr. Philip Lupo (epidemiologist) (R.637a–38a, 640a, 642a, 646a (Tr. 10/17/13 a.m. at 37, 38, 75, 84; Tr. 10/17/13 p.m. at 22)) and Dr. Richard Finnell (medical geneticist, teratologist, and embryologist) (R.753a–54a, 756a–57a, 759a, 761a–62a (Tr. 10/22/13 a.m. at 18–19, 50–51, 64, 80–81)). The jury also heard from Dr. Lin, via deposition, that having excluded all other potential causes for Blake's cleft lip and palate, it was his opinion, within reasonable medical certainty, that Topamax caused Blake's oral clefts. R.1453a–54a, 1465a–70a (Plt. Exh. 1266 at 30–32, 35–37, 39, 72–73, 75–78, 80, 82–86, 89–92, 113–114, 246–247, 249).

Based on this evidence, the jury found that plaintiff met her burden to prove by a preponderance of the evidence that the warnings of Topamax's harmful side-effects contained in that medication's label in 2006 and 2007, when the medication was prescribed to Ms. Czimmer, failed to adequately warn of the medication's actual harmful side-effects and that

Janssen therefore breached its duty to warn. The jury further found that plaintiff established that had an adequate warning been provided to the prescribing healthcare provider, that adequate warning would have prevented Ms. Czimmer from receiving the drug. Moreover, there was no evidence presented that Ms. Czimmer's filing of this action was untimely.

The jury, having heard and seen all of the evidence, determined that Janssen was negligent and that Janssen's negligence was a factual cause of Blake's injuries. Consequently, on October 30, 2013, the jury entered a verdict for the Plaintiff in the total amount of $4,002,184.68.

B. Relevant Procedural History

Plaintiff April Czimmer filed this lawsuit in the Court of Common Pleas of Philadelphia County in May 2011.

In July 2013, Judge Arnold L. New entered an order recognizing under FDA regulations Janssen did not have the ability to unilaterally change the pregnancy category applicable to Topamax from C to D. Rather, as Judge New later recognized in clarifying his order, although Janssen had the ability to request a change in the pregnancy category applicable to Topamax, the FDA's approval was necessary before Janssen could alter its

warning label to identify Topamax as in pregnancy category D rather than in pregnancy category C.

As a result, during the trial of this case, plaintiff through her counsel did not urge the jury to hold Janssen liable for having failed to place Topamax into pregnancy category D. Rather, plaintiff advanced a traditional negligent failure to warn claim against the manufacturer of a brand–name prescription drug, focusing on the specific warnings of Topamax's established potential to cause birth defects, including cleft lip and cleft palate, about which Janssen was aware in 2006 and 2007 and which Janssen unquestionably had the ability to add to the warning label for the medication without needing to obtain any advance permission from the FDA.

This case proceeded to trial before Senior Judge Victor J. DiNubile, Jr., one of the most experienced trial judges serving in the Philadelphia Court of Common Pleas. As is his practice, Judge DiNubile allowed the parties to present to the jury all of the relevant and contested evidence on the issues of what sort of birth defect warnings Topamax should have contained in 2006 and 2007 based on the risks of the drug known to Janssen at that time, whether the drug would have been prescribed to Ms. Czimmer

had the drug contained accurate and appropriate birth defect warnings in 2006 and 2007, and whether the drug was the factual cause of Blake Czimmer's cleft lip and palate. The jury, after hearing all of the relevant evidence, resolved each of these issues in plaintiff's favor.

Following the jury's verdict, Janssen filed a timely post–trial motion requesting either judgment notwithstanding the verdict or a new trial. On January 2, 2014, Judge DiNubile issued a 14–page opinion thoroughly and decisively rejecting all of the grounds for j.n.o.v. or a new trial that Janssen had presented. Janssen thereafter appealed from the denial of its post–trial motion to this Court.

III. SUMMARY OF THE ARGUMENT

Janssen's Brief for Appellant offers a hodgepodge of arguments, none of which comes close — individually or in combination — to providing any basis for disturbing either the jury's verdict or the trial judge's denial of Janssen's motion for post–trial relief.

On the issue of federal preemption, Janssen leads with an irrelevant red herring. Counsel for plaintiffs did not ask, nor did the trial court allow, the jury to find Janssen liable based on Janssen's failure to categorize Topamax as a pregnancy category D medication. Thus, Janssen's argument that federal law would preempt liability predicated on the medication's pregnancy category completely misses the mark, since the jury was neither asked to, nor was the jury permitted to, make any such finding.

Janssen's second preemption–related argument is equally without merit. The defendant argues that it introduced clear evidence to satisfy the demanding defense that the federal Food and Drug Administration would not permit Janssen to warn prescribers of Topamax's known human birth defect risk because the FDA did not allow Janssen to add that sort of a warning to the medication's Patient Package Insert (PPI). Yet Janssen's argument is a non sequitur.

The PPI provides warning to *the patient*. The medication's warning label published in the Physician's Desk Reference is directed to *the prescriber*, a trained medical professional who must determine whether a prescription drug's potential benefits outweigh its potential risks.

As the jury understood from the testimony presented, the FDA's disallowance of a particular warning from the PPI in no way establishes that the same warning could not have been included in the warning label directed to the trained professional prescribers of medications. Indeed, here the FDA specifically told Janssen that information concerning Topamax's risk of birth defects to humans should be included in the warning label directed to prescribers, but Janssen failed to add any such warning to that warning label, despite Janssen's undisputed ability to do so.

Janssen next argues that the tremendously experienced trial judge in this case incorrectly instructed the jury on the question of "cause–in–fact" under Virginia law. Janssen's arguments in this regard cannot survive scrutiny. Not only did the trial judge accurately instruct the jury on this point when the instructions are viewed in their entirety, as applicable law establishes they must be, but it was Janssen's proposed jury instructions that failed to accurately convey the actual elements of Virginia law's factual

cause requirements. Moreover, the unequivocal evidence establishing factual cause that plaintiffs introduced at trial render the supposed error identified by Janssen harmless at worst, because the jury's verdict, which shows an acceptance of plaintiffs' factual cause evidence, shows that the jury would have found for plaintiffs on this point no matter how stringent Virginia's factual cause requirement happened to be.

Thirdly, Janssen's Brief for Appellant quarrels with the jury's finding that an adequate warning of Topamax's actual human birth defect risks would have caused Ms. Czimmer's prescriber to not have prescribed that medication. The jury heard all of the relevant evidence on this point and returned a finding for plaintiffs on this issue. The evidence at trial, viewed in the light most favorable to plaintiffs, more than suffices to uphold this finding. The medical professional who prescribed Topamax to Ms. Czimmer at the relevant time could not have testified more clearly that she would not have prescribed Topamax if the label had contained the warnings about human birth defects that plaintiffs established the label could have and should have contained. Janssen's brief also fails to establish that the trial judge abused his considerable discretion in excluding two other pieces of irrelevant and unfairly prejudicial evidence that Janssen

sought to place before the jury on this point, nor can Janssen establish that any such error was anything other than harmless given the clear testimony from Ms. Czimmer's prescriber to establish warning causation.

Unable to prevail on liability, Janssen devotes the last arrow in its appellate quiver to the issue of damages, maintaining that Blake and his parents should be prohibited from recovering damages for the harm and expenses incurred as a result of Blake's injuries until he reaches the age of majority. The trial court's rejection of Janssen's argument on this point can be upheld one of two ways. First, the evidence of record fails to establish that Blake's parents did not file suit within two years of when a reasonable person in their circumstances would have realized that Topamax was the cause of Blake's birth defects. And second, the trial court correctly recognized that it was proper to allow Blake in his own right to recover these damages so long as no double recovery was available to his parents.

For all of these reasons, which are explained in more detail below, the trial court neither erred as a matter of law nor abused its discretion in denying Janssen's motion for post–trial relief. This Court should therefore affirm the trial court's order denying Janssen's post–trial motion and uphold the jury's verdict in this case.

IV. ARGUMENT

A. The Trial Court Correctly Ruled That Federal Law Does Not Preempt Plaintiff's Negligent Failure To Warn Claim Against The Manufacturer Of Brand–Name Tomapax, And Janssen's Arguments To The Contrary Are Based On Irrelevancies And Misdirection

1. Plaintiff has prevailed on a traditional negligent failure to warn claim against the manufacturer of a brand–name prescription drug that the U.S. Supreme Court has held is not preempted by federal law

In *Wyeth* v. *Levine*, 555 U.S. 555 (2009), the U.S. Supreme Court held, with regard to the manufacturer of a brand name prescription drug, that "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Id.* at 570–71. The Supreme Court proceeded to explain that "[i]mpossibility preemption is a demanding defense." *Id.* at 573.

Thus, in *Levine*, the U.S. Supreme Court ruled that the FDA's approval of a drug's warning label does not insulate the manufacturer of an FDA–approved drug from liability on a state law failure to warn claim unless the FDA specifically precluded the manufacturer from giving the

very warnings that the plaintiff claims should have been given. As the U.S. Supreme Court's opinion in *Levine* explains, "absent *clear evidence* that the FDA would not have approved a change to [a medication's] label, we will not conclude that it was impossible for [the drug's manufacturer] to comply with both federal and state requirements." *Id.* at 571 (emphasis added).

The U.S. Supreme Court recognized in *Levine* that whether the FDA would or would not reject the particular warning label that the plaintiff claims the medication should have contained constituted a finding of fact based on the evidence before the jury at trial. *See id.* at 572. In this case, the trial court permitted the jury to hear all of the evidence that the parties wished to present on the issue of federal preemption, and the jury's verdict in plaintiff's favor represents the jury's rejection of Janssen's federal preemption defense.

The record is replete with evidence that more than adequately supports the jury's findings in this regard. The evidence that plaintiff introduced at trial established that Janssen had actual knowledge that Topamax could cause birth defects in humans from at least 2000, and certainly by 2006, and that Janssen negligently chose to hide that relevant

safety information from the prescribing healthcare providers. Plaintiff's labeling and safety surveillance expert, Dr. Peggy Pence, testified that the label for Topamax was inadequate in 2006 and 2007 in the follow respects:

- Janssen's pre–clinical studies revealed incidences of cleft palate birth defects in different species — mice (13) and rabbits (4) — after exposure to Topamax. R.562a–64a, 567a (Tr. 10/16/13 a.m. at 40, 41–42, 45). These defects, in addition to other birth defects at increasing dosages, was a signal of teratogenicity and increases the likelihood that Topamax caused birth defects in humans. R.561a, 563a–64a, 567a (*Id.* at 39, 41–42, 45). Janssen failed to specifically include the cleft palate animal findings in Topamax's label. R.567a (*Id.* at 45).

- Janssen knew, by August 1998, that six humans had been born with birth defects after in utero exposure to Topamax. R.569a (*Id.* at 49). Four of those children were born with hypospadias. R.570a (*Id.* at 50). Janssen unilaterally changed its labeling to reflect these four occurrences because Janssen knew these constituted "reasonable evidence of a potential association with Topamax." R.572a–74a (*Id.* at 52–54).

- Dr. Jeff Nye, the Vice President of Scientific Partnership Strategy in Neuroscience at Janssen (R.576a (*id.* at 56)), knew "that by 2000 and up to 2006 . . . that Topamax could cause birth defects." R.578a (*Id.* at 60). Janssen's labeling failed to reflect this knowledge. R.578a–79a (*Id.* at 60–61).

- By 1999, Janssen knew — via a report it compiled in 2000 — that a birth defect or death had occurred in forty of sixty–three fetuses exposed in utero to Topamax. R.580a (Tr. 10/16/13 a.m. at 62). Janssen knew the death of a fetus indicated "potential evidence of drug toxicity." R.581a (*Id.* at 63). Mr. Michael Kaufman, Director of Regulatory Affairs for Janssen Research since 2002, was aware of this information by

2000. R.1424a–27a (Plt. Exh. 1260, Deposition of Michael Kaufman). In 2000, Janssen nevertheless failed to change its label to reflect this knowledge or distribute a "Dear Doctor" letter. R.582a–83a (Tr. 10/16/13 a.m. at 64, 65).This information was never reflected in Topamax's labeling, nor communicated to physicians before 2011. R.583a (*Id.* at 65).

- Janssen's informed consent forms distributed to clinical research participants on and before 2001, conveyed that Topamax "has the potential to cause serious birth defects in children." R.585a (*Id.* at 73). Janssen never included this risk in its label at any time before 2007. R.585a, 587a (*Id.* at 73, 75).

- In 2003, Janssen's "Safety Signal Assessment Report" identified four children who had been born with cleft lip or cleft lip with cleft palate. R.589a–91a (*Id.* at 88–90). In 2003, Janssen knew these reports reflected an important safety signal. R.592a (Tr. 10/16/13 a.m. at 91). Despite this important safety signal in 2003, Janssen nevertheless failed to update its labeling to reflect its knowledge before 2011. R.593a (Tr. 10/16/13 a.m. at 92).

- In its 2005 pregnancy report, Janssen identified eight cases of cleft lip and/or palate that resulted following in utero exposure to Topamax. R.596a (*Id.* at 95). Although Janssen could have unilaterally changed its labeling to reflect the increased oral cleft cases, it did not do so. R.597a (*Id.* at 96).

- In 2005, Janssen knew from the Morrow study that Topamax (monotherapy) had the highest malformation rate of any anti–epileptic drug in its class and that a fetus exposed to Topamax in utero was 2.75 times more likely to experience a birth defect than a fetus not exposed to Topamax. R.599a–604a (*Id.* at 98–103). Although Janssen knew this information was "clinically significant," Janssen never updated its labeling before 2007 to reflect this known data. R.604a–05a, 607a (*Id.* at 103–04, 106).

- Edward Osifchin, a Manager of Regulatory Medical Writing for J&J PRD, LLC (a sister company to Janssen), testified that the PDR sentence in the 2006 and 2007 label, that "[t]here are no studies using Topamax in pregnant women," "[a]s written, it's not completely correct."R.1448a–49a (Plt. Exh. 1264 at 57–60). That was so because Janssen had the Morrow study from 2005.

- In addition, the 2006 and 2007 Topamax warnings and labels did not state the following that was known to Janssen by that time and that should have been included:

  - that "Topamax has the potential to cause serious birth defects in children."

  - that "Topamax can cause cleft lip and palate."

  - and that women of childbearing years must use contraception when taking Topamax. R.609a–12a (Tr. 10/16/13 a.m. at 108–111).

Rather, the 2006 (R.3895a (Plt. Exh. 1210)) and 2007 (R.3907a (Plt. Exh 1211)) Topamax label in the Physician's Desk Reference ("PDR") stated only the following concerning pregnancy risks:

> Pregnancy: Pregnancy Category C
>
> Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. . . .
>
> . . .
>
> There are no studies using TOPAMAX® in pregnant women. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

> In post–marketing experience, cases of hypospadias have been reported in male infants exposed in utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established.

Id.

The jury in this case heard that under the "Changes Being Effected" or CBE regulation of the federal Food and Drug Administration, Janssen did not need prior FDA approval to add to its label directed to prescribers for Topamax specific mention of the particular birth defect risks that the drug presented that were known to Janssen in 2006 and 2007, as described above. The U.S. Supreme Court discussed the "Changes Being Effected" regulation in *Levine*, 555 U.S. at 568–71.

As in *Levine*, here Janssen is unable to point to any "clear evidence that the FDA would not have approved a change" to the warning label for Topamax in 2006 or 2007 concerning the medication's actual known birth defect risks. Janssen's argument that simply because the FDA approved a particular warning label demonstrates the FDA would have rejected a more informative and more accurate warning label was itself rejected by the U.S. Supreme Court under the similar circumstances presented in *Levine* and should likewise be rejected by this Court. *See Levine*, 555 U.S. at

558–59 ("The question we must decide is whether the FDA's approvals provide Wyeth with a complete defense to Levine's tort claims. We conclude that they do not.").

2. Janssen's argument concerning federal preemption and Topamax's pregnancy category is irrelevant and incorrect

The very first argument Janssen raises in its Brief for Appellant consists of nothing more than a completely irrelevant red herring. Plaintiff did not ask the jury to hold Janssen liable because Janssen should have changed the pregnancy category for Topamax from C to D. Because the jury's finding against Janssen could not have rested on that basis, Janssen's preemption argument concerning this issue is irrelevant to this case.

As noted above in the Statement of the Case, in July 2013, Judge Arnold L. New entered an order recognizing under FDA regulations Janssen did not have the ability to unilaterally change the pregnancy category applicable to Topamax from C to D. R.509a (order). Rather, as Judge New later recognized in clarifying his order, although Janssen had the ability to request a change in the pregnancy category applicable to Topamax, the FDA's approval was necessary before Janssen could alter its

warning label to identify Topamax as in pregnancy category D rather than in pregnancy category C. (*See* Judge New's Order dated 1/28/14, attached hereto as Exhibit A).

During the trial of this case, plaintiff adhered completely to Judge New's ruling on the subject of pregnancy categories. Indeed, a review of plaintiff's counsel's closing argument to the jury, and the trial court's instructions to the jury, reveals that neither plaintiff's counsel nor the trial court even once suggested to the jury or asked the jury to find Janssen negligent because Janssen had failed to change Topamax's pregnancy category from C to D. R.913a–42a, 944a–70a, 973a–93a (Tr. 10/30/13 a.m. at 18–47, 98–124, 125–144).

Thus, Janssen's lengthy and convoluted argument about how the doctrine of "impossibility preemption" recognized in the U.S. Supreme Court's ruling in *PLIVA, Inc.* v. *Mensing*, 131 S. Ct. 2567 (2011) — a decision that exclusively concerned federal preemption of warnings applicable to *generic* medications (a holding not applicable here, because Topamax is a brand–name prescription drug governed by the U.S. Supreme Court's ruling in *Levine*) — should cause this Court to grant j.n.o.v. in favor of

Janssen based on preemption due to Topamax's pregnancy category entirely misses the mark.

The jury in this case was not asked by plaintiff, nor permitted by the trial court, to find that Janssen should have labeled Topamax as a pregnancy category D drug, and thus Janssen's argument that federal law would preempt any such finding provides no basis whatsoever for the entry of j.n.o.v. in Janssen's favor.

3. Janssen cannot satisfy its heavy burden of establishing federal preemption under *Wyeth* v. *Levine* because the FDA never rejected any of plaintiff's proposed warnings from the label directed to prescribers

This Court should reject Janssen's attempt to fit within *Levine*'s extremely limited exception to preemption because Janssen mischaracterized its 2005 and 2006 submissions to the FDA and the agency's response to those submissions. Janssen can only prevail under the *Levine* "clear evidence" standard if it demonstrates that before Ms. Czimmer's date of conception, in December 2006 or through the first critical weeks of her first trimester, Janssen "attempted to give" a warning that Topamax could cause cleft lip and/or palate, "but was prohibited from

doing so by the FDA." *See Levine*, 555 U.S. at 572. Janssen comes nowhere near satisfying these requirements to prove preemption, because Janssen never attempted to warn prescribers that Topamax causes cleft lip and/or palate, nor did the FDA prohibit Janssen from doing so.

Janssen begins by asserting that "Janssen attempted to insert language in the Topamax labeling about reports of human birth defects, but FDA rejected and removed that language and directed Janssen to refer to animal data instead." Brief for Appellant at 28. However, the very next sentence of Janssen's appellate brief makes clear that Janssen is referring exclusively to the Patient Package Insert (PPI), rather than the warning label directed to the prescriber of the medication.

Indeed, this Court in *Coleman* v. *Wyeth Pharmaceuticals, Inc.*, 6 A.3d 502, 512 (Pa. Super. Ct. 2010), has already recognized the distinction between "the physician–labeling information published annually in the *Physicians' Desk Reference* ('PDR') and patient package inserts for the medications at issue." As its name indicates, the Patient Package Insert contains information directed to the patient, not to the physician. Thus, the PPI contains only the most important and easy to understand risks of a medication, but the PPI is not intended by the FDA to provide the same

comprehensive catalogue of all of a prescription medication's risks in the same way that the warning label directed to prescribers must. There are of course several reasons for this, including the fact that only the prescriber decides whether to give the patient a certain prescription drug, and only the prescriber is trained to understand all of the medical and scientific terminology contained in the warning label directed to prescribers.

Understood in this correct context, the FDA's May 2, 2006 response was not a "rejection" of any birth defect warning. R.3326a, 3328a–33a (Def. Tr. Exh. 1206). Rather, the FDA was responding to Janssen's September 29, 2005 submission of a revised draft PPI — information directed towards the patient, which is undeniably not a label — that contained inappropriate adverse event information. R.3306a–07a, 3312a (Def. Tr. Exh. 1196); R.845a–50a (Tr. 10/29/13 a.m. at 96–101). Janssen's proposed PPI contained language that "[b]irth defects have been reported, including a minor malformation of the penis called hypospadias." R.3312a. On May 6, 2006 the FDA sent Janssen a proposed PPI that did not include the "birth defects" sentence because "the PPI is not expected to contain all known/possible side effects." R.3323a (Def. Tr. Exh. 1206); R.845a (Tr. 10/29/13 a.m. at 96).

The FDA's May 2006 email further informed Janssen that if the information was "important for prescribers and patients, its prominence in the label should be elevated * * * to Warning or Precautions . . . ." R.3332a (Def. Tr. Exh. 1206); R.847a–48a (Tr. 10/29/13 a.m. at 98–99). But, as the evidence at trial showed, Janssen did not take any action to include birth defect warnings, including a causation warning, in the label directed to the drug's prescribers. Dr. Pence's testimony illustrates the difference between a PPI and a drug's labeling, and that the FDA's May 2, 2006 response actually invited — rather than, as Janssen insists, rejected — Janssen to include the proposed warning in Topamax's labeling:

> Q. And this would have been Janssen. It says, "The PPI" — the Patient Package Insert — "is not expected to contain all known possible side effects." Did I read that correctly?
>
> A. (DR. PENCE) Yes.
>
> Q. Is that generally the rule for Patient Package Inserts?
>
> A. That's correct.
>
> Q. All right. Where are these side effects that are known supposed to be listed?
>
> A. The clinically significant side effects are supposed to be in the professional labeling that goes to the doctor.

Q. All right. And it continues: "For this reason, information from the postmarketing section is not usually included in the PPIs." Did I read that correctly?

A. Yes.

Q. All of these birth defects that we've been talking about all day today, were they postmarketing experience birth defects?

A. Yes, they're postmarketing experience.

Q. And the FDA is actually saying they don't go here?

A. That's correct. They're saying tell the doctors.

Q. And they continue: "If this information is important for prescribers and patients, its prominence in the label should be elevated in the package insert to warnings or precautions and then this information can be placed in the PPI." Do you see that?

A. Yes, I do.

Q. What's the rationale behind there?

A. Because doctors are the ones who have medical training and the experience and understanding to be able to talk with the patient and help them to understand the potential risk versus the potential benefit. And the patient doesn't have the general — the general patient doesn't have that information or the ability to make that decision without the doctor's guidance.

Q. And did Janssen follow up on the recommendation here by the FDA and include all of the birth defect reports that we've been talking about today in their label?

A. No, they did not.

R.632a–34a (Tr. 10/16/13 p.m. at 46–48).

Janssen's own regulatory expert, Dr. Dena Hixon, agreed that a PPI is "designed to go to the patient." R.845a (Tr. 10/29/13 a.m. at 96). For this reason, Dr. Hixon concurred with the FDA that a PPI "is not expected to contain all known or possible side effects." *Id.* Dr. Hixon also agreed that, as opposed to the PPI, the "label is primarily designed for the doctor." *Id.* (Q. "And so when you have an adverse outcome that not many people would know about, you don't give it to patients; you give it to doctors; right? A. Right. And that was in the package insert." R.849a (*Id.* at 100)). Finally, Dr. Hixon agreed that it was inappropriate for the PPI to contain these specific adverse events; that information should have been included in the label:

> A. So basically what [the Information Comment to Sponsor from the FDA] is saying is the patient labeling doesn't need to have every side effect that has been report on use of Topamax. And if any of the side effects are at the level where they should be considered a warning or precaution, that's when they can be considered for the labeling.

R.848a (*Id.* at 99).

The FDA's response to the PPI and Janssen's inaction in light of the FDA's suggestion to include birth defect warnings in the label does not

constitute "clear evidence" that the FDA would have prohibited a stronger birth defect causation warning for Topamax contained in the mediation's warning label directed to prescribers. Moreover, Janssen has failed to cite to any case law establishing that the FDA's rejection of a specific warning *to the patient* in the PPI establishes clear evidence that the warning could not have been included in the warning label directed *to the physician* so as to give rise to preemption for purposes of *Levine*. The non–existence of any such case law, and the fact specific to this case that the FDA's exclusion of the warning from the PPI *expressly instructed* Janssen to include the birth defect warning in the labeling directed to the prescriber, *which instructions Janssen ignored*, demonstrate that the trial court properly rejected Janssen's motion for j.n.o.v. under *Levine*.

* * * * *

As demonstrated above, Janssen's arguments for j.n.o.v. stemming from federal preemption are based on irrelevancies and misdirection. The trial court, for the reasons explained above, properly rejected Janssen's request for j.n.o.v. predicated on supposed federal preemption.

B. The Trial Court's "Factual Causation" Jury Instruction Was Correct As A Matter Of Virginia Law And Therefore Does Not Necessitate Or Justify The Grant Of A New Trial

Janssen asserts that Virginia law required Czimmer to prove factual causation (or "but–for" causation) with "reasonable certainty." Br. at 35. Further, Janssen contends that the cause in question must be the sole proximate cause of an event. Br. at 33. According to Janssen, the trial court rejected Janssen's proposed points and instruction concerning Virginia law and instead charged the jury with a "substantial factor" test, presumably based on Pennsylvania law. In actuality, however, Janssen's proposed causation charges and its arguments in support thereof were themselves erroneous statements of the proximate cause law of Virginia, as well as misleading and confusing. Consequently, the trial court did not abuse its discretion in delivering the charge that the trial court actually used to define "factual cause," and Janssen's request for a new trial on this ground should be denied.

Based on the ruling of the Supreme Court of Virginia in *Ford* v. *Boomer*, 736 S.E.2d 724, 732–33 (Va. 2013), Janssen argues on appeal that the trial court's inclusion of the phrase "substantial cause" when instructing the jury on the issue of factual cause was the opposite of what Virginia law

requires. Yet the trial court's instruction in this case used the combined phrase "substantial cause or factual cause." R.983a–84a (Tr. 10/30/13 a.m. at 135–36). Moreover, the trial court appropriately instructed the jury that the two were to be interpreted in the same manner and were interchangeable:

> BY THE COURT:
>
> Now, I sometimes use the word "factual cause" in place of substantial factor. A few years ago we had a state judicial conference in Hershey, and we have it every summer. And we have about 50 judges in there. And they were discussing causation in cases like this, and there were 50 different opinions as to how to define it. And I found, some said use factual cause. Some said use substantial factor. I think the words are synonymous. So I have placed substantial factor in my question. But if you want to use factual cause in thinking about it, you can.
>
> But whether you use substantial factor or factual cause, it's a legal cause.

Id. Janssen has not shown that the use of these interchangeable phrases, considering the totality of the instruction, was either an erroneous statement of the law or prejudicial.

Janssen further argues that the trial court gave an erroneous statement of the "but–for" causation standard of Virginia, but Janssen's

argument in this regard ignores the actual verbiage of the trial court's jury charge on this point.

Virginia law generally defines "[a] proximate cause" as "an act or omission that, in natural and continuous sequence unbroken by a superseding cause, produces a particular event and without which that event would not have occurred." *Williams* v. *Joynes*, 677 S.E.2d 261, 264 (Va. 2009); *see also Boomer*, 736 S.E.2d at 728 ("the first element of proximate causation in fact, is "often described as the 'but for' or sine qua non rule."). The plaintiff must prove proximate cause by a preponderance of the evidence. *Hailey* v. *Johnson*, 113 S.E.2d 664, 666 (Va. 1960).

In this case, the totality of the charge gave a clear and legally proper instruction for "a factual cause" under Virginia law. The Court instructed the jury that they "must find a causal connection" (i.e., "without which that event would not have occurred") "between that negligence" (i.e., an "act or omission") "and harm." R.975a–76a, 982a–84a (Tr. 10/30/13 a.m. at 127–128, 134–35, 135–36). Further, it was the plaintiff's burden to show this causal connection by a preponderance of the evidence. R.976a (Tr. 10/30/13 a.m. at 128). These instructions were reiterated several times by the trial court:

BY THE COURT:

> But when we talk about liability and negligence, it's a two–step process. Not only must you find negligence, but you must find a causal connection between that negligence and harm, in this case, to the child. One without the other is not enough.
>
> . . . If you find negligence but no causation, you don't answer Question 3 involving damages.
>
> Now, the plaintiff has the burden of proving by what we call a fair preponderance or fair weight of the evidence the liability and damages in this case; that is to say, the plaintiff must prove the negligence of Janssen and that that negligence caused the cleft lip or cleft palate in Blake and Blake's damages all by what we call a fair preponderance or fair weight of the evidence. [explanation of preponderance of the evidence followed].

R.975a–76a (*Id.* at 127–28).

> Now, if you should reach Question 2, that would be the second phase of determining liability. As I've said, in order to find liability here, you have to find negligence, and you have to find the requisite causal connection between that negligence and harm to the child in this case as I have put it in Question 2. . . . .

R.982a (*Id.* at 134).

> But what I said or what I've given you in Question 2 is: Was the Defendant Janssen's negligence a substantial factor in bringing about Blake Czimmer's cleft lip/cleft palate? That's the issue here. Did he suffer the cleft lip or cleft palate arising from the negligence of the Defendant Janssen?

R.983a (*Id.* at 135).

> But whether you use substantial factor or factual cause, it's a legal cause. In order for the plaintiff, Blake Czimmer, to recover in this case, the defendant's negligent conduct must have been a substantial factor or factual cause in bringing about his cleft lip/cleft palate.

R.984a (*Id.* at 136).

Additionally, factual cause under Virginia law requires the act to produce the injury "in natural and continuous sequence unbroken by a superseding cause[.]" *Williams*, 677 S.E.2d at 264. An injury is proximately caused by a defendant's negligence if it is the natural and probable consequence of the negligence. *AES Corp.* v. *Steadfast Ins. Co.*, 725 S.E.2d 532, 537 (Va. 2012). "To impose liability upon one person for damages incurred by another, it must be shown that the negligent conduct was a "necessary physical antecedent of the damages." *Boomer*, 736 S.E.2d at 728 (quoting *Wells* v. *Whitaker*, 151 S.E.2d 422, 428 (Va. 1966)). It requires a plaintiff to show "why and how the incident happened." *Hodge* v. *Wal–Mart Stores, Inc.*, 360 F.3d 446, 451 (4th Cir. 2004) (citation omitted). The evidence establishing the causal connection must be "sufficient to take the question out of the realm of mere conjecture, or speculation, and into the realm of legitimate inference." *Atrium Unit Owners Ass'n* v. *King*, 585 S.E.2d 545, 548 (Va. 2003) (citation omitted).

The above instructions — whether Janssen's negligence was a substantial factor in "bringing about" the injuries and whether Blake suffered cleft lip and palate "arising from" Janssen's negligence —properly conveyed to the jury that they must find that Blake's injuries were a natural and probable consequence of Janssen's negligence and that the causal connection must be more than conjecture or speculation.

The trial court also correctly instructed the jury in accordance with Virginia law when the trial court told the jury that there may be also more than one proximate cause of an event. *Doherty* v. *Aleck*, 641 S.E.2d 93, 97 (Va. 2007). Virginia does not require that proximate cause be established "with such certainty as to exclude every other possible conclusion." *Wooldridge* v. *Echelon Service Co.*, 416 S.E.2d 441, 443 (Va. 1992). Furthermore, the facts may be established by circumstantial evidence, and a jury may draw reasonable inferences and deductions from such evidence. *Id.* Such evidence "must be sufficient to establish that the result alleged is a probability rather than a mere possibility." *Atrium Unit Owners Ass'n*, 85 S.E.2d at 548 (citation omitted). With regard to these concepts, the trial court instructed the jury as follows:

> BY THE COURT:
>
> Now, keep in mind, you can have more than one cause that is a substantial factor or factual cause in bringing about a given end.

R.984a (Tr. 10/30/13 a.m. at 136).

The trial court's instructions, as shown above, accurately and clearly instruct the jury on the substance of Virginia law to be considered. Janssen, in its Brief for Appellant, has failed to show otherwise.

By contrast, the proposed charges that Janssen asked the trial court to deliver regarding factual cause under Virginia law were properly rejected as either legally flawed or misleading and confusing.

One of Janssen's proposed instructions was misleading and legally flawed as it changed a plaintiff's burden of proof if there was more than one possible cause of an injury, from preponderance of evidence to "reasonable certainty." Under Virginia law, a plaintiff is not required to establish proximate cause "with such certainty as to exclude every other possible conclusion." *Wooldridge*, 416 S.E.2d at 443. The Court correctly rejected this charge.

Janssen's proposed "factual cause" instruction failed to include a full definition of "factual cause," whereas the "factual cause" charge given by

this Court properly included a complete definition. The "factual cause" sentence proposed by Janssen contained the misleading statement that plaintiff must prove than an act or omission of Janssen was the "sole 'proximate cause'" of injury. "Sole" proximate cause in Virginia is only found in instructions for intervening superseding cause defenses — which were not any part of this case. *See Williams*, 677 S.E.2d at 264–65; *Atkinson* v. *Scheer*, 508 S.E.2d 68, 72 (Va. 1998) ("a superseding cause of an injury 'constitutes a new effective cause and operates independently of any other act, making it and it only the proximate cause of injury.'") (citation omitted).

As the Supreme Court of Pennsylvania explained in *Commonwealth, Dep't of Transp.* v. *Patton*, 686 A.2d 1302 (Pa. 1997), "[w]hen a challenge is made to the jury instructions, the appellate court must look at the charge in its entirety, against the background of evidence in the case, to determine whether an error of law was committed and whether prejudice resulted." *Id.* at 1305.

Similarly, in *Goldmas* v. *Acme Markets, Inc.*, 574 A.2d 100 (Pa. Super. Ct. 1990), this Court observed:

> It is now well established in this Commonwealth that portions of a jury charge are not reviewed for error in isolation. Rather, an appellate court is bound to examine the charge in its entirety against its evidentiary background. From the examination we must determine, first, whether any error was committed and, if so, whether the error was prejudicial to the complaining party.

Id. at 104. As the Supreme Court's ruling in *Patton* and this Court's ruling in *Goldmas* demonstrate, whether or not a trial court's jury instructions are erroneous can only be evaluated based on the evidentiary background in the case. *See also Buckley*, 744 A.2d at 305 (directing that the evidence must be viewed in the light most favorable to the verdict winner when considering arguments for a new trial).

The evidentiary background in this case demonstrates that even if the challenged instruction was erroneous as a matter of Virginia law, which for the reasons explained above it was not, any such error was harmless error. Notably, Janssen's appellate brief does not dispute the sufficiency of the evidence to establish that Ms. Czimmer's ingestion of Topamax was the factual cause of Blake's cleft lip and palate. The lack of any challenge to the sufficiency of that evidence no doubt results from the fact that plaintiff's medical experts were unequivocal in their testimony that Topamax was the medical cause of those injuries.

Plaintiff presented the videotaped trial testimony of Kant Lin, M.D., Blake Czimmer's board certified, pediatric craniofacial plastic surgeon. R.1450a–70a (Plt. Exh. 1266, Deposition of Kant Lin, M.D.). Dr. Lin is also Professor of Plastic Surgery at the University of Virginia, as well as the Chief of the craniofacial division and head of the multi–disciplinary cleft lip and palate team at the university. R.1450a, 1452a (Plt. Exh. 1266 at 7–8, 27–28).

Dr. Lin offered his opinion, to a reasonable degree of medical certainty, that "I believe Topamax is the cause of Blake Czimmer's cleft lip and palate deformities." R.1466a (*Id.* at 72–73). In support of that opinion, Dr. Lin described the timing of the formation of the lip and palate in the first trimester of pregnancy and Ms. Czimmer's corresponding ingestion of Topamax during that most critical time. R.1465a–66a (*Id.* at 89–90).

Dr. Lin then explained the process that he employs in cleft lip and palate cases to determine what has caused a particular child's oral clefts and why he concluded — based on his experience and training, his examination and treatment of Blake, his discussions with Blake's family, the Ms. Czimmer's medical records, including records of her Topamax ingestion, review of the medical literature, and his ability to exclude the

other potential causes of the cleft lip and palate — that Topamax was indeed the cause of the cleft lip and palate that Blake suffered from at birth. R.1453a–54a, 1465a–70a (*Id.* at 30–32, 35–37, 39, 72–73, 75–78, 80, 82–86, 89–92, 113–114, 246–247, 249).

The jury in this case viewed Dr. Lin's videotaped testimony as follows:

> Q. Doctor, throughout your care and treatment of Blake, and up until today, have you formed an opinion as to what caused his cleft lip and cleft palate?
>
> A. Yes, I have.

R.1466a (*Id.* at 72–73).

> Q. What is your opinion as to the cause of Blake Czimmer's cleft lip and cleft palate?
>
> A. I believe that Topamax is the cause of Blake Czimmer's cleft lip and palate deformity.
>
> Q. Do you base that opinion upon a reasonable degree of medical certainty?
>
> THE WITNESS: Yes, I do.

R.1466a (*Id.* at 91–92).

> Q. Have you been able to rule out other potential factors of Blake's cleft lip and cleft palate based upon a reasonable degree of medical certainty?

> THE WITNESS: Based on my review of the literature and the science behind all of the confounders that are involved in this situation, I have come to the conclusion with a sufficient certainty to render that medical opinion, which is that Topamax was the cause of Blake Czimmer's cleft. I considered all of the others in making that decision.

R.1470a (*Id.* at 113–14).

Dr. Lin appropriately, and with the requisite degree of medical certainty, ruled out other potential comorbidities, leaving only Topamax as the cause of Blake's oral clefts:

> Q. Did you initially consider genetics as a potential factor to Blake's oral cleft?
>
> A. Yes, I do.
>
> Q. Did you interview the family about the family history?
>
> A. Yes, I did.
>
> Q. What was their family history as it related to oral clefts?
>
> A. There was no family history.

R.1467 (*Id.* at 77–78).

> Q. Using the same standard I talked about before, within a reasonable degree of medical certainty, did you exclude genetics as a cause of Blake's oral clefts?
>
> THE WITNESS: Yes.

R.1467a (*Id.* at 249).

Q. What did the scientific literature say with regard to Effexor and oral clefts?

THE WITNESS: The literature that I have reviewed shows that there is an association, but it's very inconsistent and, as far as I can conclude, very weak.

R.1467a (*Id.* at 82).

Q. Using the standard of reasonable medical certainty, can you exclude Effexor as the cause of Blake's cleft lip and cleft palate?

THE WITNESS: Yes.

R.1467a (*Id.* at 246–47).

Q. What, if anything, in your opinion did Effexor have to do with causing Blake's cleft lip and cleft palate?

A. Nothing.

R.1467a (*Id.* at 84–85).

Q. Let me ask it this way. Do you consider April Czimmer to be obese?

A. I do not.

Q. Do you consider her to be overweight?

A. Minimally.

Q. Have you reviewed literature that discusses obesity and oral clefts?

A. Yes, I have.

Q. And what was your conclusion about that literature once you read it?

THE WITNESS: There is also an association of maternal weight with clefts. But, again, the evidence is extremely weak about any causality related to that.

R.1468a (*Id.* at 83–84).

Q. Using the standard of reasonable medical certainty, can you exclude weight as — the mother's weight as the cause for Blake's cleft lip and cleft palate?

THE WITNESS: Yes.

R.1468a (*Id.* at 247).

Q. What, if anything, did April's weight have to do with Blake's cleft lip and cleft palate?

THE WITNESS: Nothing.

R.1468a (*Id.* at 85).

Q. Doctor, when you met with April that first visit after Blake was born, did she report a smoking history to you?

A. Yes, she did.

Q. What did Miss Czimmer testify to in her deposition as to the amount of smoking she engaged in during her pregnancy with Blake?

THE WITNESS: My recollection of that is that she smoked four cigarettes intermittently, and that often times she didn't even smoke the full cigarette.

> Q. When you were assessing these medical records, did you consider smoking as a potential factor when you were looking at factors that could have caused Blake's cleft lip and cleft palate?
>
> A. Yes, I did.

R.1468a (*Id.* at 85–86).

> Q. Within a reasonable degree of medical certainty, can you exclude smoking as the cause of Blake — April's smoking as the cause of Blake Czimmer's oral clefts?
>
> A. Yes.

R.1468a–69a (*Id.* at 246).

Based on Dr. Lin's testimony, which the jury's verdict shows the jury found to be credible and believable, the evidence in support of the jury's factual cause finding would have resulted in the jury's finding that factual cause existed even if plaintiff had to satisfy the strict "sole cause" standard that Virginia law does not reflect. In other words, even if Janssen's argument based on the jury instructions that Virginia law supposedly required were legally correct, which it is not, any error in failing to give those instructions was clearly harmless error in light of the unambiguous testimony from Dr. Linn establishing factual cause.

Therefore, because the Court provided a legally accurate, and clear, causation instruction and verdict interrogatory under Virginia law, and because Janssen cannot show prejudice in any event, Janssen's request for a new trial on this issue should be denied.

C. The Trial Court Properly Rejected Janssen's Request For J.N.O.V. On Inadequate Warning Causation, As Ms. Czimmer's Prescriber Specifically Testified That Warnings Of Topamax's Actual Birth Defect Risks Would Have Prevented The Drug's Being Prescribed To Ms. Czimmer

In this case, Lisa Basye, P.A., Ms. Czimmer's prescribing healthcare provider, testified at trial (by deposition) that she would not have prescribed Topamax if the label warned that Topamax carried a "risk to an unborn fetus," and/or increased the risk of cleft lip and palate, and/or could cause cleft lip and palate. R.1517a–18a (Plt. Exh. 1267 at 48–53). Janssen's argument to the contrary, that Ms. Basye was aware of the drug's possible risks of birth defects, mischaracterizes the witness's testimony concerning her lack of knowledge of the true and accurate birth defects risks of Topamax and the inadequacy of the label.

Ms. Basye was not aware that Topamax was a teratogen in humans, that it increased the risk of cleft lip and palate, or that the drug could cause

those specific injuries. Neither the Topamax PDR label nor any sales representatives advised her of those risks. According to her testimony as presented to the jury, had Ms. Basye been told of those risks in 2006, she would not have prescribed Topamax. There was, therefore, abundant evidence of the inadequacy of the Topamax label in 2006 and 2007 and that the inadequate warning was the cause of the injuries Blake suffered.

April Czimmer was a patient of Lisa Basye, a licensed physician assistant, when in December 2006 she became pregnant with Blake while taking Topamax for migraines. R.1507a, 1512a–17a (Plt. Exh. 1267 at 8–9, 11, 26, 32–33, 36–39, 43–45). Dr. Linford Gehman was Ms. Basye's supervising physician. R.1507a (Plt. Exh. 1267 at 9–10); R.1568a (Plt. Exh. 1270 at 103). Dr. Gehman testified, via deposition, that he was not the prescriber of any of the Topamax prescriptions in 2006 and 2007 for Ms. Czimmer; rather, the prescriber was Ms. Basye. R.1568a–69a (Plt. Exh. 1270 at 103–04, 105).

Under Virginia law, Ms. Basye had the legal authority to prescribe Topamax, as well as the authority she was given by Dr. Gehman to prescribe the medication. R.1507a–08a (Plt. Exh. 1267 at 8–9, 11, 14, 15); R.1568a–69a (Plt. Exh. 1270 at 103–04, 105). It was Ms. Basye who undertook the risk/benefit analysis in deciding whether to prescribe

Topamax to Ms. Czimmer and to continue her on the medication, both before and during her pregnancy with Blake. R.1508a–09a, 1515a (Plt. Exh. 1267 at 16–18, 38–39); R.1568a (Plt. Exh. 1270 at 103–04). Dr. Gehman admitted that he was not involved in the care and treatment of Ms. Czimmer during the time she was prescribed Topamax and his role was limited to supervising Ms. Basye by reviewing her medical record entries. R.1568a (Plt. Exh. 1270 at 103).

Because Dr. Gehman was not the prescriber of Topamax, his testimony was not required on the adequacy of the warnings. Dr. Gehman testified that Ms. Basye had the authority to prescribe the class of drug in which Topamax was categorized (legal and actual authority). R.1568a (*Id.* at 103–04).

The jury heard Ms. Basye testify that in 2006 and 2007, she relied on the Topamax information Janssen provided in the PDR to determine whether to prescribe the drug to Ms. Czimmer for migraines. R.1508a, 1510a, 1515a–16a (Plt. Exh. 1267 at 16, 20–21, 40–41). She expected the PDR to be complete and accurate regarding the risks of the medication. R.1510a (*Id.* at 19–21). Janssen sales representatives also provided information to Ms. Basye about Topamax. R.1513a (*Id.* at 33–34). Topamax's pregnancy

category and teratogenic effects, including a risk of cleft lip and palate, were of particular importance to her risk/benefit analysis, particularly because for less severe conditions such as migraine in women of child–bearing years, she would seek to minimize the risks of any medications she was prescribing. R.1509a–11a, 1515a–16a (*Id.* at 19, 21–23, 40–41). Ms. Basye discussed the risks and benefits of medications with her patients, including Ms. Czimmer, and would have told her that Topamax had a risk of cleft lip and palate if she had known that information. R.1509a–10a, 1517a (*Id.* at 19–21, 49). Ms. Czimmer testified that when she was prescribed Topamax, if she would have known the drug "could cause birth defects or cleft lip and cleft palate[,]" she would not have accepted a prescription for Topamax from Ms. Basye. R.714a (Tr. 10/21/13 a.m. at 63).

According to her undisputed testimony, Ms. Basye was not aware in 2006 and 2007 that Topamax had the potential to cause the injury Blake suffered, cleft lip and palate. R.1517a–18a (*Id.* at 49, 50):

> Q. Did you have any knowledge back in 2006 or 2007 that Topamax could cause cleft lip or cleft palate?
>
> A. No.

R.1518a (*Id.* at 51).

Reviewing the 2006 PDR, Ms. Basye testified it did not warn that Topamax carried an increased risk of cleft lip and/or palate:

> Q. Does that PDR, that label, warn you as a prescriber that Topamax carries with it an increased risk of cleft lip and cleft palate?
>
> . . .
>
> A. No.

R.1518a (*Id.* at 50).

Perhaps most importantly, there was more than sufficient evidence for the jury to decide that had an adequate warning been given to Ms. Basye that Topamax had an increased risk of cleft lip and palate, or that the drug could cause cleft lip or palate, she should would have altered her prescribing practices and *would not have prescribed* Topamax to Ms. Czimmer:

> Q. If you had been aware back in August of 2006 when you prescribed Topamax that there was a risk to her unborn fetus of cleft lip and cleft palate, would that have altered your prescribing habits?
>
> THE WITNESS: Yes.

R.1517a (*Id.* at 49).

> Q. Would you have prescribed Topamax to April Czimmer in August of 2006 if you had known there was a risk to her unborn fetus?
>
> A. No.

Id.

> Q. Would you have ever prescribed Topamax to April if you had known that there was an increased risk of cleft lip and cleft palate?
>
> A. I don't believe so.

R.1517a (*Id.* at 50).

> Q. Did you have any knowledge back in 2006 or 2007 that Topamax could cause cleft lip or cleft palate?
>
> A. No.
>
> Q. Would April Czimmer have received Topamax from you if you had known that?
>
> . . .
>
> THE WITNESS: No.

R.1518a (*Id.* at 51).

Under Pennsylvania law and Virginia law, which both recognize the learned intermediary doctrine, *see Talley* v. *Danek Medical, Inc.*, 179 F.3d 154 (4th Cir. 1999) (applying Virginia law), the foregoing testimony from Ms. Basye is precisely the very type of testimony needed to establish warning

causation — that due to the drug manufacturer's negligent failure to warn of the medication's actual risk, the drug was prescribed to the patient, whereas it *would not* have been prescribed to the patient if the warning label contained an accurate and complete warning of the drug's known or knowable risks. *See*, *e.g.*, *Simon* v. *Wyeth Pharmaceuticals, Inc.*, 989 A.2d 356, 368 (Pa. Super. Ct. 2009).

In its argument in support of j.n.o.v. on the issue of warning causation, Janssen advances a couple of different arguments that fail to amount to any reversible error. First, Janssen argues that because Ms. Basye had the practice of recommending to women that they should remain on birth control while taking Topamax, Ms. Basye already fully appreciated the medication's birth defect risks and thus an adequate warning would have had no further effect.

To begin with, Janssen's argument in this regard is itself contrary to the facts of this case. As the facts of this case clearly demonstrate, Ms. Basye recognizes a difference between drugs that may present harm to a pregnant woman and drugs that definitely pose a risk of birth defects, including cleft lip and cleft palate, to a pregnant woman's fetus. In the first category of medications, that may present harm, she will prescribe them if the patient

promises to stay on birth control. But, recognizing that such a promise is not foolproof, as the facts of this case themselves demonstrate, Ms. Basye *will not prescribe a medication presenting the actual risk of birth defects* even to a female patient who promises to remain on birth control while taking the medication.

The fact that an adequate warning label for Topamax would have caused Ms. Basye not to have prescribed the medication to Ms. Czimmer conclusively refutes Janssen's argument that Ms. Basye was already fully familiar with the risks Topamax posed to the potential fetus of a woman who may become pregnant.

Secondly, Janssen complains that it was not permitted to introduce evidence that Ms. Czimmer had prescribed an actual pregnancy category D drug to Ms. Czimmer. But the trial judge correctly excluded that evidence as entirely irrelevant. To begin with, the trial court repeatedly reminded the jury that Janssen did not have the unilateral ability to change Topamax's pregnancy category (R.552a–53a, 574a–75a (Tr. 10/16/13 a.m. at 25–26, 54–55)), so because Topamax was not a category D drug when Ms. Basye prescribed it to Ms. Czimmer, the fact that Ms. Basye prescribed a different category D drug was irrelevant. Moreover, although Ms. Basye

did testify that she would not have prescribed Topamax to Ms. Czimmer if it was a category D drug, the trial judge repeatedly instructed the jury during trial that Janssen did not have the ability to unilaterally change the label to make Topamax a category D drug. R.552a–53a, 574a–75a (Tr. 10/16/13 a.m. at 25–26, 54–55).

Neither Ms. Basye's previously prescribing the category D drug Paxil to Ms. Czimmer,* nor her action of declining a Topamax refill during the second trimester of Ms. Czimmer's pregnancy, have any bearing on any issue in this case, the trial court correctly ruled.

As this Court explained in *Rettger* v. *UPMC Shadyside*, 991 A.2d 915 (Pa. Super. Ct. 2010), "[o]ur Rules of Evidence vest the trial court with the authority to determine the admissibility of evidence as well as to control the scope of examination. Rule 403 stresses the importance of clear, concise, and expeditious presentation, allowing for the exclusion of evidence that is confusing, cumulative, or unfairly prejudicial." *Id.* at 925 (internal citation omitted). This Court's ruling in *Rettger* goes on to note that "[a]ppellate

* The evidence unambiguously established that Ms. Czimmer never took Paxil during her pregnancy with Blake, nor immediately before that pregnancy, rendering evidence relating to Paxil irrelevant yet potentially even more unfairly prejudicial to plaintiffs' case.

review of the court's rulings under these rules is limited to determining whether the trial judge abused his discretion. As applied to rulings on the evidence, this standard requires not only technical error but also demonstrated harm; '[e]videntiary rulings which did not affect the verdict will not provide a basis for disturbing the jury's judgment.'" *Id.* at 925 (internal citations omitted).

Moreover, the Pennsylvania Rules of Evidence instruct the trial court to exclude irrelevant evidence and evidence whose potential for unfair prejudice exceeds the evidence's probative value. *See* Pa. R. Evid. 402 ("Evidence that is not relevant is not admissible."); Pa. R. Evid. 403 ("Although relevant, evidence may be excluded if its probative value is outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury, or by considerations of undue delay, waste of time, or needless presentation of cumulative evidence.").

Lastly, even if the trial court's exclusion of these two items of evidence somehow amounted to a clear abuse of discretion, which it cannot, any such error would be harmless at worst. Ms. Basye's testimony could not be more clear that had Topamax's warning label directed to prescribers contained an adequate warning of the medication's birth defect

risk to humans, Ms. Basye would not have prescribed Topamax to Ms. Czimmer. That is what plaintiffs had to prove to prevail, and neither item of excluded evidence casts any doubt on that unequivocal testimony from Ms. Basye. After all, Ms. Basye herself knew the facts that Janssen says should not have been excluded from the jury's consideration, and yet she still gave the same definite testimony about what the impact of an adequate warning label would have been — no Topamax prescription for Ms. Czimmer.

For all of the foregoing reasons, the trial court did not err in denying Janssen's motion for j.n.o.v. on this issue of warning causation.

D. The Trial Court Correctly Ruled That Blake Czimmer's Claim For Future Healthcare Costs Until His Age Of Majority Was Not Time–Barred

Under Pennsylvania law, expiration of the statute of limitations is an affirmative defense, and the defendant therefore has the obligation to introduce evidence in support of that affirmative defense in order for the statute of limitations to bar all or part of a plaintiff's claim.

Here, Janssen failed to introduce the evidence necessary to establish that Blake Czimmer's claim for future healthcare costs until the age of

majority was time–barred. In its Brief for Appellant, Janssen argues that Ms. Czimmer's testimony on cross–examination that "I later had an aha moment and put the two and two together in my own head" R.743a (Tr. 10/21/13 a.m. at 121) meant that Ms. Czimmer realized as of October 2007 that Topamax had caused her son's cleft lip and palate. However, taken in context, it is clear that Ms. Czimmer's "aha moment" did not involve realizing that Topamax had caused Blake's cleft lip and palate. Rather, Ms. Czimmer's testimony on cross–examination relating to when she realized that Topamax was likely the cause of Blake's cleft lip and palate establishes that it was not until fewer than two years before this lawsuit was filed that she realized, despite the exercise of due diligence, that Topamax was a likely cause of those conditions. R.741a–44a (Tr. 10/21/13 a.m. at 119–122).

Pennsylvania's discovery rule tolls the running of the applicable statute of limitations until the point where the complaining party "knows or reasonably should know that he has been injured and that his injury has been caused by another party's conduct." *Crouse* v. *Cyclops Indus.*, 745 A.2d 606, 611 (Pa. 2000); *Wilson* v. *El–Daief*, 964 A.2d 354, 359 (Pa. 2009) ("Under the discovery rule, 'the applicable limitations period commences when the plaintiff learns that she has an injury and its cause.'"). If the injured party

could not ascertain when he was injured and by what cause within the limitations period, "despite the exercise of reasonable diligence," then application of the discovery rule is appropriate. *Simon* v. *Wyeth Pharmaceuticals, Inc.*, 989 A.2d 356, 365–66 (Pa. Super. 2009). "It is only when 'reasonable minds would not differ in finding that a party knew or should have known on the exercise of reasonable diligence of his injury and its cause' that a court may determine that the discovery rule does not apply as a matter of law." *Coleman* v. *Wyeth Pharmaceuticals, Inc.*, 6 A.3d 502, 511 (Pa. Super. Ct. 2010) (citation omitted). "Knowledge of an injury alone is not sufficient to trigger such inquiry." *Id.* at 510. "One must have some reason to suspect that the injury was caused by a third party to impose a duty to investigate further." *Id.* at 510–11.

Moreover, considerations of whether the plaintiff was reasonably diligent in discovering his or her injury and that the injury was caused by a third party, are to be applied with reference to individual characteristics. *Id.* at 510–11. The standard "is sufficiently flexible . . . to take into account the differences between persons and their capacity to meet certain situations and the circumstances confronting them at the time." *Id.* at 510 (citation omitted).

The application of the discovery rule, according to *Coleman*, fundamentally requires "an understanding of the state of medical warnings regarding [Topamax] during the relevant time period . . . because . . . the discovery rule involves issues of [plaintiff's] constructive and actual knowledge of a causal relationship between" the medication and the injury. *Id.* at 512.

Here, *Coleman* compels the Court's rejection of Janssen's statute of limitations argument. As in *Coleman*, Janssen's argument that Ms. Czimmer knew Topamax caused Blake's birth defects in 2007 defies logic because Janssen simultaneously contends even it did not know Topamax could cause birth defects at that time.

The plaintiff presented sufficient evidence that in 2006 and 2007, when Ms. Czimmer became pregnant while ingesting Topamax, the medication was a pregnancy category C drug, i.e., a medication that has not been shown to be harmful to human fetuses. R.3895a, 3907a (Plt. Exh. 1210, 2006 PDR; Plt. Exh. 1211, 2007 PDR); R.1515a, 1518a (Plt. Exh. 1267 at 39–40, 52–53). Neither the 2006 nor the 2007 PDR disclosed that a causal relationship existed between Topamax and cleft lip and/or palate birth defects.

Here, as in *Coleman*, the PDR and labeling information did not causally link Topamax with congenital birth defects and largely dismissed that connection. *See Coleman*, 6 A.3d at 516, 519–20 (neither the diagnosis itself or taking the plaintiff off the medication when the cancer diagnosis was made were sufficient to automatically put the plaintiffs on notice of a connection between the medication and the injury).

Significantly, in this case the record reveals that there was no discussion, at any time, between the healthcare providers, including Ms. Basye, and Ms. Czimmer that there was any connection between Topamax and Blake's birth defects. R.1518a (Plt. Exh. 1267 at 50–51); R.741a–42a (Tr. 10/21/13 a.m. at 119–120); R.747a–49a (Tr. 10/21/13 p.m. at 45–47).

Even if Ms. Czimmer had inquired whether Topamax caused the Blake's birth defects, the information Janssen disseminated failed to demonstrate a connection, nor were any of her healthcare providers aware of such a connection. Again, Janssen wants to preclude the Czimmers' claims based upon knowledge of a causal connection in 2007, while Janssen, throughout this litigation, has denied, or minimized the connection between Topamax and birth defects.

Janssen's Topamax's label (until 2011), including the 2006 and 2007 full prescribing information, denied (or largely dismissed) a relationship to birth defects: "a causal relationship with topiramate has not been established." R.3895a, 3907a (Plt. Exhs. 1210, 1211). Even at trial, Janssen's experts maintained that Topamax does not cause birth defects:

> Q. Doctor, in all of these roughly 3,000 animals that were tested with Topamax in these studies, was there ever a baby rat, rabbit, or mouse born with a cleft lip?
>
> A. (DR. SCIALLI) No, sir.
>
> Q. What about a cleft lip and a cleft palate?
>
> A. No, sir, none.
>
> Q. What significance, if any, is that finding of no cleft lip and/or no cleft lip and cleft palate in those 3,000 animals?
>
> A. That would not support the idea that the drug causes cleft lip with or without cleft palate in human beings.

R.790a (Tr. 10/23/13 p.m. at 29).

> Q. Do you think it's been established, based on those eight studies, that Topamax is a known general cause for cleft lip and cleft palate, based on those eight studies?
>
> A. No, sir.

R.798a (*Id.* at 64).

As in *Coleman*, Janssen's proposition that Ms. Czimmer either did conclude or should have concluded that Blake's cleft lip and palate were connected to her Topamax use during pregnancy defies logic because Janssen maintains that no connection exists between Topamax and birth defects. Thus, this Court should apply *Coleman* and similarly reject Janssen's argument that Ms. Czimmer knew or should have known the cause of Blake's birth defects in October or November of 2007, and therefore any claim to recover from Janssen on account of Blake's pre–majority health care costs is time–barred. See *Coleman*, 6 A.3d at 519.

Judge DiNubile, however, concluded that although in his view the parents' direct claim to recover these medical expenses was "clearly time–barred" (Rule 1925(a) opinion at 10), under Pennsylvania law Blake Czimmer had the ability in his own right to recover his pre–majority medical expenses so long as his parents had not already recovered those damages.

In so ruling, Judge DiNubile relied on the Commonwealth Court of Pennsylvania's ruling in *Shafer–Doan* v. *Commonwealth of Pa., DPW*, 960 A.2d 500 (Pa. Commw. Ct. 2008). Therein, the Commonwealth Court ruled that "we conclude that a minor is not prevented from seeking medical

expenses incurred while he is a minor, * * * as long as such a claim is not duplicated by the parents." *Id.* at 516.

Even more recently, the Supreme Court of Pennsylvania upheld the above–quoted holding from *Shafer–Doan* in *E.D.B. ex rel. D.B.* v. *Clair*, 987 A.2d 681 (Pa. 2009). In *E.D.B.*, Pennsylvania's highest Court described with approval the Commonwealth Court's observation in *Shafer–Doan* that "the prohibition against a minor receiving compensation for his or her medical expenses incurred during minority [w]as a 'common law anachronism,' rooted in a now–repudiated tradition that considered children to be the property of their father."

In sum, both the Commonwealth Court's ruling in *Shafer–Doan* and the Supreme Court's ruling in *E.D.B.* persuasively support Judge DiNubile's holding in this case that Blake Czimmer had the ability to recover his medical expenses until the age of majority so long as no double recovery existed. Of course, no double recovery could exist here in light of Judge DiNubile's conclusion that Blake Czimmer's parents' claim to recover those expenses was "clearly time–barred." Rule 1925(a) opinion at 10.

Janssen asks this Court to rely on the so–called "common law anachronism" that both the Commonwealth Court and the Supreme Court of Pennsylvania have criticized and rejected as a basis to allow Janssen to avoid having to account for the damages that Blake Czimmer will incur until he reaches the age of majority for the injuries he sustained due to his mother's ingestion of a drug bearing inadequate risks of the potential harm to the fetus of a pregnant woman. Judge DiNubile properly refused to grant Janssen such an unfair windfall. This Court should affirm Judge DiNubile's lawful and sound ruling rejecting Janssen's attempt to invoke the statute of limitations to deny recovery for Blake Czimmer's substantial pre–majority medical expenses.

Finally, even if Janssen's statute of limitations argument had any merit, which it does not, a new trial would not be required here because the trial court on this record can separate the portion of the future medical expenses award that Janssen concedes is proper from the portion that Janssen contends is improper. *See Paves* v. *Corson*, 801 A.2d 546, 548–50 (Pa. 2002) (a new trial motion should be denied where the trial court can separate the damages properly awarded from any damages improperly awarded). The Czimmer's expert, Valerie Parisi, R.N., presented more than

sufficient evidence that would enable the trial court to determine the portion of the future damages award relates to Blake Czimmer after he reaches the age of eighteen. R.768a–83a (Tr. 10/23/13 a.m. at 55–70). Thus, even if Janssen's statute of limitations argument had merit, which it does not for the reasons previously discussed, Janssen's motion for new trial should nevertheless be denied because the trial court on remand can readily ascertain the valid portion of the jury's damages award.

V. CONCLUSION

For all of the foregoing reasons, this Court should uphold the trial court's judgment and affirm the trial court's denial of Janssen's post–trial motion.

Respectfully submitted,

Dated: June 25, 2014

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CERTIFICATION OF COMPLIANCE WITH TYPE–VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

This brief complies with the type–volume limitations of Pa. R. App. P. 2135(a)(1) because this brief contains 12,916 words excluding the parts of the brief exempted by Pa. R. App. P. 2135(b).

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CERTIFICATE OF SERVICE

I hereby certify that I am this day serving a true and correct copy of the foregoing document upon the persons and in the manner indicated below which service satisfies the requirements of Pa. R. App. P. 121:

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