Meridia Litigation on the Launching Pad

by

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The diet drug Meridia (sibutramine) is receiving close attention from lawyers as a topic of personal injury litigation because diet drugs are a favorite amongst these attorneys. Since Public Citizen petitioned the FDA to recall Meridia in March 2002, an avalanche of litigious interest predictably ensued. Interest was further stoked by calls from Public Citizen for a criminal investigation of Meridia sponsor Abbott because they failed to file adverse event reports via Medwatch, the FDA Safety Information and Adverse Event Reporting Program, in some cases including at least one death.

Epidemiological questions remain to be answered before the future of Meridia litigation can be predicted with confidence. These epidemiological questions are addressed in this article along with the history, mechanism of action, and disclosure issues pertaining to Meridia.

Coming to terms with Meridia

Meridia is the trade name used in the U.S. for the compound named sibutramine. In the U.K., sibutramine is marketed and sold under the trade name Reductil. Since trade names may vary depending on formulation and the country where the drug is registered, medical and scientific discussions (including this one) use the generic name, sibutramine.

Sibutramine can be considered a "pro-drug", because it is essentially inactive. Rather, both therapeutic and side effects of this drug depend on the formation of either or both of two metabolites, desmethylsibutramine (M1) and didesmethylsibutramine (M2) (see Figure 1). Sibutramine is converted into these two metabolites over time. For convenience in this article, the term SIBUT will be used to refer to sibutramine plus these two active metabolites.

Sibutramine is a substituted amphetamine, i.e., is amphetamine with chemical additions made to various parts of the molecule. Unlike other substituted amphetamines such as fenfluramine, SIBUT is claimed to only inhibit the reuptake of a neurotransmitter, but not stimulate release. Only weak and incomplete experimental results suggest that SIBUT does not release but only inhibits the uptake of neurotransmitters.

The sponsor claims, and many of the clinical publications echo, that SIBUT inhibits only serotonin and norepinephrine uptake, for which the term "SNRI" (serotonin norepinephrine reuptake inhibitor) has been coined, reminiscent of the term "SSRI" (selective serotonin reuptake inhibitor) that characterizes the class of antidepressants including Prozac and Paxil. In fact, SIBUT also inhibits dopamine uptake. There is a slightly preferential action on serotonin and norepinephrine (compared to dopamine), but the selectivity is small enough that it is essentially not worth mentioning.

SIBUT acts on both the central nervous system (brain) and peripheral nervous system (everything outside the brain). In the brain, SIBUT acts on all three neurotransmitters, dopamine, serotonin, and norepinephrine, in that order of importance. In the periphery, dopamine is essentially absent, and the actions on norepinephrine and serotonin are the significant ones, respectively.

An important term concerning SIBUT that was debated but ultimately not included in the labeling is "sympathomimetic". This old and dusty term refers to a drug whose administration causes responses similar to activation of the sympathetic nervous system, predominantly norepinephrine (synonymous with noradrenaline) and epinephrine (synonymous with adrenaline). The classic effects of a sympathomimetic are an increase in cardiac output and vasoconstriction, which together cause an increase in blood pressure. The term sympathomimetic carries connotations that alert physicians to a spectrum of safety issues including abuse potential, insomnia, and cardiovascular actions.

A Thumbnail History

SIBUT was discovered by the Boots Pharmaceuticals Inc., in Nottingham, England and the U.S. composition of matter patent was published on April 17, 1984. The U.S. patent for use of SIBUT as a dietary agent was published on July 25, 1995. Boots Pharmaceuticals was purchased in 1995 by

BASF AG, in Ludwigshafen, Germany, and merged with Knoll Pharmaceutical Co., in Mt. Olive, N.J., which was the North American subsidiary of BASF Pharma. On March 2, 2001, Abbott Laboratories acquired the pharmaceutical business of BASF, which included the global pharmaceutical operations of Knoll.

The FDA approved the New Drug Application of Meridia on November 22, 1997, marking its entry onto the U.S. market.

Public Citizen submitted a petition to the FDA requesting the recall of SIBUT on March 19, 2002.

Basic chemistry and pharmacology

The formation of these two metabolites of sibutramine is an extremely simple process: one methyl (CH3) group is removed from the nitrogen atom (N) to form the secondary amine Metabolite 1 (BTS 54 354); and a second methyl group is removed from the nitrogen atom (N) to form the primary amine Metabolite 2 (BTS 54 505). The terms "primary" and "secondary" here have nothing to do with the sequence of N-demethylation nor with the importance or abundance of metabolites.

The amphetamine structure is contained in sibutramine and its metabolites (see Figure 1). But the substitutions are sufficiently large in that significant departures from the pharmacology of amphetamine may occur. Pharmacological activity is much higher in the metabolites than the parent compound.

Human data suggest that sibutramine is 100 percent metabolized to these products in the ratios 40% M1 and 50% M2 (FDA Review and Evaluation of Pharmacology and Toxicology Data, Oct. 3, 1996, p.6). It is also very noteworthy that mice, rats, and rabbits all produce much smaller amounts of M1, making it necessary to profile both M1 and M2 in these animals directly. The extent of conversion of sibutramine to metabolites appears to be much less complete in rodents compared to humans.

Table 1 has been the basis for the common but probably erroneous assertion that SIBUT acts preferentially via serotonin and norepinephrine uptake inhibition rather than dopamine inhibition. The compounds M1 and M2 would not be possible to obtain by typical research laboratories (e.g., university laboratories) unless the sponsor elected to supply the compounds to a laboratory. This offers one explanation as to why there have not been more studies to attempt to replicate or re-examine the fundamental pharmacological properties of these compounds other than the studies performed in the sponsor's laboratory or sponsor-designated laboratories.

Sponsor strategy

The reason that Boots Pharmaceutical decided to retarget SIBUT as an anorectic (appetite suppressant) for the therapeutic indication of obesity is not a matter of public record.

However, one can speculate on a number of reasons:

1. The market for anorectics was (and is) much better than that for antidepressants, taking into account the market fragmentation for antidepressants and the arrival on the market of the first selective serotonin reuptake inhibitors (SSRIs) led by Prozac (fluoxetine).

2. SIBUT presumably did not show remarkable efficacy as an antidepressant; otherwise that would be a common note in clinical studies aimed primarily at obesity.

3. The property of inhibiting dopamine uptake has been tainted ever since the unsuccessful attempt by Hoechst (now Aventis) to market nomifensine, partly due to the abuse potential of this and other dopamine uptake inhibitors.

Mechanisms of Action

SIBUT inhibits reuptake and may stimulate the release of the biogenic amine neurotransmitters dopamine, norepinephrine, and serotonin in the central nervous system (brain and spinal cord) and in the peripheral nervous system. Thus SIBUT increases the actions of these neurotransmitters. Other actions of sibutramine and its metabolites such as direct action at neurotransmitter receptors are possible, but these possibilities have not been thoroughly investigated based on the available literature. Generally the inhibition of uptake is sufficient to explain most actions of SIBUT.

Therapeutic mechanism of action

By virtue of SIBUT's inhibition of the reuptake of the biogenic amines dopamine, norepinephrine, and serotonin, it is able to increase their actions in the central nervous system and peripheral nervous system. Peripheral actions of these neurotransmitters may cause inhibition of appetite, as for instance peripheral release of adrenaline does. But the more significant inhibition of appetite is likely due to the central action on dopamine and serotonin. Since feeding behavior originates in the brain, it is possible to attribute SIBUT's anorectic qualities to its action in that portion of the human body.

Two aspects of anorectic activity are documented: a decrease in appetite and an increase in satiety. Although some authors reported

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Potencies of Sibutramine, M1 and M2 as *In Vitro* Inhibitors of Monoamine Reuptake in Human Brain

	Potency to Inhibit Monoamine Reuptake (Ki, nM)		
	Serotonin	Norepinephrine	Dopamine
Sibutramine	298	5451	943
M1	15	20	49
M2	20	15	45

Table 1. This table means essentially that it takes 20 times less M1 or M2 to perform the same action as sibutramine to inhibit the ability of human neurons to recapture the neurotransmitters serotonin, norepinephrine, or dopamine. Taken from FDA-approved sibutramine label.

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thermogenic activity (increase in calorie consumption) by SIBUT, this result may not be reproducible – i.e., it may not be true.

Side effect mechanism of action

The documented side effects of SIBUT (other than drug interactions) can generally be explained by a mechanism that is identical to the drug's therapeutic mechanism. Thus blood pressure and heart rate increase predictably, as reported in the vast majority of clinical studies.

But there are other potential side effect mechanisms that bear investigation. There is a direct action of sibutramine on the glucose transporter of muscle cells by a mechanism that is not fully characterized.

Very significantly, a change in the density of noradrenergic innervation in the periphery has been observed in animal studies. This has significant implications for the safety of SIBUT because it demonstrates the potential for long-term changes in sympathetic tone with regional specificity. This sort of phenomenon may underlie primary pulmonary hypertension and irregular perfusion of the heart by the carotid arteries.

Side effect descriptions

The usual side effects associated with SIBUT are typical of those expected of a sympathomimetic, amphetamine-like drug, under chronic administration (Table 2.). These are not the more serious, permanent adverse events, which are typically associated with

drugs that have a sympathomimetic, amphetamine-like profile. This is one reason why the basic science of finding whether SIBUT is amphetamine-like (able to cause release of biogenic amines) rather than simply a reuptake inhibitor is extremely important.

The serotonin syndrome.

Another class of reactions is sporadically reported to have occurred with SIBUT in combination with other drugs. Collectively, these reactions occurring together or individually are referred to as "serotonin syndrome"(see Table 3). Typically this occurs in the population at large when two or more drugs acting by a serotonergic mechanism are used simultaneously, thus causing serious injury.

Drug interactions

Two categories of drug interactions are of concern: interactions based on the known mechanism of action of SIBUT on biogenic amines, and interactions based on metabolism and elimination of SIBUT.

Biogenic amine uptake inhibition

Any drug that alters the function of dopamine, serotonin, or norepinephrine in the brain or peripheral nervous system has a strong potential for adverse interactions with SIBUT. The number of drugs that act via the biogenic amines is huge. For instance, the very popular SSRIs such as Prozac (fluoxetine), Zoloft (sertraline), and Paxil (paroxetine) all have potentially dangerous interactions with SIBUT. Dopaminergic drugs, which are typically used to treat schizophrenia and attention deficit disorder, including. Ritalin (methylphenidate), L-dopa (Levodopa)

Permax (pergolide), and Reglan (metoclopramide) also have the potential for adverse reactions with SIBUT.

A number of antidepressants (amitryptiline, desmethylimipramine) that interact with the noradrenergic system and local anesthetics used in dental care can trigger potential lethal interactions with SIBUT.

The common herbal supplement Ephedra contains very powerful sympathomimetic agents that are also dangerous in combination with SIBUT. Caffeine, a phosphodiesterase inhibitor, is likely to exaggerate the effects of SIBUT and cause the same dose of SIBUT to have larger effects. SIBUT may also have adverse interactions with migraine drugs that act on biogenic amines.

The biogenic amines are very idiosyncratic systems that vary significantly from one individual to another, especially the serotonergic system. Thus a higher rate of differences among patients is expected with a drug that acts on all three biogenic amine systems compared to, for instance, a purely noradrenergic drug.

Metabolic interactions

Sibutramine is metabolized primarily in the liver via the cytochrome oxidase P450 enzyme known as CYP 3A4. This pathway is remarkable because there is a substantial genetic heterogeneity in this enzyme that was determined by debrisoquine metabolism before the advent of molecule genetics. In practical terms, this means that some individuals will metabolize the drug much more slowly than others resulting in higher blood levels from the same dose.

A significant number of drugs are metabolized by this route including dextromethorphan (a common ingredient of over the counter cough syrups) and Prozac (fluoxetine). Using any of these drugs at the same time as SIBUT can result in higher than expected blood levels of SIBUT. Grapefruit juice also contains a large amount of substances metabolized by CYP 3A4 making this a significant dietary interaction.

➢ Sleep difficulties
➢ Irritability
➢ Unusual impatience or excitation
➢ Dry mouth
➢ Hypertension
➢ Tachycardia
➢ Palpitations

Table 2. Amphetamine-like sympathomimetic effects associated with chronic SIBUT use.

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MERIDIA MULTIDISTRICT LITIGATION

by

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On Aug. 13, the Federal Judicial Panel on Multidistrict Litigation (JPML) ordered the transfer and coordination of the federal actions entitled *In re: Meridia Products Liability Litigation*, MDL No. 1481. The cases were centralized to the United States District Court for the Northern District of Ohio, Eastern Division in Akron, Ohio, before U.S. District Judge James Gwin. The consolidation and coordination of the above mentioned federal actions into a single district is the most efficient way to help resolve numerous cases nationwide.

Meridia, also known as sibutramine, is an anti-obesity medication that was originally tested, designed, manufactured, marketed and sold by Defendant Knoll Pharmaceuticals prior to its acquisition by Abbott Laboratories in 2001. Meridia is one of few remaining diet drugs still on the market. Unlike the combination of Pondimin (fenfluramine) or Redux (dexfenfluramine) and phentermine (fen-phen), which created a feeling of satiety by boosting production of a brain chemical called serotonin, Meridia works by slowing the body's dissipation of the serotonin that it produces naturally. Meridia is described as a Serotonin and Norepinephrine Re-uptake Inhibitor (SNRI) because it inhibits the reuptake of both chemicals in the brain that have been associated with satiety. Meridia is still on the market and available in three strength capsules: 5 mg, 10 mg, and 15 mg. The drug is classified as a Schedule IV controlled substance.

Today sibutramine is marketed in seventy (70) countries and sold as Reductil in Europe. It is estimated that 8.5 million people worldwide have taken sibutramine since its approval in November, 1997.

An estimated 2 million people in the United States currently take the medication. Meridia is one of the nation's most widely advertised prescription drugs with Abbott spending over $60 million on direct-to-consumer advertising in 2000. In 2001, the sale of sibutramine helped Abbott earn global revenue of $200 million. Already in the first quarter of 2002, Abbott has seen 212 percent growth in sales compared to the first quarter of 2001.

Meridia has been strongly associated with serious cardiovascular injuries and death as a result of substantial increases in blood pressure, heart rate, and arrhythmia. Studies have shown that sibutramine has amphetamine-like effects including nervousness, hyperactivity, increased energy, anxiety, increased insomnia, tremor and dry mouth.

The British Department of Health has reported 200 adverse reactions and two deaths associated with the use of Reductil. In France, drug regulators have reported 100 adverse events. To date, at least 34 deaths worldwide have been associated with sibutramine. Between the period of November 22, 1997 and September 30, 2001, the FDA received the following reports regarding Meridia: 397 reports of people with serious adverse reactions, including 152 hospitalized patients and 29 deaths (19 deaths were the result of cardiovascular causes such as heart attacks). Included in the 19 cardiac deaths were 10 people 50 years of age or younger, including three women under the age of 30. Furthermore, 143 patients reported arrhythmia.

On March 15, 2002, the FDA announced that it was monitoring overseas reports of deaths and adverse events associated with sibutramine, the active ingredient found in Meridia. The FDA said that since sibutramine's U.S. launch as Meridia in 1997, the agency has received a total of 5,000 adverse reaction reports, with 306 being cardiac events. The total includes domestic and foreign reports.

On March 19, 2002, Public Citizen, a consumer watchdog group, petitioned the FDA to remove Meridia from the market.

"Not only does this drug contribute to major cardiovascular problems, but its effectiveness in lowering obesity is meager," said Dr. Sidney Wolfe, director of Public Citizen's Health Research Group.

Data from Public Citizen's petition showed that the average yearly weight loss for patients taking a standard 10 mg dose was only six and a half pounds more than those taking a

placebo. According to the FDA, the agency is examining Public Citizen's petition as well as the deaths and illnesses linked to the drug.

The Benefits of a Meridia Mutltidistrict Litigation

As a result of Meridia's troubled history, many consumers have suffered tremendous economic and non-economic injury. Many legal issues have arisen in the multitude of individual and class action suits that have been filed against Abbott Laboratories, Knoll Pharmaceutical Co., BASF Corp., GlaxoSmithKline, Knoll AG, and BASF AG. Currently, there are more than 20 federally filed complaints against the makers of Meridia.

Congress enacted 28 U.S.C. 1407 to allow for the consolidation of Federal cases, "when civil actions involving one or more common questions of fact are pending in different districts...[and it has been determined] that transfers for such proceedings will be for the convenience of parties and witnesses and will promote the just and efficient conduct of such actions."

The Meridia lawsuits filed in different districts warrant consolidation since there are many common questions of fact such as whether Meridia was and is toxic and safe; whether persons who took Meridia are at an increased risk of developing serious injuries, including, but not limited to arrhythmia, increased heart rate and increased blood pressure; and whether the Defendant's adequately tested Meridia prior to distribution and sales in the marketplace. In addition, consolidation to one centralized location will allow for a level of convenience for those parties and witnesses involved in this litigation.

In order for the plaintiffs to efficiently manage mass tort litigation in a MDL setting, committees are formed. Typically, a Plaintiffs' Steering Committee (PSC) is formed that involves attorneys who contribute their legal services to the litigation. Lead counsel is appointed to oversee the management of the litigation process. An executive committee is established to assist the lead counsel in overseeing subcommittees that are formed to specifically focus on certain areas of the litigation process. Some examples of subcommittees include the Settlement Committee, Science Committee, Discovery Committee and Law and Briefing Committee. The Science Committee, for example, would focus on understanding how the drug works and how it effects the human body. The Science Committee would also retain experts to educate and demonstrate why the drug may or may not be harmful. One of the responsibilities of the Discovery Committee would be to ensure that the necessary documents are obtained and produced. These sub-committees are the driving force that move this complex litigation toward a resolution.

In cases involving mass torts such as in Meridia, there can be millions of pages of documents to obtain and analyze. To ensure that this is accomplished, a document depository is established. This is a centralized location where attorneys analyze the documents to determine which ones are relevant to the litigation. The team of attorneys from several different law firms analyze the documents produced. This team effort allows for an efficient, cost effective way to advance the litigation.

State attorneys involved in the Meridia litigation may also benefit from the MDL process. Attorney's who have filed their claims in state courts may have access to deposition transcripts and documents obtained by the MDL. This is yet another reason how an MDL setting can promote an efficient resolution to claims.

In the Meridia MDL, a Case Management Conference has been scheduled for Friday, Sept. 20, before U.S. District Judge James S. Gwin in Akron, Ohio. The Court has provisionally appointed Stanley M. Chesley of Waite, Schneider, Bayless & Chesley in Cincinnati and John R. Climaco of Climaco, Lefkowitz, Peca, Wilcox & Garofoli in Cleveland to serve as co-lead counsel for the Plaintiffs. In addition, the Court has provisionally appointed the following attorneys to the Plaintiffs' Steering Committee: Richard Arsenault of Neblett, Beard & Arsenault in Alexandria La., Daniel E. Becnel, Jr. of the Law Offices of Daniel E. Becnel, Jr., in Reserve, La., Turner Branch, Elizabeth J. Cabraser of Lieff, Cabraser, Heimann & Bernstein, in San Francisco, Carl Franklovitch of Franklovitch, Anetakis, Colantonio & Simon in Wheeling, W.Va., Paul Gellar of Cauley Geller Bowman & Coates in Boca Raton, Fla., Don Hildre of Dougherty, Hildre, Dudek & Haklar in San Diego, Will Kemp of Harrison, Kemp & Jones in Las Vegas, Richard A. Lockridge of Lockridge, Grindal & Nauen in Minneapolis, Kenneth B. Moll of Kenneth B. Moll & Associates in Chicago, Stephen B. Murray, Jr. of the Murray Law Firm in New Orleans, Diane Nast of Roda & Nast in Lancaster, Pa., and Richard Schiffrin of Schiffrin & Barroway in Bala Cynwyd, Pa.

Pursuant to LR 16.3(a), and subject to further discussion at the Case Management Conference, the Court has recommended that the Meridia MDL be assigned to the Mass Torts track.

In conclusion, when involved in litigation such as Meridia, it is imperative that there be a mechanism through which cases get resolved in an efficient, organized and cost effective manner. The consolidation and coordination of the Meridia federal cases into a single district for pre-trial discovery and proceedings is clearly the best mechanism to achieve that goal.

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