

APPEAL NO. 35500

IN THE SUPREME COURT OF APPEALS OF WEST VIRGINIA

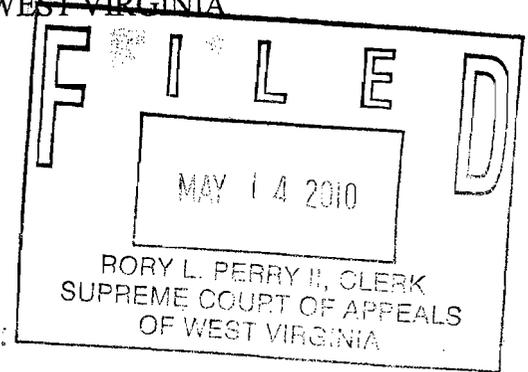
STATE OF WEST VIRGINIA, EX REL.,
DARRELL V. McGRAW, JR.,
ATTORNEY GENERAL,

Appellee,

v.

JOHNSON & JOHNSON and JANSSEN
PHARMACEUTICA PRODUCTS L.P.,

Appellants.



On Appeal From The Circuit Court
Of Brooke County, Civil Action No.
04-C-156

APPELLANTS' BRIEF

May 14, 2010

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INTRODUCTION

The circuit court below imposed \$4,475,000 in civil penalties against defendant-appellant Janssen Pharmaceutica Products, L.P. (“Janssen”), and its parent corporation, Johnson & Johnson, under the West Virginia Consumer Credit and Protection Act (“CCPA”) without holding a trial on the central question in the case: whether the scientific communications at issue were false or misleading. Janssen offered substantial scientific evidence showing that the challenged communications concerning two prescription medications were truthful and non-misleading, but the circuit court refused to consider any of that evidence. Instead, the court entered partial summary judgment in favor of the State, holding that two “informal and advisory” letters sent by an employee of the U.S. Food and Drug Administration (“FDA”) precluded Janssen’s scientific defense as a matter of law. According to the circuit court, Janssen’s decision to cooperate with the requests from an FDA employee in those letters transformed the letters into official FDA findings, thereby foreclosing Janssen from litigating the core issue in this suit. That ruling should be reversed for four reasons.

First, the circuit court’s ruling violates settled preclusion law, which demands a prior judgment rendered after adjudication. The letters the State relied on here – which the FDA’s *Regulatory Procedures Manual* deems “informal and advisory” – were neither judgments nor rendered after adjudication.

Second, the circuit court’s summary judgment ruling is preempted by federal law. The circuit court ruled that a pharmaceutical company must confront its federal regulators if it wishes to preserve its ability to defend itself in later court proceedings, creating an irreconcilable conflict with the FDA’s goal of using informal and advisory warning letters to provoke cooperation, rather than confrontation, from regulated entities.

Third, because the challenged conduct at issue concerns speech, the circuit court's failure to make an independent evaluation of the evidence Janssen offered in support of its statements violates the First Amendment.

Fourth, the State relied exclusively on informal and advisory letters from an FDA employee that were inadmissible hearsay, and on letters Janssen sent after the conduct at issue here was completed which were inadmissible subsequent remedial measures. As a result of the State's failure to offer admissible evidence that could support a judgment in its favor, this Court should remand the case for entry of judgment in Janssen's favor.

Not only did the circuit court err in granting the State partial summary judgment, it further erred when it imposed a civil penalty against Janssen, warranting reversal on two additional grounds.

First, the State failed to prove that Janssen acted with the actual malice that the First Amendment requires to justify punishment of speech. Indeed, the State failed to produce any evidence on this issue, and judgment should be entered in Janssen's favor on the State's civil penalty claim.

Second, the circuit court failed to articulate a sufficient justification for the civil penalties it imposed, and those civil penalties are excessive.

KINDS OF PROCEEDINGS AND NATURE OF THE RULINGS BELOW

This is a civil penalty action under the CCPA, W. Va. Code §§ 46A-6-101 *et seq.*, challenging statements concerning two Janssen prescription pharmaceutical products: Risperdal®, an antipsychotic medication, and Duragesic®, a patch that delivers a continuous dose of a narcotic pain medicine through the skin.

After discovery closed, the circuit court denied defendants' motion for summary

judgment on the Risperdal claim, and entered partial summary judgment for the State on the grounds that Janssen's statements about both Risperdal and Duragesic were misleading as a matter of law. The court based that decision on its conclusion that Janssen's decision to comply with two informal and advisory "warning letters" from the director of the FDA's Division of Drug Marketing, Advertising and Communications ("DDMAC") "preclude[d]" Janssen from denying the State's allegation that the statements in question were false and misleading under the CCPA. The case then proceeded to a bench trial focused on the remaining issues: whether Janssen engaged in a repeated course of willful violations and whether a civil penalty should be imposed. During the trial, the State presented no witnesses. It also stipulated to having Janssen's witnesses testify by affidavit, and to the competency and admissibility of their testimony. The State further waived any cross-examination of Janssen's witnesses.

On February 25, 2009, the circuit court awarded the State \$4,475,000 in civil penalties without ever addressing the medical and scientific evidence Janssen placed in the record or the credibility of Janssen's witnesses. On March 31, 2009, the court denied the defendants' timely motions to alter or amend the findings, and for judgment or a new trial. On March 10, 2010, this Court granted defendants' petition for appeal.

STATEMENT OF FACTS

I. BACKGROUND OF RISPERDAL

Risperdal and Psychotic Disorders

Until the 1950s, when the first antipsychotic medications were approved, there was no effective treatment for the tragic and debilitating psychotic disorder known as schizophrenia. (*See U.S. Dept. of Health and Hum. Serv., NIMH, Schizophrenia ("Schizophrenia")* at 9 (2007 ed.) (Defs.' S.J. Ex. 2).) Even when the first generation of so-called "typical" antipsychotics

became available around that time, their practical effectiveness was limited because they tended to produce “extrapyramidal” side effects – including persistent muscle spasms and tremors – that were severe enough to cause patients to stop taking medication. For years, researchers worked to develop antipsychotic drugs that would not cause those same effects.

As a result of that research, a second generation of antipsychotic drugs began emerging in the early 1990s. (*See id.*) Although these drugs are sometimes referred to collectively as “atypical antipsychotics,” they in fact vary widely from each other in composition; their main commonality is that they were developed around the same time and rarely produce extrapyramidal side effects. (*See* Peter M. Haddad & Sonu G. Sharma, *Adverse Effects of Atypical Antipsychotics: Differential Risk and Clinical Implications*, 21 *CNS Drugs* 911, 929-31 (2007) (Defs.’ Tr. Ex. 38).) Risperdal (generically known as risperidone) is one of these second-generation drugs. In 1993, the FDA approved Risperdal as safe and effective for the management of the manifestations of psychotic disorders, including schizophrenia. (*See* Defs.’ S.J. Ex. 1 (FDA approval letter).)

Evidence of a Possible Link Between Some Atypical Antipsychotics and Diabetes

In the late 1990s, some research began to indicate a possible association between non-insulin-dependent (Type II) diabetes and two atypical antipsychotics made by companies that are not party to this suit, clozapine (marketed as Clozaril®) and olanzapine (marketed as Zyprexa®). (*See Consensus Statement: Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes* (“*Consensus Statement*”) at 598 (Feb. 2004) (Defs.’ S.J. Ex. 3).) On May 1, 2000, in response to that research, FDA officials requested that all manufacturers of atypical antipsychotics reanalyze existing clinical data to determine whether there could be a connection between atypical antipsychotics in general and diabetes. (Defs.’ S.J. Ex. 4 (Letter dated May 1,

2000).) Janssen cooperated with that request and pooled its data. (*See* Defs.' S.J. Ex. 6 (Letter of Aug. 10, 2000).) Janssen's pooled data showed that a "substantial body of evidence" suggested "that risperidone is not associated with alterations in glycemic control." (*Id.* at 2.)

Nevertheless, Janssen continued studying whether there might be some connection between Risperdal and diabetes. In 2003, Janssen convened a panel of twenty-five medical experts to look into the issue. (*See* Defs.' S.J. Ex. 7 (Executive Summary: Antipsychotics and Diabetes/Glucose Metabolism 4 (2003)).) After reviewing the available data, those experts unanimously "agreed that there was convincing evidence that the effect on glucose metabolism was lower with risperidone than with other antipsychotic drugs, in particular, clozapine and olanzapine." (*Id.* at 24.) Limitations in the available data, however, prevented the experts from determining whether that difference was statistically significant. (*Id.*) The experts also agreed that there was a correlative association between the underlying condition of schizophrenia itself and diabetes. (*Id.* at 22.) One possible theory for this association is that individuals suffering from schizophrenia lead relatively sedentary lifestyles, which in turn leads to obesity, a known risk factor for diabetes. (*See Consensus Statement* at 597.)

In August 2003, a separate group of researchers released a preliminary abstract identifying the early results of an epidemiological study of data compiled from schizophrenia patients being treated with antipsychotics by the U.S. Department of Veterans Affairs. (Defs.' S.J. Ex. 8 at S154 ("Cunningham & Lambert abstract").) The preliminary abstract compared the relative diabetes risks in the study data for four atypical antipsychotic drugs versus typical antipsychotics; the abstract did not compare atypical antipsychotics to each other. (*Id.*) The study's authors concluded in the abstract that "[r]isk of diabetes among veteran patients with schizophrenia appears to be increased with the use of olanzapine, risperidone, and quetiapine and

should be taken into consideration in managing patients with this condition.” (*Id.* at S154-S155.)

The abstract was never accepted for publication in any peer-reviewed journal.

Although the Cunningham & Lambert abstract did not compare atypical antipsychotics to each other in assessing possible diabetes risks, other studies available around the same time did. In the same month in which the Cunningham & Lambert abstract was released (August 2003), a study published in a peer-reviewed journal concluded that “risperidone and quetiapine [patients] had estimated odds [of developing type 2 diabetes] that were *less* than those of *untreated* patients, although the difference was not statistically significant.” (*See* Frank Gianfrancesco, et al., *Antipsychotic-Induced Type 2 Diabetes: Evidence from a Large Health Plan Database*, 23 J. OF CLINICAL PSYCHIATRY 328, 334 (2003) (Defs.’ Tr. Ex. 27) (emphasis added).) A separate study of Department of Veterans Affairs data by researchers Leslie and Rosenheck shortly after the release of the Cunningham & Lambert abstract concluded that (1) clozapine and olanzapine posed a higher risk of diabetes than Risperdal, (2) Risperdal was associated with no greater risk of diabetes than typical antipsychotics, and (3) the data “do not support the claim that weight gain and elevated risk of diabetes mellitus are a ‘class effect’ of all atypical antipsychotic medications.” (*See* Douglas L. Leslie & Robert A. Rosenheck, *Incidence of Newly Diagnosed Diabetes Attributable to Atypical Antipsychotic Medications*, 161 AM. J. OF PSYCHIATRY 1709, 1710 (2004) (Defs.’ Tr. Ex. 61).) Unlike the Cunningham & Lambert abstract, the Leslie and Rosenheck study was published in a peer-reviewed journal. (*See id.*)

The FDA Requests a Revised Label

In September 2003, in apparent response to the Cunningham & Lambert abstract, the FDA requested that all manufacturers of atypical antipsychotics, as a class, add a diabetes and hyperglycemia warning to their package insert labels. (*See* Defs.’ S.J. Ex. 9 (9/11/03 Letter).)

Janssen responded that it did not think a class warning was appropriate because the bulk of the available data suggested that there was no class-wide diabetes risk. Janssen further stated that, based on its interpretation of the available data, Risperdal in particular had a lower diabetes risk than some other atypical antipsychotics. (*See* Defs.' S.J. Ex. 10 (9/24/03 Letter).)

Notwithstanding Janssen's belief that the available data did not justify any "class warning," it cooperated with FDA officials and agreed to add the warning to Risperdal's approved label. Before a final label was agreed upon, however, FDA officials agreed to one of Janssen's proposed changes. After reviewing the data Janssen submitted, the FDA agreed to omit a statement that "[t]he available data are insufficient to provide reliable estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics." (*See* Defs.' Tr. Ex. 64 at 7.) On October 29, 2003, Janssen submitted a proposed revised label to the FDA, which included the modified class warning, alerting prescribers to a potential association between atypical antipsychotics and diabetes (and other hyperglycemic conditions); the FDA subsequently approved that new label. (*See* Defs.' S.J. Ex. 14 ("Revised Label").)

Although the FDA-approved Revised Label alerted prescribers to a possible association between atypical antipsychotics and diabetes, it also observed that there was scientific uncertainty surrounding that issue. It noted the increased background rate of diabetes in schizophrenia patients, observing that the higher background diabetes rate complicated efforts to draw definitive conclusions from the data. (*Id.*) The Revised Label also explained that "the relationship between atypical antipsychotic use and hyperglycemia-related adverse events in patients treated with atypical antipsychotics" was "not completely understood," and that "[p]recise risk estimates for hyperglycemia-related adverse events in patients treated with

atypical antipsychotics” were “not available.” (*Id.*)

On November 10, 2003, Janssen mailed the Revised Label to Risperdal prescribers, along with a cover letter notifying them of the change. (Defs.’ S.J. Ex. 15 (“November 2003 Risperdal letter”).) The State’s Risperdal claim is based on the contents of that letter, which is attached to this brief for the Court. The letter begins by referencing the Revised Label, and explaining that the FDA “requested all manufacturers of atypical antipsychotics to include a warning regarding hyperglycemia and diabetes mellitus in their product labeling.” (*Id.* at 1.) The letter directs the reader to “please find updated prescribing information,” which was enclosed “[i]n an effort to keep you updated with the most current product information.” (*Id.*)

The letter then explains Janssen’s views about the state of scientific knowledge concerning any potential link between Risperdal and diabetes, citing all eight of the epidemiological studies concerning atypical antipsychotics and diabetes that had been published in peer-reviewed journals at that time:

Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

(*Id.* (footnotes omitted).)

On November 21, 2003, FDA officials requested that Janssen send doctors what is known as a “Dear Health Care Provider” letter informing them of the Revised Label. (Defs.’ S.J. Ex. 24.) In response to that request, Janssen submitted the November 2003 Risperdal letter, noted that the letter had already been sent with the Revised Label, and asked that the FDA treat it as satisfying its desire for a “Dear Health Care Provider” letter. (Defs.’ S.J. Ex. 25.)

The Risperdal Warning Letter

Janssen received no communication from any part of the FDA on this issue until nearly five months later. In April 2004, it received a “warning letter” from the Director of DDMAC. (See Pl.’s Tr. Ex. 3 (“Risperdal warning letter”).) A “warning letter” is an “informal and advisory” letter, which identifies a possible regulatory violation in the hopes of resolving the issue through cooperation. (See Defs.’ Trial Ex. 72 (2004 FDA *Regulatory Procedures Manual*) § 4-1-1.) Through warning letters, FDA officials seek to spur dialogue with the regulated company in the hopes of achieving “voluntary compliance” and avoiding the need for any formal enforcement proceedings. (See *id.*) Although a warning letter “communicates the Agency’s position on a matter, it does not commit FDA to taking enforcement action.” (*Id.*) The “FDA does not consider Warning Letters to be final Agency action on which it can be sued.” (*Id.*)

The Risperdal warning letter expressed the writer’s opinion that the November 2003 Risperdal letter was “false and misleading” in that it suggested that Risperdal does not increase the risk of diabetes and is associated with a lower risk of diabetes than some other antipsychotics. Janssen disagreed with the Risperdal warning letter, and responded by noting that its statements in the November 2003 Risperdal letter were correct as a matter of science, and by providing a detailed discussion of the relevant data to support that position. (Defs.’ S.J. Ex. 28 (4/28/04 letter).)

Despite its disagreement with DDMAC, Janssen voluntarily agreed to stop using the November 2003 Risperdal letter and to issue a new letter to healthcare providers. (See Pl.’s Tr. Ex. 6 (“July 2004 Risperdal letter”).) The July 2004 Risperdal letter does not admit any wrongdoing, does not acknowledge that the November 2003 Risperdal letter misstated the relevant scientific data, and does not state that Risperdal is associated with diabetes. Instead, it

indicates that DDMAC sent the Risperdal warning letter, summarizes the warning letter's contents, and reproduces within the body of the letter the Revised Label's hyperglycemia and diabetes class warning. (*See id.*)

After Janssen sent the July 2004 Risperdal letter to healthcare providers, DDMAC closed the matter without further action. (Defs.' S.J. Ex. 31.) The FDA has never initiated any enforcement action related to the November 2003 Risperdal letter, and no federal judgment ever resulted from Janssen's interactions with DDMAC over this issue.

II. BACKGROUND OF DURAGESIC

Duragesic and the Treatment of Chronic, Severe Pain

Duragesic, approved by the FDA in 1991, is a patch applied to the skin that delivers a continuous dose of the powerful narcotic pain medicine fentanyl. It is used for treatment of moderate to severe chronic pain that cannot be managed by less potent drugs. (Defs.' Tr. Ex. 229, Ex. B ("Upmalis Report").) For many patients, Duragesic holds significant advantages over oral medication. (*Id.*) For example, it provides a more constant dose of medicine, and also avoids the need to take a pill orally, which can be extremely painful for patients with severe digestive disorders or suffering from oral or throat cancers. (*Id.*)

In August 2003, Janssen began distributing a three-by-five-inch, fourteen-page promotional "file card" to physicians. (Defs.' Tr. Ex. 213 ("Duragesic file card").) The State's Duragesic claim is based on the contents of that file card. The Duragesic file card opens like a booklet, displaying two pages at a time, and contains a note on the odd-numbered pages directing the reader to "[p]lease see important safety information, including Boxed Warnings on pages 13-14." (*Id.*) Pages 13 and 14 reprint Duragesic's FDA-mandated boxed warnings and encourage the reader to "[p]lease see full Prescribing information." (*Id.*) Janssen submitted the file card to

the FDA on October 3, 2003. (*See* Defs.' Tr. Ex. 214.) It heard nothing back for nearly a year.

The State's challenges to the file card fall into two categories. The first consists of statements regarding Duragesic's effectiveness (specifically, its effectiveness in treating back pain) and the frequency of possible side effects (like constipation). The second concerns page 9 of the file card, entitled "Low Reported Rate of Mentions in DAWN Data." DAWN, the Drug Abuse Warning Network, compiles data from emergency room visits deemed related to drug abuse. The State challenges that statement, asserting that it "represents that Duragesic is less abused than other opioid drugs," which the State attacks on the theory that "DAWN data cannot provide the basis for a valid comparison among these products, because, DAWN is not a clinical trial database." (*See* Amend. Compl. ¶ 66.) In fact, Page 9 of the file card discloses the limitations inherent in the DAWN data, displaying the following information in bullet points: the DAWN data "do not distinguish between" different fentanyl products (Duragesic is one of many fentanyl products); "DAWN only captures drug abuse events that result in [emergency department] admissions"; and DAWN contains "[n]o data on severity of adverse events or hospital admissions." (*See* Duragesic File Card at 9.)

The Duragesic Warning Letter

Eleven months after Janssen submitted the Duragesic file card to the FDA, DDMAC's Director sent Janssen a warning letter concerning the file card. (*See* Pl.'s Tr. Ex. 102 ("Duragesic warning letter").) DDMAC challenged certain safety and efficacy representations and challenged the use of DAWN data, asserting that the "file card . . . suggests that Duragesic is less abused than other opioid drugs," even though, in DDMAC's view, "DAWN data cannot provide the basis for a valid comparison among these products" because "DAWN is not a clinical trial database." (*See id.* at 2.) DDMAC did not discuss the qualifiers on the same page.

Janssen responded to DDMAC that the statements in the file card were valid, and provided ample scientific support for them. (Ex. 36 to Defs.' Opp'n to Pl.'s Mot. for S.J. (9/17/04 letter).) For example, Janssen defended its assertions of safety and efficacy by providing detailed references to the medical literature supporting those statements. (*Id.* at 4-7.) Janssen likewise noted that the file card set forth the limitations inherent in the DAWN data and also provided the relevant data suggesting that fentanyl has a "low abuse potential." (*Id.* at 1-4.)

Nevertheless, Janssen again opted not to challenge its regulators, but instead cooperated with DDMAC officials and agreed to stop using the file card. Janssen also agreed to issue a letter to healthcare providers. (*See* Pl.'s Tr. Ex. 6 103 ("February 2005 Duragesic letter").) That letter neither admits any wrongdoing nor asserts that the Duragesic file card misstated the relevant scientific data; it does not state that Janssen's reliance on DAWN data was improper or misleading. (*See id.*) Instead, it indicates that DDMAC issued a warning letter, identifies the warning letter's allegations, and directs prescribers to Duragesic's boxed warning and prescribing information. (*Id.*) The FDA never instituted any enforcement action, and no federal judgment resulted from Janssen's interactions with DDMAC.

III. THE STATE'S LAWSUIT

After Janssen cooperated with DDMAC and sent out the July 2004 Risperdal letter, the State filed this CCPA action against Janssen and its parent corporation, Johnson & Johnson, alleging that the November 2003 Risperdal letter was false or misleading. (Compl.) Later, when Janssen received the Duragesic warning letter, the State amended its complaint to add a CCPA claim based on the Duragesic file card. (Amend. Compl.) The State's substantive allegations are virtually identical to the allegations set forth in the Risperdal and Duragesic warning letters.

After discovery closed, the State moved for partial summary judgment, asserting that the

November 2003 Risperdal letter and the Duragesic file card ~~should~~ be deemed “false or misleading” in violation of the CCPA as a matter of law. The State’s sole basis for seeking partial summary judgment was that Janssen had “allowed the Warning Letters to become final with respect to FDA findings that Janssen violated federal law by making false or misleading statements” by cooperating with DDMAC, and Janssen was therefore precluded from litigating the central liability issue in this suit: whether the November 2003 Risperdal letter and the Duragesic file card were in fact false or misleading under the CCPA. (*See* Pl.’s S.J. Mot. at 20.)

Janssen opposed the State’s partial summary judgment motion, explaining that “informal and advisory” DDMAC warning letters not only do not have any issue-preclusive effect, they are inadmissible hearsay when presented (as they were here) to prove the truth of their own allegations. (Defs.’ Opp’n to Mot. for S.J.) Janssen separately moved for partial summary judgment on the Risperdal claim, asserting, *inter alia*, that the State could not present any admissible evidence that the November 2003 Risperdal letter made untrue or scientifically unreasonable statements; that the State had no evidence that Janssen engaged in willfully deceptive conduct; and that the State’s attack on Janssen’s reasonable scientific opinions violated the First Amendment. (*See* Defs.’ Mot. for S.J.) In response, the State offered no expert or scientific evidence. (*See* Pl.’s Opp’n to Mot. for S.J.) Instead, the State rested its opposition to Janssen’s summary judgment motion entirely on the Risperdal warning letter and the July 2004 Risperdal letter. (*See id.*)

IV. THE CIRCUIT COURT’S SUMMARY JUDGMENT RULING

The circuit court granted the State’s motion for partial summary judgment and denied Janssen’s motion for summary judgment on the Risperdal claim. (*See* S.J. Order.) Relying entirely on Janssen’s interactions with DDMAC, the circuit court refused to consider Janssen’s

scientific evidence, concluding that Janssen's decision to reach a mutually agreeable resolution with its regulator pertaining to the issues raised in DDMAC's warning letters foreclosed Janssen from challenging the allegations in the warning letters in this lawsuit. (*Id.* at 29.) The court stated it would "give deference to the FDA's findings and actions" as contained in the DDMAC warning letters. Based on this "deference," the court then found Janssen's challenged statements about Risperdal and Duragesic false or misleading under the CCPA as a matter of law. In reaching that conclusion, the court declined to consider any of the scientific evidence (both factual and expert) Janssen had proffered supporting the challenged statements. (*Id.* at 32.) The court thus agreed with the State that the issue of whether Janssen had made false or misleading statements "was resolved at the federal level in a way that *precludes* reaching a contrary result here." (*Id.* at 2 (emphasis added).) Based on that ruling, the court held that the November 2003 Risperdal letter and Duragesic file card were not entitled to any free-speech protection because they were "false or misleading" as a matter of law. (*See id.* at 33-35.)

The circuit court later denied Janssen's motion to reconsider the award of partial summary judgment. (*See* Order Concerning Defs.' Mot. for Reconsid.) In so doing, the court "affirm[ed] its prior holding that the warning letters sent by the FDA were not informal or advisory b[ut] rather required mandatory action." (*Id.* at 2.) The court also clarified that by "giving deference" to DDMAC, it meant it would "not revisit the correctness of the" assertions set forth in the DDMAC warning letters. (*Id.* at 3.)

V. THE TRIAL EVIDENCE

Shortly after entering partial summary judgment for the State, the court held a bench trial on the remaining issues--whether Janssen engaged in a "repeated course of willful violations," and, if so, what amount of civil penalty, if any, to impose. At the penalty bench trial, the State

again relied exclusively on the DDMAC warning letters, the July 2004 Risperdal letter, and the February 2005 Duragesic letter. The State also entered into a series of stipulations, waiving its right to present several forms of evidence or to test Janssen's evidence. The State stipulated that it would not offer any evidence that anyone "relied on, or was misled by," or "sustained physical, emotional or economic harm" as a result of the Risperdal letter or the Duragesic file card or statements made by Janssen representatives relating to those materials. (Trial Evid. Stip. No. 2.) The State also stipulated to the admissibility of Janssen's expert testimony at trial without objection, waived cross-examination of Janssen's witnesses, and withdrew its own witnesses, including its proposed experts. (Trial Evid. Stip. No. 4, 6.)

Janssen's Unchallenged Risperdal Evidence

Janssen put on a substantial evidentiary case. With respect to Risperdal, Janssen presented the written, unchallenged testimony of two expert witnesses: Dr. Ramy Mahmoud, the author of the November 2003 Risperdal letter and former Chief of the Department of Epidemiology at Walter Reed Army Institute of Research (Defs.' Tr. Ex. 88), and Dr. Harvey Hammer, a practicing psychiatrist with clinical experience pre-dating the first generation antipsychotics in the 1950s (Defs.' Tr. Ex. 86). Dr. Mahmoud testified that epidemiological data included in Janssen's exhaustive response to a May 2000 request of the FDA for all information on the possible association between atypical antipsychotics and diabetes suggested that (1) the risk for diabetes varies for different antipsychotics and (2) any such risk is lower with Risperdal than with some other antipsychotics, particularly Zyprexa. (*Id.* ¶¶ 6, 8-12.) He also testified about the panel of twenty-five experts that Janssen commissioned in 2003, as well as the panel's unanimous conclusion that the effect on glucose metabolism was lower with Risperdal than with other atypical antipsychotics. (*See* Defs.' S.J. Ex. 7 at 24.)

In addition, Dr. Mahmoud testified about the development of a “Consensus Statement” issued in February 2004 by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists and the North American Association for the Study of Obesity. (*See Consensus Statement* at 598.) As he explained, these organizations concluded that “the data consistently show an increased risk for diabetes in patients treated with clozapine or olanzapine The risk in patients taking risperidone and quetiapine is less clear; some studies show an increased risk for diabetes, while others do not.” (*Id.*) Dr. Mahmoud further discussed the published Leslie and Rosenheck study, which concluded that the available evidence did not suggest any uniform class-wide association between diabetes and atypical antipsychotics. (*See Defs.’ Tr. Ex. 61.*)

For his part, Dr. Hammer testified that it “is beyond any reasonable degree of medical doubt” that the eight studies cited in the November 2003 Risperdal letter support the letter’s assertions. (*Defs.’ Tr. Ex. 86, Ex. C at 12-13.*) He explained that the four studies which had compared Risperdal users to unmedicated patients found no statistically significant evidence of any association between Risperdal use and an increased risk of diabetes. He further testified that seven of the eight studies suggested that Zyprexa was associated with a greater risk of diabetes than Risperdal. (*See id.* at 13.) He stated that DDMAC’s emphasis on one outlier study in that group of eight was misplaced, particularly because that study’s data had significant limitations, which the study’s own authors acknowledged. (*See id.*) Dr. Hammer also noted that DDMAC had taken a statement from one study about the risk of diabetes in users of Risperdal over age 50 out of context, ignoring the study’s conclusion that, “[f]or the entire group, the odds of having a diagnosis of diabetes mellitus were significantly greater for patients receiving clozapine, olanzapine and quetiapine but not risperidone.” (*Id.*) Dr. Hammer testified that the research

conducted after the November 2003 Risperdal letter was used has continued to support the statements in that letter. (*See* Defs.' Tr. Ex. 86, Ex. B at 8.)

Janssen's Unchallenged Duragesic Evidence

With respect to the Duragesic file card, Janssen offered undisputed testimony from professors of anesthesiology at both the Ohio State University (Dr. Constantino Benedetti) and Children's Hospital of Pittsburgh (Dr. Lynn Broadman) that there was substantial evidence to support the claims on effectiveness in treating back pain and low incidence of side effects. (Defs.' Tr. Exs. 226, 227.) Janssen also offered the testimony of John Coleman, a former U.S. Drug Enforcement Administration official and one of the leading experts on drug abuse. Without contradiction, Mr. Coleman testified that (1) the FDA (through divisions other than DDMAC) and a number of other federal agencies regularly use DAWN data to gauge levels of drug abuse, (2) there was substantial evidence in the drug abuse literature to suggest that Duragesic was less abused than other narcotic agents, and (3) experts in the drug abuse field believe that Duragesic is less subject to abuse than other narcotic agents. (Defs.' Tr. Ex. 228.)

VI. THE CIRCUIT COURT'S FINAL ORDER

The circuit court issued a Final Order on February 25, 2009, assessing \$4,475,000 in civil penalties. (*See* Final Order.) In finding that Janssen's statements were "false or misleading" in violation of the CCPA, the circuit court relied entirely on its summary judgment ruling. (*See id.* at 40 ("The Court has granted the State's motion for partial summary judgment on the issue of whether defendants' statements were false or misleading, and the Court will not revisit that issue here.")) Having already concluded that Janssen's statements were "false or misleading" as a matter of law, the court decided that Janssen's statements were not entitled to any protection under federal and state free-speech principles. (*See id.* at 27-30, 37.) The circuit court likewise

determined that the November 2003 Risperdal letter and the Duragesic file card were “willfully” false and misleading based entirely on Janssen’s interactions with the FDA. (*See id.* at 5-26.)

In setting the amount of the penalty, the circuit court counted as a separate violation each copy of the November 2003 Risperdal letter and the Duragesic file card sent or given to a West Virginia physician, as well as each sales call in which (it was stipulated) statements were made “consistent with” those made in the Risperdal letter or Duragesic file card. (*See id.* at 51-56.) The court imposed a civil penalty of \$500 for each copy of the November 2003 Risperdal letter or Duragesic file card that had been delivered to a West Virginia physician, and an additional civil penalty of \$5,000 for each “sales call” by a Janssen sales representative to a West Virginia physician in which information consistent with information with one of those documents was communicated. (*See id.* at 68-69.) The court concluded that the fine was *per se* proper because the per-violation penalty was within the statutory range of \$0 to \$5,000 per violation. (*Id.* at 69-73.) The court denied Janssen’s post-trial motions. (*See Order Re. Defs.’ Post-trial Mots.* (entered Mar. 31, 2009).)

Janssen and Johnson & Johnson petitioned this Court for appeal from the judgment below, and the Orders underlying it. This Court granted the petition on March 10, 2010.

ASSIGNMENTS OF ERROR

This appeal assigns five independent errors made to the judgment below:

1. The circuit court improperly treated “informal and advisory” warning letters as preclusive;
2. The circuit court’s decision to use Janssen’s cooperation with DDMAC as a basis for issue preclusion is preempted by federal law because it discourages cooperation with federal regulators;
3. The circuit court misapplied the relevant First Amendment principles;
4. The judgment below rests on inadmissible evidence; and

5. The circuit court failed to articulate a sufficient justification for the civil penalties it imposed, and those civil penalties are excessive.

This appeal is pursued on behalf of both defendants, Janssen and Johnson & Johnson. For ease of reading, however, this brief generally refers only to Janssen. Johnson & Johnson, whose liability is entirely derivative of Janssen's, also presses every argument asserted by Janssen.

STANDARD OF REVIEW

This Court reviews a circuit court's ultimate conclusion on the merits for abuse of discretion, but reviews any underlying summary judgment rulings or legal conclusions *de novo*. See *State ex rel. McGraw v. Imperial Mktg.* ("*Imperial Mktg. II*"), 203 W. Va. 203, 214, 506 S.E.2d 799, 810 (1998); *Public Citizen, Inc. v. First Nat'l Bank in Fairmont*, 198 W. Va. 329, 334, 480 S.E.2d 538, 543 (1996). A circuit court's factual findings receive deference when the circuit court has had the advantage of observing the demeanor of testifying witnesses, but "issues of fact are open for review on appeal where" – as here – "the findings below are based entirely on documentary evidence, such as written affidavits, or depositions." *State Farm Mut. Auto. Ins. Co. v. Am. Cas. Co.*, 150 W. Va. 435, 441, 146 S.E.2d 842, 846 (1966).

ARGUMENT

The circuit court's decision to grant the State partial summary judgment based on "informal and advisory" letters must be set aside for four reasons. First, it violates settled issue preclusion law. Second, giving preclusive effect to warning letters the FDA itself deems informal and advisory is preempted because it undermines the FDA's ability to regulate informally. Third, in placing exclusive reliance on DDMAC's so-called "fact finding" to declare Janssen's communications misleading, the circuit court abrogated its duty under the First Amendment to conduct independent fact-finding on matters bearing on protection of speech. Fourth, the court's decision was based on inadmissible hearsay and evidence of subsequent

remedial measures – the only evidence offered by the State to support its claim – and Janssen was thus entitled to summary judgment in the proceedings below.

The circuit court also erred by imposing a civil penalty for two additional reasons. First, the circuit court violated the First Amendment by imposing a civil penalty and punishing Janssen’s exercise of constitutionally-protected speech without a finding or evidence that Janssen acted with “actual malice” – that is, reckless disregard for the truth. Second, the circuit court failed to articulate a sufficient justification for the amount of civil penalties it imposed, which is excessive.

I. THE CIRCUIT COURT ERRED IN GRANTING SUMMARY JUDGMENT AND GIVING PRECLUSIVE EFFECT TO “INFORMAL AND ADVISORY” WARNING LETTERS.

A. The Circuit Court Misapplied Preclusion Law.

The warning letters at issue in this case were issued by an individual at DDMAC, a division within the FDA, *sua sponte*, in the absence of any type of administrative proceeding. Neither before nor after the warning letters were issued was any administrative or judicial hearing held – no oaths were given and no witnesses testified or were cross-examined. All that occurred was an exchange of letters between Janssen and DDMAC in which Janssen disagreed with the position of DDMAC, but nonetheless agreed to accommodate DDMAC’s request, *without any admission of wrongdoing*.

Despite this lack of any administrative hearing – or even an FDA procedure authorizing a hearing – the circuit court found that the warning letters constituted “the FDA’s official judgment as to the matters addressed in the letter.” (S.J. Order at 28-29.) The circuit court accordingly deferred, as a matter of law, to DDMAC’s so-called “findings” in the warning letters and effectively – if not explicitly – applied the doctrine of issue preclusion. *See Conley v.*

Spillers, 171 W. Va. 584, 586, 301 S.E.2d 216, 217 (1983) (issue preclusion “is designed to foreclose relitigation of issues in a second suit”). Because Janssen never litigated the truth or falsity of its challenged statements about Risperdal and Duragesic at the administrative level, the circuit court committed clear error in giving preclusive effect to the unproven allegations in DDMAC’s warning letters. See Franklin D. Cleckley, Robin J. Davis, & Louis J. Palmer, Jr., *Litigation Handbook on West Virginia Rules of Civil Procedure* (hereinafter “Cleckley, Davis, & Palmer”) § 8(c) at 200 (3rd ed. 2008) (“The central inquiry on collateral estoppel is whether a given issue has been actually litigated by the parties in the earlier suit.”).

Issue preclusion has four elements, all of which must be satisfied if it is to apply: (1) the issue to be precluded must be identical to one previously litigated and decided; (2) the prior action must have resulted in a final judgment on the merits; (3) the party to be precluded had to be a party to a prior action (or in privity with a party); and (4) the party to be precluded had to have a full and fair opportunity to litigate the issue in the prior action. See *McHan v. Comm’r*, 558 F.3d 326, 331 (4th Cir. 2009) (discussing federal claim preclusion requirements); *State v. Miller*, 194 W. Va. 3, 9, 459 S.E.2d 114, 120 (1995) (discussing West Virginia law on issue preclusion). See also *Taylor v. Sturgell*, 128 S. Ct. 2161, 2171 (2008), (“[t]he preclusive effect of a federal-court judgment is determined by federal common law.”); Cleckley, Davis, & Palmer § 8(c) at 200-01 (citing *Holloman v. Nationwide Mutual Ins. Co.*, 217 W. Va. 269, 617 S.E.2d 816 (2005); *Arnold Agency v. West Virginia Lottery Comm’n*, 206 W. Va. 583, 526 S.E.2d 814 (1999)).

Without question, the required elements are absent here.

1. An Informal and Advisory Warning Letter Is Not a “Judgment”

FDA regulations provide that statements of FDA employees, such as the statements from

DDMAC employees contained in the Risperdal and Duragesic warning letters, do “*not* necessarily represent the formal position of FDA, and do[] *not* bind or otherwise obligate or commit the agency to the views expressed,” except in circumstances which do not apply here. 21 C.F.R. § 10.85(k) (emphasis added). *See also Wyeth v. Levine*, 129 S. Ct. 1187, 1197 (2009) (“the FDA’s belief that a drug is misbranded *is not conclusive*” (emphasis added)). In keeping with these regulations, the FDA has stated that a warning letter is “*informal and advisory*.” (*Regulatory Procedures Manual* § 4-1-1 (emphasis added).) Although a warning letter “communicates the Agency’s position on a matter,” it “does not commit FDA to taking enforcement action.” (*Id.*)

The FDA’s interpretation of its regulations – and its characterization of a warning letter as non-binding, informal and advisory – is controlling unless “plainly erroneous.” *See Auer v. Robbins*, 519 U.S. 452, 461 (1997) (federal agency’s interpretation of its own regulation controls unless plainly erroneous or inconsistent with the regulation). Yet, without explanation, the circuit court ignored the FDA’s interpretation of its own regulations and held to the contrary that the “warning letters were *not* informal and advisory.” (Order Concerning Defs. Mot. for Reconsid. at 2 (emphasis added)). The circuit court thus defied rather than deferred to the FDA in concluding incorrectly that a warning letter is sufficiently “final” or “binding” to be accorded preclusive effect.

Every court to have considered this issue – other than the circuit court in this action – has agreed that an FDA warning letter does not constitute a final agency action. *See Dietary Supplemental Coalition, Inc. v. Sullivan*, 978 F.2d 560, 563 (9th Cir. 1992) (“We have held that regulatory letters [from FDA officials] do not constitute final agency action.”); *Schering-Plough Healthcare Prods., Inc. v. Schwarz Pharma, Inc.*, 547 F. Supp. 2d 939, 946 (E.D. Wis. 2008)

(letters from Director of FDA's Office of Generic Drugs, which asserted that product was "misbranded," did not constitute "any official position"); *Genedo Pharm. N.V. v. Netherlands Antilles Co.*, 308 F. Supp. 2d 881, 885 (N.D. Ill. 2003) ("Statements of lower-level agency officials likewise do not rise to the level of final agency action – *even when they are contained in warning letters* or other official regulatory correspondence." (emphasis added)); *Prof'ls & Patients for Customized Care v. Shalala*, 847 F. Supp. 1359, 1365 (S.D. Tex. 1994) ("Warning letters issued by the FDA are deemed to be informal communications that do not constitute final agency action. Warning letters merely establish a dialogue between the FDA and the [recipient] and do not necessarily lead to further sanctions." (citation omitted)), *aff'd* 56 F.3d 592 (5th Cir. 1995); *Estee Lauder, Inc. v. FDA*, 727 F. Supp 1, 5 (D.D.C. 1989) (regulatory letter from FDA official, which asserted violation of federal law, "was by its very nature informal and advisory"). Thus, court after court has credited the FDA's position that "warning letters" are just that: letters that warn, but have no legal effect. In reaching a contrary conclusion, the circuit court ignored the FDA's position, ruling erroneously that the DDMAC warning letters Janssen received "were *not* informal or advisory." (Order Concerning Defs.' Mot. for Reconsid. at 2 (emphasis added).)

Such letters could not, in fact, be considered "judgments" because they are not issued in an adjudicatory capacity. *Rowe v. Grapevine Corp.*, 206 W. Va. 703, 710, 527 S.E.2d 814, 821 (1999) (administrative document cannot be given preclusive effect unless it was "rendered pursuant to the agency's adjudicatory authority and the procedures employed by the agency must be substantially similar to those used in a court"). *Accord* *Cleckley, Davis, & Palmer* § 8(c) at 202 ("For issue preclusion to attach to quasi-judicial determinations of administrative agencies, . . . the prior decision must be rendered pursuant to the agency's adjudicatory authority and the procedures employed by the agency must be substantially similar to those used in a court."). *See*

also *Reich v. Youghioghney & Ohio Coal Co.*, 66 F.3d 111, 115 (6th Cir. 1995) (“the principle of res judicata has no application to administrative agencies’ exercise of powers other than their quasi-judicial powers”). A warning letter simply asserts the position of an agency official in the hope of provoking a dialogue. It neither purports to finally resolve any issues nor results from any adjudicatory proceeding. There is no viable theory under which a letter issued under such circumstances may be considered a “judgment” for preclusion purposes.

2. Janssen Did Not Fully and Fairly Litigate When Corresponding with DDMAC.

Just as significantly, the DDMAC warning letters cannot be accorded any preclusive effect because Janssen never fully and fairly litigated the issues the circuit court deemed precluded. “The central inquiry on collateral estoppel [issue preclusion] is whether a given issue has been actually litigated by the parties in the earlier suit.” Cleckley, Davis, & Palmer, § 8(c) at 200. Because Janssen did not engage in any litigation with DDMAC regarding the warning letters, the issues discussed in those letters were not “actually litigated,” and Janssen had *no* opportunity to litigate them.

This Court has been especially reluctant to give preclusive effect to administrative proceedings because the relaxed procedures generally followed in that context run counter to the requirement of full and fair litigation. *Page v. Columbia Nat. Res.*, 198 W. Va. 378, 393, 480 S.E.2d 817, 832 (1996) (“in view of the relaxation of procedural rules and evidentiary requirements in the administrative proceedings . . . we are of the opinion that only rarely, *if at all*, will administrative proceedings provide the same full and fair opportunity to litigate matters as will a judicial proceeding” (emphasis added)). *See also Horkulic v. Galloway*, 222 W. Va. 450, 459, 665 S.E.2d 284, 293 (2008). The DDMAC warning letters at issue here were issued without *any* proceeding, administrative or otherwise, so they cannot – under any circumstances –

be accorded preclusive effect.

Here, the circuit court conceded that no administrative hearing was held when it based its decision on the conclusion that Janssen *could have instituted* administrative proceedings to challenge the warning letters pursuant to 21 C.F.R. § 10.33, but made a “*business decision*” not to do so. (See S.J. Order at 25 & n.16.) The circuit court was wrong even in its supposition that Janssen could have itself instituted administrative proceedings in response to receipt of the DDMAC warning letters. The regulation cited by the court, 21 C.F.R. § 10.33, permits the *Commissioner* to reconsider a matter, and establishes procedures for an interested person to seek “reconsideration of part or all of a decision of the Commissioner.” The warning letters were not “a decision of the Commissioner”; rather, they were simply letters signed by a DDMAC official. Contrary to the circuit court’s understanding, the FDA regulatory scheme provided no formal administrative procedure within which Janssen could challenge the substance of DDMAC’s allegations in the letters. Further, as stated in the FDA’s *Regulatory Procedures Manual*, “FDA does not consider Warning Letters to be final agency actions on which it can be sued.” *Regulatory Procedures Manual* § 4-1-1.

Whether Janssen would ever have had an opportunity to contest the merits of DDMAC’s claims in an adjudicatory setting is speculative. Getting to a formal adjudication would have required a refusal by Janssen to comply with DDMAC’s request, followed by an FDA decision to adopt DDMAC’s claims in the warning letter and, with the concurrence of the Department of Justice, the institution of an enforcement proceeding in a United States district court. See e.g., 21 U.S.C. §§ 332-334. Had such an enforcement proceeding occurred, the FDA would have borne the burden of proof and been required to prove that Janssen’s statements were indeed false and misleading. Reason is upended when a West Virginia circuit court can take a letter on DDMAC

letterhead and, as a matter of law, convert it into a judgment when the FDA itself would be required to prove the claims made in the warning letter with actual evidence.

At any rate, issue preclusion can only attach to issues that have been actually litigated; no doctrine allows preclusion of issues that could theoretically have been pressed in some administrative challenge that was never initiated. *See* Cleckley, Davis, & Palmer § 8(c) at 200 (issue preclusion “extends to only those matters which were actually litigated in the former proceeding, as distinguished from those matters that might or could have been litigated therein”). Regardless of whether Janssen might have initiated an administrative challenge, it is undisputed that there was no actual litigation of the issues. It was thus improper for the circuit court to invoke issue preclusion.

3. By Resolving the Core Liability Issue on the Basis of the DDMAC Warning Letters, the Circuit Court Denied Janssen Due Process.

The circuit court’s application of issue preclusion here was so extreme that it violated Janssen’s due process rights. By applying issue preclusion, the circuit court resolved the core liability issues raised by this suit without providing Janssen any opportunity to defend itself against the State’s CCPA allegations through the submission of relevant evidence at a trial, thus violating Janssen’s basic due process right to present every available defense. *See* U.S. Const. amend. XIV, § 1; W. Va. Const. art. III, § 3-10; *Lindsey v. Normet*, 405 U.S. 56 (1972) (due process requires an opportunity to present every available defense); *In re Charleston Gazette FOIA Request*, 222 W. Va. 771, 777, n.2, 671 S.E.2d 776, 782, n.2 (2008) (“The idea that due process of law prohibits all courts from denying a defendant the right to present a defense to a cause of action is something firmly rooted in our jurisprudence.”). The circuit court’s application of issue preclusion, and its grant of partial summary judgment to the State, cannot stand.

B. The Circuit Court's Summary Judgment Ruling in Favor of the State Is Preempted by Federal Law.

The circuit court's summary judgment ruling also must be set aside because it interferes with the FDA's regulatory authority. The circuit court's ruling requires that FDA-regulated companies confront rather than cooperate with federal regulators if they are to preserve their right to defend themselves in any later State enforcement proceeding. That decision directly undermines the FDA's ability to regulate through cooperative and informal means, and it is preempted by federal law. *See Buckman Co. v. Pls.' Legal Comm.*, 531 U.S. 341 (2001). *See also* U.S. Const. art. VI.

Buckman illustrates why the circuit court's preclusion ruling is preempted. The plaintiffs in *Buckman* sued a consulting company, alleging that the company had defrauded the FDA into approving the device that injured them. (*See id.* at 343.) All nine Justices agreed that the claims were preempted. The Court observed that "the relationship between a federal agency and the entity it regulates is inherently federal in character because the relationship originates from, is governed by, and terminates according to federal law." (*Id.* at 347.) But state fraud-on-the-FDA claims interfere with that relationship because they "exert an extraneous pull on the scheme established by Congress." (*Id.* at 353.) As the Court explained, the FDCA "amply empowers the FDA to punish and deter fraud against the Agency," and the FDA uses that power to "achieve a somewhat delicate balance of statutory objectives" – facilitating the availability of beneficial drugs and devices while ensuring that consumers are protected from dangerous products. (*Id.* at 348.) But that balance "can be skewed by allowing fraud-on-the-FDA claims under state tort law." (*Id.*) Such claims not only create "an incentive to submit a deluge of information that the Agency neither wants nor needs," but also discourage companies from seeking approval of beneficial drugs and devices in the first place. (*Id.* at 350-51.) Thus, state-law fraud-on-the-FDA

claims alter how FDA-regulated companies interact with the FDA in ways the agency itself is powerless to counteract. And because such claims interject the states into the middle of the FDA regulatory process, they are preempted.

The circuit court's summary judgment ruling equally interjects State law into the FDA's regulatory process, and the ruling is thus preempted under *Buckman*. A State law expressly prohibiting cooperation with FDA officials would be preempted; the circuit court's adoption of that same policy through the application of issue preclusion is likewise preempted.

Reversing the circuit court's preclusion ruling would not leave CCPA or other State law *claims* preempted or any class of potentially aggrieved plaintiffs without recourse, as was the case in *Buckman*. To the contrary, where the State has admissible evidence of wrongdoing, it can present that evidence to reach the trier of fact on the question of whether that evidence justifies a finding that the challenged conduct violates the CCPA. Here, the circuit court's ruling relieved the State entirely of the obligation to present evidence and meet its burden of proof, and in the process all but demanded that companies challenge FDA officials. The FDA has made clear that it wants companies to cooperate with its officials, and that warning letters are designed to achieve that regulatory objective. Accordingly, as compared to the fraud-on-the-FDA claims at issue in *Buckman*, the circuit court's application of issue preclusion entails a substantially greater interference with the federal regulatory regime. The circuit court's issue preclusion ruling is preempted.

C. The Circuit Court Violated Janssen's First Amendment Rights by Failing to Conduct Independent Fact-Finding.

At the summary judgment stage of the proceedings below, the circuit court not only granted summary judgment to the State on the question of whether Janssen's communications were false and misleading as a matter of law, but also rejected most of Janssen's remaining

defenses. Thus, without engaging in independent fact-finding, the court rejected Janssen's argument that its challenged communications were entitled to First Amendment protection, holding that "false or misleading" statements are not entitled to constitutional protection. (See S.J. Order at 35 ("[A]s a result of this Court finding the defendants' communications were misleading, the Court must deny the defendants' First Amendment argument."))

The circuit court violated the First Amendment by giving conclusive deference to DDMAC's warning letters. As this Court has observed, "whenever there is a First Amendment defense to actions under state law, the state court is required to be a judge of both the facts and the law." *Maynard v. Daily Gazette Co.*, 191 W. Va. 601, 603, 447 S.E.2d 293, 293-94 (1994). See also *Freedman v. Maryland*, 380 U.S. 51, 58 (1945) ("only a judicial determination in an adversary proceeding ensures the necessary sensitivity to freedom of expression"). But the circuit court did not make factual determinations about Janssen's challenged conduct. It undertook no independent analysis of whether the statements at issue were supported by the scientific evidence upon which they relied, nor did it consider the opinions of expert witnesses proffered by Janssen in opposition to the State's summary judgment motion. Instead, it deferred conclusively to the views expressed by DDMAC in the Risperdal and Duragesic warning letters.

The circuit court's failure to make any independent factual determinations about the speech at issue, in and of itself, warrants reversal. Where speech is challenged, the law requires that a plaintiff prove its case in a court, that the defendant be afforded the opportunity to muster evidence to defend against that proof at trial, and that at the conclusion, specific factual findings be made on the question of whether the challenged speech is actionable. The circuit court denied Janssen any opportunity to defend the content of its communications when it held that Janssen's decision to reach a mutually agreeable resolution of the issues raised in DDMAC's warning

letters foreclosed Janssen from challenging the allegations in the warning letters and declined to make any factual findings before granting partial summary judgment to the State, warranting reversal.

D. Janssen Was Entitled to Judgment Because the State's Evidence Was Inadmissible.

In opposing summary judgment, and again at trial, the State – which had the burden of proof on all issues – was obliged to present sufficient admissible evidence to support a judgment in its favor. *See* W. Va. R. Civ. P. 52(c); W. Va. R. Civ. P. 56(e); *Powderidge Unit Owners Ass'n v. Highland Props.*, 196 W. Va. 692, 698, 474 S.E.2d 872, 878 (1996) (only evidence admissible at trial may be considered on summary judgment). In order to obtain civil penalties under the CCPA, the State was obliged to show that (a) Janssen engaged in “unfair or deceptive acts or practices,” W. Va. Code § 46A-6-104, and (b) Janssen “engaged in a course of repeated and willful violations,” W. Va. Code § 46A-7-111(2). But the State’s only “evidence” that Janssen’s statements were false or misleading consisted of DDMAC warning letters and Janssen’s subsequent letters to healthcare providers, which simply stated that the FDA had sent warning letters and enclosed the FDA approved labels. Those documents are inadmissible.

1. DDMAC Warning Letters Are Inadmissible Hearsay.

The DDMAC warning letters offered by the State are classic hearsay: out-of-court statements offered to prove the truth of the matters asserted in them. *See* W. Va. R. Evid. 801(c). Indeed, those letters were *only* admitted as evidence of the matters asserted in them. Significantly, the State never alleged that Janssen engaged in any misconduct after receiving the warning letters, so those letters were not relevant to show notice. The record could not be clearer that the *only* basis for introducing the warning letters was to prove that the allegations they contain are true.

But the warning letters – informal and advisory opinions of FDA employees – are hearsay and not admissible to prove the allegations they contain. Such non-official letters do not satisfy the “[p]ublic records and reports” hearsay exception set forth in West Virginia Rule of Evidence 803(8). In relevant part, that Rule excepts from the hearsay rule,

(C) in civil actions and proceedings and against the state in criminal cases, factual findings resulting from an investigation made pursuant to authority granted by law, unless the sources of information or other circumstances indicate lack of trustworthiness.

The informal and advisory DDMAC letters at issue here are not “factual findings” resulting from an official “investigation.” They are therefore not admissible under Rule 803(8).

In interpreting Rule 803(8), this Court has observed that, “[g]enerally, ‘interim agency reports and preliminary memoranda do not satisfy Rule 803(8)(C) requirements.’” *See Gamblin v. Ford Motor Co.*, 204 W. Va. 419, 423, 513 S.E.2d 467, 471 (1998). In *Gamblin*, this Court held that a letter from the National Highway Traffic Safety Administration’s Acting Chief Counsel was not admissible to prove matters asserted in the letter because it did not contain any formal findings of fact. (*See id.*) Thus, although the letter could be used for impeachment, it was not substantive evidence of the matters asserted in it. *See* 204 W. Va. at 424, 513 S.E.2d at 472.

For the same reason, “informal and advisory” warning letters, which “do[] not necessarily represent the formal position of FDA,” 21 C.F.R. § 10.85(k), do not satisfy the public records exception. Indeed, courts throughout the country have agreed that warning letters are inadmissible hearsay when offered to prove the truth of the matters asserted in them. As one court put it, the rule that unofficial statements of agency employees are not admissible “is in accord with other circuits that have held that interim agency reports or preliminary memoranda

do not satisfy Rule 803(8)(C)'s requirements." *Smith v. Isuzu Motors, Ltd.*, 137 F.3d 859, 862 (5th Cir. 1998). *See also Toole v. McClintock*, 999 F.2d 1430, 1434-35 (11th Cir. 1993) (interim FDA report inadmissible hearsay); *United States v. Gray*, 852 F.2d 136, 139 (4th Cir. 1988) (holding inadmissible "a tentative internal report not purporting to contain agency factual findings"); *Brown v. Sierra Nevada Mem'l Miners Hosp.*, 849 F.2d 1186, 1189-90 (9th Cir. 1988) (same for preliminary investigation report by Board of Medical Quality Assurance); *City of New York v. Pullman, Inc.*, 662 F.2d 910, 915 (2d Cir. 1981) (same for interim recommendation by transit authority staff member to the transit authority); *Local No. 1 (ACA) v. Int'l Bhd. of Teamsters*, 461 F. Supp. 961, 982 n.9 (E.D. Pa. 1978), *rev'd in part on other grounds*, 614 F.2d 846 (3d Cir. 1980) (rejecting an opinion letter from the Labor Department in part because it was hearsay and not admissible even under the public records exception). Thus, the informal and advisory DDMAC warning letters that the State used to prove its case are not admissible under the public records exception and are inadmissible to prove the truth of their own allegations. The circuit court erred in admitting them.

2. The Letters Janssen Sent Healthcare Providers After Receiving Warning Letters Are Not Probative of Any Disputed Fact and Are Inadmissible Subsequent Remedial Measures.

Likewise, Janssen's July 2004 Risperdal letter and February 2005 Duragesic letter are not admissible, and the circuit court erred in relying on them as substantive evidence of wrongdoing. Even a cursory review of the letters debunks the circuit court's assumption that those letters admit any wrongdoing. The letters simply relate that DDMAC had sent warning letters, briefly summarize the warning letters, and then refer prescribers to the FDA-approved labels. At most, they show that the DDMAC warning letters were sent, which is not relevant to any issue raised by this litigation. In addition, the July 2004 Risperdal letter and February 2005 Duragesic letter

are inadmissible subsequent remedial measures. *See, e.g., Cameron v. Otto Bock Orthopedic Indus., Inc.*, 43 F.3d 14, 17-18 (1st Cir. 1994) (“Dear Customer” letter sent after plaintiff’s injury inadmissible under Federal Rule of Evidence 407 to show warnings insufficient at time of plaintiff’s injury). This Court has long prohibited plaintiffs from using evidence of subsequent remedial measures to show culpability. *See, e.g., Mabe v. Huntington Coca-Cola Bottling Co.*, 145 W. Va. 712, 718, 116 S.E.2d 874, 877-78 (1960) (“any precaution for the future is not to be construed as an admission of responsibility in the past”). *See also* Franklin D. Cleckley, *Handbook on Evidence for West Virginia Lawyers* § 4-7 (2007) (“There is near unanimous agreement that this evidence [of subsequent remedial measures] is inadmissible.”). That prohibition, now codified in West Virginia Rule of Evidence 407, prevents admission of the July 2004 Risperdal letter and February 2005 Duragesic letter as evidence of culpability.

Accordingly, neither the DDMAC warning letters nor the subsequent letters Janssen sent to healthcare providers were admissible as evidence of culpability. The record on appeal contains *no* other “evidence” of culpability. Accordingly, as the case comes before this Court, the record is entirely devoid of admissible evidence supporting the State’s claims. Because the State bears the burden of proof in this suit, Janssen was entitled to judgment on both claims. This Court should reverse and direct the circuit court to enter an appropriate judgment in Janssen’s favor.

II. THE CIRCUIT COURT’S IMPOSITION OF A CIVIL PENALTY WAS ERRONEOUS AND SHOULD BE REVERSED.

A. The Circuit Court Violated the First Amendment When It Punished Janssen’s Speech by Imposing Civil Penalties.

The circuit court’s imposition of a civil penalty violated Janssen’s First Amendment right to free speech because the record does not support *punishment* of Janssen’s speech, which

addressed matters of public concern. Speech on matters of public concern can only be punished upon a finding that it was made with “actual malice” – that is, knowledge of its falsity or reckless disregard of its truth. The circuit court did not make such a finding, nor would the record here support one. The circuit court concluded only that Janssen intended to mail the Risperdal letter and distribute the Duragesic file card. On that ground alone, the circuit court held that Janssen’s action was “willful” because it was “intentionally performed.” (Final Order at 45.) But the constitutional inquiry focuses on whether the person sending a communication knows or acts in reckless disregard of a belief that it is *false*, which could not be shown by the simple fact that Janssen intentionally mailed the letter and distributed the file card. Because the record cannot support a finding that Janssen acted with actual malice, this Court should direct the circuit court to enter an order awarding judgment for Janssen on the State’s civil penalty claim.

1. Speech on Issues of Public Concern Can Only Be Punished if Made With “Actual Malice.”

The United States Supreme Court has held that speech on issues of public concern is entitled to special protection. See *Gertz v. Robert Welch, Inc.*, 418 U.S. 323, 342, 349 (1974); *New York Times Co. v. Sullivan*, 376 U.S. 254, 279-80 (1964). It has repeatedly held that only false statements made with “actual malice” – in other words, with subjective knowledge that they were false or with reckless disregard of whether they were false or not – are subject to government-imposed sanctions. *Hustler Magazine v. Falwell*, 485 U.S. 46, 52 (1988); *Gertz*, 418 U.S. at 349; *Garrison v. Louisiana*, 379 U.S. 64, 74 (1964) (“[O]nly those false statements made with the high degree of awareness of their probable falsity demanded by *New York Times* may be the subject of either civil or criminal sanctions.”).

The need to prove actual malice is not limited to defamation actions; it is necessary whenever government action (like a lawsuit by a state seeking to extract monetary penalties from

a company that disseminated its views publicly) would restrict or penalize speech on a matter of public concern. *See New York Times*, 376 U.S. at 265 (“[T]he test is not the form in which state power has been applied but, whatever the form, whether such power has in fact been exercised.”); *see also Illinois ex rel. Madigan v. Telemarketing Assocs.*, 538 U.S. 600, 620 (2003) (“[e]xacting proof requirements” of Illinois law, including proof of knowledge of falsity, intent to mislead and reliance and “clear and convincing” evidentiary burden imposed on State, were “sufficient” to satisfy First Amendment). The circuit court thus was wrong when it concluded that Janssen should “not be tried under the same standards as an action for defamation because the two are fundamentally different types of speech.” (Final Order at 31.)

2. Janssen’s Communications Involved Matters of Public Concern.

Janssen’s speech – communications to health care professionals about the safety of two FDA-approved prescription drugs – involves matters of “public concern.” *See Connick v. Meyers*, 461 U.S. 138, 146 (1983) (declaring that speech involves matter of “public concern” when it relates to “any matter of political, social, or other concern to the community”); *Roe v. San Francisco*, 109 F.3d 578, 585 (9th Cir. 1997) (“[I]t is sufficient that the speech concern matters in which even a relatively small segment of the general public might be interested.”). The November 2003 Risperdal letter encloses new labeling information from the FDA and then, citing to every then existing peer-reviewed epidemiological study examining the risk of diabetes associated with Risperdal, expresses Janssen’s opinion about what that research suggested, noting the need for confirmatory research. (Defs.’ S.J. Ex. 15.) The Duragesic file card contains FDA prescribing information and warnings, and data showing Duragesic’s effectiveness, possible side effects, reported mentions in the Drug Abuse Warning Network (DAWN) data compilation and the limitations relevant to interpretations of the significance of DAWN data.

(Def.' Tr. Ex. 213.) As the circuit court itself observed, Janssen's challenged communications addressed matters of public health (Final Order at 31), and thus concerned issues of public concern.

Relying on *Dun & Bradstreet, Inc. v. Greenmoss Builders, Inc.*, 472 U.S. 749 (1985), the circuit court reasoned that Janssen's communications did not concern a public issue because they were directed to health-care professionals rather than the public at large. (Final Order at 33-35.) *Dun & Bradstreet*, however, involved a credit agency's report on a private company sent to five paying customers who were contractually barred from sharing the report with third parties. In contrast, the November 2003 Risperdal letter was sent to 750,000 health care professionals nationwide, with no restriction on subsequent dissemination, and comments on the medical basis for the FDA-mandated warning it enclosed. A statement concerning regulation of a prescription medication disseminated on such a wide scale is not a matter of purely private concern. Indeed, the circuit court's treatment of the letter as not addressing a matter of public concern cannot be reconciled with its own finding that the letter deserved punishment *because* it addresses a matter of public health. (Final Order at 31.)

The circuit court also erred when it found that dissemination of Janssen's statements by mail, rather than through the news media, reduced them to matters of private concern. (Final Order at 34.) This finding contradicts binding precedent. *Consolidated Edison Co. v. Public Service Commission*, 447 U.S. 530, 532 (1980), for example, concerned a statement mailed by an operator of a nuclear power plant to its customers describing the benefits of nuclear power. Despite the utility's obvious commercial interest in this issue and the fact that the statement was mailed rather than transmitted through the media, the mailing was found to be a direct statement on a matter of public concern entitled to full constitutional protection. The same is true here.

Indeed, the mailing to customers in *Con Edison* was cited by the Supreme Court in *Central Hudson Gas & Electric Corp. v. Public Service Commission*, 447 U.S. 557, 562 n.5 (1980), as *the* prototypical example of a statement on a matter of public concern by a commercial entity. (*Id.*) *Con Edison* makes clear that direct comments on public issues made by a commercially interested entity *in a mailing* are matters of public concern.

3. The November 2003 Risperdal Letter Is also Protected as an Expression of Reasonable Scientific Opinion.

The November 2003 Risperdal letter not only addresses matters of public concern, it is also protected as an expression of reasonable scientific opinion. As this Court has held, “[a] statement of opinion which does not contain a provably false assertion of fact is entitled to full constitutional protection.” *Maynard*, 191 W. Va. at 607, 447 S.E.2d at 299. Statements of opinion in general, and on scientific matters in particular, are fully-protected. *See, e.g., Board of Trustees of Leland Stanford Jr. University v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991); *McMillan v. Togus Reg’l Office, Dep’t of Veteran Affairs*, 294 F. Supp. 2d 305, 316, 317 (E.D.N.Y. 2003), *aff’d* 120 F. App’x 849 (2d Cir. 2005) (government censorship of “the complex debate and interplay among the scientists that comprises modern science can only distort and confuse”).

The apparent basis for the FDA’s September 2003 request for a class-wide warning was the Cunningham & Lambert abstract, which suggested an increased risk of diabetes associated with atypical antipsychotics generally. Whether there is a class effect, and whether the risk of diabetes associated with individual atypical antipsychotics should be differentiated, remains to this day subject to scientific debate. (*See, e.g.,* Defs’ Tr. Ex. 86, Ex. B at 8 (unchallenged expert testimony that “the literature continues to suggest that Risperdal is less likely associated with diabetes than other [atypical] antipsychotics (Zyprexa and Clozaril)”).) Against this backdrop,

Janssen's letter identified the relevant scientific studies, along with the need for further research to confirm Janssen's interpretation of the data. That letter enjoys constitutional protection because it expresses good faith opinions regarding an issue about which scientists disagreed at the time it was sent that formed the basis for a government action. The First Amendment establishes a conclusive presumption that uninhibited debate will protect the interest of the public far better than government censorship.

The circuit court's decision to punish the November 2003 Risperdal letter rests on fundamental misconceptions about that letter. To begin, the circuit court concluded that the November 2003 Risperdal letter modified the FDA-approved label. (*See, e.g.*, S.J. Order at 24; Final Order at 10-14, 35-36, 50, 51, 60.) It is undisputed, however, that the Revised Label said exactly what the FDA had approved, and that each copy of the November 2003 Risperdal letter transmitted *a complete copy of that label*. The letter expressed *Janssen's* reasonable interpretation of the available data, but did not contradict anything in the FDA-approved label – which itself noted the scientific uncertainty surrounding the issue.

The circuit court also erred in viewing the November 2003 Risperdal letter as an unqualified factual assertion that “(1) taking Risperdal has no more risk of diabetes than taking nothing and (2) Risperdal has less risk of diabetes than some other atypical antipsychotics.” (S.J. Order at 24). In fact, the letter did not make any definitive statements, but instead made clear that no final conclusions could be drawn from the available data. The letter reported that the FDA had required all manufacturers of atypical antipsychotics (including Janssen) to include a warning regarding hyperglycemia and diabetes in their product labeling. The enclosed Revised Label stated that “[h]yperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics

including Risperdal.” And in connection with that, the November 2003 Risperdal letter cited the relevant studies and provided Janssen’s view of what they showed, noting that “confirmatory research is still needed”:

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

(footnote omitted). A statement opining that peer-reviewed studies contain a body of evidence suggesting possible conclusions is not a factual assertion, particularly when prefaced by disclosure that “confirmatory research is still needed.” Such statements “cautiously phrased in terms of apparency” are protected, especially because the only fact Janssen implied – the existence of studies – is demonstrably true. *See Maynard*, 191 W. Va. at 606, 447 S.E.2d at 298.

4. The Circuit Court Erred When It Imposed a Civil Penalty Without Evidence of Actual Malice.

The civil penalty sought by the State pursuant to West Virginia Code § 46A-7-111(2) is punitive, not compensatory, in nature. *See State ex rel. McGraw v. Imperial Mktg.* (“*Imperial Mktg. I*”), 203 W. Va. 203, 219, 506 S.E.2d 799, 815 (1998). Indeed, the circuit court itself “agree[d] in principle” with the State’s assertion that the penalties are punishment. (S.J. Order at 21.) Accordingly, for a civil penalty to survive First Amendment scrutiny in this case, it must be supported by a finding, based on clear and convincing evidence, that Janssen acted with actual malice, which includes at a very minimum reckless disregard for the truth of the matters communicated. *Gertz*, 418 U.S. at 342 (actual malice must be shown through “clear and convincing proof”); *see Madigan*, 538 U.S. at 620 n.9 (noting that government must bear burden

of proof); *Philadelphia Newspapers, Inc. v. Hepps*, 475 U.S. 767, 776 (1986) (when speech is of public concern, plaintiff bears burdens of proving falsity and malice). The Supreme Court has emphasized that the “cases are clear that reckless conduct is not measured by whether a reasonably prudent man would have published, or would have investigated before publishing. There must be sufficient evidence to permit the conclusion that the defendant in fact entertained serious doubts as to the truth of his publication.” *St. Amant v. Thompson*, 390 U.S. 727, 732 (1968). The circuit court did not make such a finding, and the record would not have supported such a finding.

Instead, the circuit court found only that “willful” wrongdoing (which is necessary to maintain a CCPA civil penalties claim) occurred because Janssen intended its communications to be distributed in their final form (that is, the documents contained no typographical errors) (*see* Final Order at 48-49), and that Janssen “attempt[ed] to convince the FDA that the FDA was wrong.” (*See* S.J. Order at 21-22; Final Order at 59-60.) But intending that the November 2003 Risperdal letter and Duragesic file card be distributed in their final forms does not meet the constitutional requirement for imposition of a penalty for protected speech. The mere fact that Janssen intended to say what it did does not establish that Janssen believed its statements to be (allegedly) false or made them with reckless disregard for the truth. And in basing a penalty on Janssen’s efforts to persuade the FDA that its statements were scientifically correct, the circuit court violated Janssen’s constitutional right to petition the government and belied its own conclusion that Janssen’s communications did not concern the public issue of Janssen’s “debate or disagreement with the FDA.” (Final Order at 36.) *See* U.S. Const. amend. I, XIV; W. Va. Const. art. III, § 3-16; *see also infra* § II.B.2 at 43.

The State offered no evidence at the summary judgment stage or during trial that Janssen

acted with actual malice. With the circuit court's summary judgment preclusion ruling in hand, the State withdrew all of its witnesses and waived the right to challenge any of Janssen's evidence or to cross-examine any of Janssen's witnesses. As a result, not a single live witness testified at trial, and the entire trial was over in a few hours. After trial, the court was left with a mountain of unchallenged evidence presented by Janssen showing that the November 2003 Risperdal letter and the Duragesic file card expressed good faith scientific opinions, which were well-grounded and reasonable. Thus, not only did the circuit court fail to make a finding of actual malice, but no evidence in the record below could support such a finding; there is only evidence refuting it. The circuit court's imposition of a civil penalty should be reversed on First Amendment grounds.

B. The Circuit Court Erred in Assessing \$4,475,000 in Civil Penalties.

The circuit court abused its discretion in imposing a massive civil penalty that bears no relation to the harm or culpability at issue here. *See Imperial Mktg. II*, 203 W. Va. at 209, 506 S.E.2d at 805 (civil penalties under CCPA reviewed for abuse of discretion).

1. The Circuit Court Failed to Articulate a Sufficient Justification for its Civil Penalty Calculation.

The CCPA provides that courts should be guided by the interpretation given by federal courts to analogous statutes, such as the Federal Trade Commission Act. *See* W. Va. Code §§ 46A-6-101 and 103. Under the Federal Trade Commission Act, federal courts have generally looked to five factors in determining the amount of a penalty: (1) the good faith or bad faith of the defendants; (2) the injury to the public; (3) the defendant's ability to pay; (4) the desire to eliminate the benefits derived by a violation; and (5) the necessity of vindicating the authority of the administrative agency involved. *See, e.g., United States v. J.B. Williams Co.*, 498 F.2d 414, 438 (2d Cir.1974) (applying similar three-factor test). The circuit court erred in its application of

these factors.

To begin, the court's findings are not supported by the record. For example, the court found that Janssen's conduct caused injury to the public despite the State's stipulation it would offer no evidence of injury. With no evidence of actual injury in the record, the circuit court instead concluded that an alleged "potential" for harm (for which there was also no evidence) constituted "harm and injury." (*See* Final Order at 63.) By definition, the mere "potential" for harm is not itself harm.

The court's additional finding that it needed to vindicate the authority of an agency was flawed. As the circuit court correctly observed, the FDA needs no vindication. (*See id.* at 66.) Nevertheless, the circuit court held that an "agency" needed to be vindicated by concluding that it was necessary to vindicate "the citizenry of West Virginia." (*Id.* at 66-68.) The citizenry of West Virginia is not an "agency," but rather constitutes the "public." The public's interests are addressed by courts considering whether penalties are warranted under the "injury to the public" prong. As noted, the State stipulated that it would offer no evidence of any such injury and the circuit court found only the potential for but no actual injury.

The circuit court further erred by shifting the burden of proof. Because the State had the burden of proof, it was obliged to both establish the need for a civil penalty and a basis for justifying whatever amount of civil penalties it asserted was appropriate. But, rather than starting with the presumption that no civil penalty was needed and forcing the State to prove the need for a penalty, the circuit court started from the presumption that the maximum statutory fine was appropriate and then placed the burden on Janssen to show why a lesser fine was proper. (*See id.* at 51 (stating that the court would determine "whether the penalty should be \$5,000 or less").) The court compounded that error by failing to articulate a sufficient basis for the civil

penalty it selected; it arbitrarily imposed a \$500 fine for each printed material disseminated and a \$5,000 fine for each sales call, even though the record is devoid of evidence regarding the circumstances of any of sales calls. *See Imperial Mktg. II*, 203 W. Va. at 214, 506 S.E.2d at 810 (circuit court must articulate sufficient basis for selecting civil penalty to permit meaningful appellate review). The award cannot stand.

2. The Circuit Court Relied on Constitutionally Improper Considerations.

The circuit court also erred when it based its civil penalty award on two constitutionally improper factors. *First*, the court relied heavily on Janssen's interactions with the FDA, particularly Janssen's initial attempts to persuade the FDA that Janssen's statements were scientifically correct. In this way, the court penalized Janssen for exercising its constitutional right to petition the government. *See* U.S. Const. amend. I, XIV; W. Va. Const. art. III, § 3-16. *See also United Mine Workers v. Pennington*, 381 U.S. 657 (1965); *E.R.R. Presidents Conf. v. Noerr Motor Freight, Inc.*, 365 U.S. 127 (1961). Although the circuit court insisted it was not relying on Janssen's interactions with the FDA, it did so expressly. (*Compare* Final Order at 60 n.40, *with id.* at 59-60.) Indeed, the court directly pointed to Janssen's "attempts to convince the FDA that the FDA was wrong" as evidence of willfulness. (*See* S.J. Order at 21-22.) A clearer infringement of Janssen's right to petition the government is difficult to imagine.

Second, the court based the award on unrelated warning letters, thereby punishing Janssen for unproven conduct not at issue here, and the court therefore violated Janssen's due process rights. *See State Farm Mut. Auto. Ins. Co. v. Campbell*, 538 U.S. 408, 422-23 (2003). Significantly, the court never even considered whether those prior warning letters addressed any of the scientific issues raised by this suit. Instead, the court relied on the mere fact that Janssen had received prior warning letters. As a result, it punished Janssen for alleged wrongdoing that

has never been proven, and which bears no relation to the allegations in this case. Its award must be reversed for that reason alone.

3. The Aggregate Penalty is Excessive.

The circuit court further erred in failing to consider whether the *aggregate* penalty was excessive in relation to the conduct at issue and the harm caused. A \$4.475 million penalty is so out of proportion to the conduct at issue here (which Janssen was not even permitted to defend) that it violates federal and state excessive fines and due process principles. *See* U.S. Const. amend. VIII, XIV; W. Va. Const. art. III, § 3-5; *State Farm*, 538 U.S. at 422-23 (due process); *United States v. Bajakajian*, 524 U.S. 321, 327-28 (1998) (excessive fines). Because the conduct at issue is speech, the civil penalty is subject to even more exacting review, given concerns that arbitrary, unfair punishment chills protected speech. *See Gertz*, 418 U.S. at 349. The State had no evidence of either bad faith or harm, and the \$4.475 million aggregate penalty therefore cannot survive scrutiny.

CONCLUSION

For these reasons, the Court should reverse the circuit court's judgment, and order judgment in favor of Janssen and Johnson & Johnson.

May 14, 2010

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JANSSEN**PHARMACEUTICA INC.**

November 10, 2003

Dear Healthcare Provider,

The Food and Drug Administration (FDA) has requested all manufacturers of atypical antipsychotics to include a warning regarding hyperglycemia and diabetes mellitus in their product labeling. In addition to Janssen, the FDA made this request to the following manufacturers:

AstraZeneca – Seroquel® (quetiapine)
Bristol-Myers Squibb – Abilify™ (aripiprazole)
Eli Lilly and Company – Zyprexa® (olanzapine)
Novartis – Clozaril® (clozapine)
Pfizer – Geodon® (ziprasidone)

In an effort to keep you updated with the most current product information available for the management of your patients, enclosed please find updated prescribing information for RISPERDAL® (risperidone).

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research¹⁻⁸ suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

For additional information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

A handwritten signature in black ink, appearing to read 'Ramy Mahmoud'.

Ramy Mahmoud, MD
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CONTAINS CONFIDENTIAL COMMERCIAL INFORMATION

References:

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RISPERDAL[®]

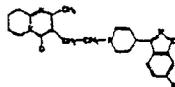
(RISPERIDONE)
TABLETS/ORAL SOLUTION

RISPERDAL[®] M-TAB[™]

(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

DESCRIPTION

RISPERDAL[®] (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinylethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-b]pyrimidin-4-one. Its molecular formula is $C_{26}H_{30}FN_4O$, and its molecular weight is 410.48. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL[®] tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 8 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL[®] M-TAB[™] is also available as a 1 mg/mL oral solution. The inactive ingredients for the solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL[®] M-TAB[™] Orally Disintegrating Tablets are available in 0.5 mg, 1.0 mg, and 2.0 mg strengths and are light coral in color.

RISPERDAL[®] M-TAB[™] Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite[®] resin, gelatin, mannitol, glycine, dimethylsiloxane, croscarmellose sodium hydroxide, aspartarins, red wax oxide, and peppermint oil.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL[®] (risperidone), like with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5HT₂) receptor antagonism. Antagonism at receptors other than D₂ and 5HT₂ may explain some of the other effects of RISPERDAL[®].

RISPERDAL[®] is a selective monoamine reuptake antagonist with high affinity (K_d of 0.12 to 7.5 nM) for the serotonin Type 2 (5HT₂), dopamine Type 2 (D₂), α₁ and α₂ adrenergic, and H₁ histaminergic receptors. RISPERDAL[®] acts as an antagonist at other receptors, but with lower potency. RISPERDAL[®] has low to moderate affinity (K_d of 47 to 253 nM) for the serotonin 5HT_{1A}, 5HT_{1B}, and 5HT_{1C} receptors, weak affinity (K_d of 620 to 800 nM) for the dopamine D₁ and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10⁻⁶ M) for cholinergic muscarinic or β₁ and β₂ adrenergic receptors.

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL[®] M-TAB[™] Orally Disintegrating Tablets are bioequivalent to RISPERDAL[®] Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 18 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 8 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α₁-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displace each other from plasma binding sites. High therapeutic concentrations of sulfamethoxazole (100 µg/mL), erythrin (10 µg/mL), and carbamazepine (10 µg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (i.e., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substances and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see Drug Interactions under PRECAUTIONS). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a model number (see 7) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of ¹⁴C-risperidone administered as a solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL[®] doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α₁-acid glycoprotein. RISPERDAL[®] doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

Short-Term Efficacy

The efficacy of RISPERDAL[®] in the treatment of schizophrenia was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-IV-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies. Among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed: these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=180) involving titration of RISPERDAL[®] in doses up to 10 mg/day (BID schedule), RISPERDAL[®] was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and respectively superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL[®] (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL[®] groups were generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL[®] dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 8 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL[®] (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL[®] dose groups were generally superior to the 1 mg RISPERDAL[®] dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=248) involving 2 fixed doses of RISPERDAL[®] (4 and 8 mg/day on a BID schedule), both RISPERDAL[®] dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 355 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL[®] (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL[®] experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

INDICATIONS AND USAGE

RISPERDAL[®] (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL[®] in schizophrenia was established in short-term (8 to 8 weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL[®] in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL[®] or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use RISPERDAL[®] for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL[®] (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with the syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concurrent serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reinduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL[®] (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated on RISPERDAL[®], drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL[®] despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Strokes, in Elderly Patients With Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 70-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL[®] is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and Diabetic Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL[®]. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of

an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these concerns, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-escalation period, probably reflecting its alpha-adrenergic antagonist properties. Syncope was reported in 0.2% (6/2807) of RISPERDAL®-treated patients in Phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizure

During premarketing testing, seizure occurred in 0.3% (8/2807) of RISPERDAL®-treated patients, two in association with hypotension. RISPERDAL® should be used cautiously in patients with a history of seizures.

Diagnosis

Exfoliative dermatitis and eosinophilia have been associated with antipsychotic drug use. Acute inflammation is a common cause of mortality and morbidity in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although discontinuance soon after prolactinemia, amenorrhea, gynecomastia, and galactorrhea has been reported with prolactin-elevating compounds, the clinical significance of elevated prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in prolactin levels may cause galactorrhea, amenorrhea, and galactorrhea and/or decrease in the reproductive capacity. Studies conducted in mice and rats (see CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorogenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when accompanied by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 6% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pruritus

Rare cases of pruritus have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce pruritus, and it is possible that RISPERDAL® may share this capacity. Severe pruritus may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 29-year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1500 patients). She experienced confusion, fever, and bruising but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Artifactual Effect

Risperidone has an artifactual effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or conditions such as intestinal obstruction, Ray's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Subsidi

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of use, consistent with good patient management, in order to reduce the risk of overdosage.

Use in Patients With Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advised in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²) and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®.

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drug, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

Pharmacokinetics

Phenylethylamine is a component of aspartame. Each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.56 mg phenylethylamine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains

0.28 mg phenylethylamine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylethylamine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone treated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 80%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be treated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, theophylline, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine

Fluoxetine (20 mg QD) has been shown to increase the plasma concentration of risperidone 2.5-2.8 fold, while the plasma concentration of 9-hydroxyrisperidone was not affected. When concomitant fluoxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C8, MP, and 3A4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.53, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 0.4, 0.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.7, and 3 times the MRHD (mice) or 0.4, 1.5, and 5 times the MRHD (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male rats. There was statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m ² (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (0.4)	0.2 (0.4)
Endocrine pancreas adenomas	rat	male	1.5 (0.4)	0.4 (0.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (0.4)	none
	rat	female	0.4 (0.4)	none
	rat	male	0 (37.5)	1.5 (0.4)
Mammary gland neoplasms, Total	rat	male	1.5 (0.4)	0.4 (0.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 8 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear (see Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes of Chinese hamster cells.

Impairment of Fertility

Risperidone (0.18 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in female dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.8 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.5-10 mg/kg or 0.4 to 8 times the maximum recommended human dose [MRHD] on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 8 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 8 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment II and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.18-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams.

regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival from Day 1 to 4 of lactation were reduced in pups born to control but reared by drug-treated dams. These effects were noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MHD on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL[®] therapy is unknown.

RISPERDAL[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL[®] on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL[®] did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in response between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated With Discontinuation of Treatment

Approximately 8% (24/2607) of RISPERDAL[®] (risperidone)-treated patients in Phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The most common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL [®]	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.5%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL[®]-treated patients compared to 0.6% of placebo patients, but given the almost 40-fold greater exposure time in RISPERDAL[®] compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL[®]-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, but 3.6% in active-control patients in the Phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

In two 8 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 8% or greater in at least one of the RISPERDAL[®] groups and at least twice that of placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, fatigue, rash, and tachycardia.

Adverse events were also elicited in one of three two trials (i.e., in the two-dose trial comparing RISPERDAL[®] at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, dizziness, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgasmic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL[®]-Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL[®]-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 8 to 8-week controlled trials. Patients received RISPERDAL[®] doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited incidences cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 1 Incidence of Treatment-Emergent Adverse Events in 8 to 8-Week Controlled Clinical Trials¹

Body System/ Preferred Term	RISPERDAL [®]		
	≤10 mg/day (N=324)	16 mg/day (N=77)	Placebo (N=142)
Psychiatric			
Insomnia	26%	23%	18%
Apathy	22%	25%	20%
Anxiety	12%	20%	8%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms ²	17%	34%	18%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	6%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory system			
Pharynx	10%	8%	4%
Coughing	3%	3%	1%
Strains	2%	1%	1%
Pharyngitis	2%	0%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%

Table 1 (continued) Incidence of Treatment-Emergent Adverse Events in 8 to 8-Week Controlled Clinical Trials¹

Body System/ Preferred Term	RISPERDAL [®]		
	≤10 mg/day (N=324)	16 mg/day (N=77)	Placebo (N=142)
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

¹ Events reported by at least 1% of patients treated with RISPERDAL[®] ≤ 10 mg/day are included, and are rounded to the nearest %. Cumulative rates for RISPERDAL[®] 16 mg/day and placebo are provided as well. Events for which the RISPERDAL[®] incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

² Includes tremor, dystonia, hypokinesia, hypertonia, hyperreflexia, oculogyric crisis, ataxia, abnormal post, involuntary muscle contractions, hyperreflexia, akathisia, and extrapyramidal disorders. Although the incidence of "extrapyramidal symptoms" does not appear to differ for the 10 mg/day group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose-response relationship (see DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relationships for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Dose Group	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Group	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.8	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL[®] (1, 4, 8, 12, and 16 mg/day) were explored for dose-relationships of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend (p<0.05) for the following adverse events: somnolence, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, asthenia/weakness/increased fatigability, and increased perspiration.

Vital Sign Changes

RISPERDAL[®] is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Change

The proportions of RISPERDAL[®] and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 8 to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL[®] (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 8 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL[®]-placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL[®]-placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL[®] administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Change

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL[®] doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-8 beats per minute).

Other Events Observed During the Premarketing Evaluation of RISPERDAL[®]

During its premarketing assessment, multiple doses of RISPERDAL[®] (risperidone) were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL[®] varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL[®] who experienced an event of the type cited on at least one occasion while receiving RISPERDAL[®]. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so generic as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL[®], they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness, **Infrequent:** impaired concentration, depression, apathy, catatonic reaction, euphoric, increased libido, anhedonia, **Rare:** emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. **Infrequent:** dysarthria, vertigo, stupor, paresthesia, confusion, **Rare:** aphasia, cholinergic syndrome, hyposensitization, tongue paralysis, leg cramps, torticollis, hypotonia, coma, rigidity, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*, **Infrequent:** flatulence, **Rare:** increased appetite, stomatitis, melena, dyspepsia, hemorroids, gastritis, **Rare:** fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophageal tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue, **Infrequent:** edema, rigors, malaise, influenza-like symptoms, **Rare:** pallor, enlarged abdomen, allergic reaction, asthenia, sarcoidosis, tussing.

Respiratory System Disorders

Infrequent: hyperinflation, bronchospasm, pneumonia, stridor, **Rare:** asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation, pruritus, increased sweating, acne, decreased sweating, alopecia, hyperhidrosis, pruritus, skin exfoliation. Rare: bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, varicella, dermatitis herpetiformis, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders

Intriguing: palpitation, hypertension, hypotension, AV block, myocardial infarction. Rare: ventricular tachycardia, atrial fibrillation, premature aortic contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Intriguing: abnormal accommodation, xerophthalmia. Rare: diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders

Intriguing: hypokalemia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. Rare: decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypoglycemia, hypocalcemia, hypomagnesemia.

Urinary System Disorders

Frequent: polyuria/polydipsia, intriguing: urinary incontinence, hematuria, dysuria. Rare: urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders

Intriguing: myalgia. Rare: arthralgia, synovitis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia, irregular menstruation, dry vagina. Intriguing: nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dyspareunia, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders

Intriguing: increased SGOT, increased SGPT. Rare: hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders

Intriguing: epistaxis, purpura. Rare: thrombocytopenia, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Intriguing: anemia, hypochromic anemia. Rare: normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction, intriguing: ejaculation failure.

White Cell and Resistance Disorders

Rare: leukocytosis, lymphadenopathy, leukopenia, Pelger-Huet anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses

Rare: bitter taste.

* Incidence based on elicited reports.

Postmarketing Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, aortic formation, cerebrovascular disorder, including cerebrovascular accident, hyperpyrexia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, malaise, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychological Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increase in dose, drug-seeking behavior).

OVERDOSEAGE

Human Experience

Postmarketing experience included eight reports of acute RISPERDAL® (risperidone) overdose with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hypotension, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 30 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL® overdose, with estimated doses of up to 800 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® overdose, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdose

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if indicated) should be performed on activated charcoal together with a laxative should be considered. Because of the rapid degradation of risperidone orally disintegrating tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundition, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of tricyclic antidepressants might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSE AND ADMINISTRATION

Usual Initial Dose

RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 16 mg on a QD regimen are also safe and effective. However, regimens of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/increments of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®; however, maximal effect was primarily seen in a range of 4 to 8 mg/day. Doses above 8 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Pediatric Use

Safety and effectiveness of RISPERDAL® in pediatric patients have not been established.

Dosage in Special Populations

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosage above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk (lower need to be treated cautiously and carefully monitored (see PRECAUTIONS)). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be treated on a twice-daily regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be considered thereafter.

Directions for Use of RISPERDAL® M-TAB™ Orally Disintegrating Tablets

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are supplied in blister packs of 4 tablet units each.

Tablet Accessing

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB™ Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB™ Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be scored once removed from the blister unit. RISPERDAL® M-TAB™ Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at dosing regimen was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "1", or "R" and the strength "2", "4", or "8".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 600 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 600 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-08, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-08, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-08, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 9 mL.

Taste indicates that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and hot/cold milk. It is NOT compatible with either cola or tea, however.

RISPERDAL® M-TAB™ (risperidone) Orally Disintegrating Tablets are scored on one side with R0.5, R1, and R2, respectively, and are packaged in blister packs of 4 (2 X 2) tablets.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-306-28, bling card of 50 tablets NDC 50458-306-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-316-28, bling card of 30 tablets NDC 50458-316-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-326-28.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

Keep out of reach of children.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).

Keep out of reach of children.

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US Patent 4,804,893

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RISPERDAL® tablets are manufactured by:

JOLLG, Gurnee, Puerto Rico or

Janssen-Cilag, S.p.A. Latina, Italy

RISPERDAL® oral solution is manufactured by:

Janssen Pharmaceutica N.V.,

Beerse, Belgium

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are manufactured by:

JOLLG, Gurnee, Puerto Rico

RISPERDAL® tablets, RISPERDAL® M-TAB™ Orally Disintegrating Tablets,

and oral solution are distributed by:

Janssen Pharmaceutica Products, L.P.,

Tarzville, NJ 06590



RISP:000016

JJWVP 0000016

CERTIFICATE OF SERVICE

I, Rebecca A. Betts, counsel for defendants-appellants Johnson & Johnson and Janssen Pharmaceutica Products, L.P., hereby certify that service of the **Appellants' Brief** was made upon counsel for plaintiff-appellee on May 14, 2010, by depositing a true copy in the United States mail, addressed as follows:

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