Testimony Before FDA Advisory Committee Meeting on Rimonabant (HRG Publication #1815)

DRAFT: The FDA uses advisory committee meetings to seek independent advice from outside experts before approving some drugs. The FDA has elected to hold an advisory committee meeting concerning rimonabant, a weight loss drug that manufacturer Sanofi-Aventis is seeking to have approved under the brand name ZIMULTI. Each advisory committee meeting includes time for public comment, and the following publication is the testimony presented by Public Citizen on this drug.

The FDA is not required to take the advice of its advisory committees; instead, the recommendations are meant to assist the FDA in its decision-making process.

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FDA Endocrine Metabolic Drugs Advisory Committee Meeting on Rimonabant:
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Introduction: Cannabinoid receptors and probable rimonabant toxicity throughout the body

The elusive idea of a magic bullet drug that has a benefit mediated through its action on one receptor site, yet is devoid of risks at a myriad of other sites in the body, is once again (as with Vioxx, Rezulin, Redux and many other drugs removed because of their toxicity) exemplified by rimonabant. Yes, there is evidence of weight loss due to inhibition of brain-located eating drives. But where else in the brain, or other parts of the body, are these CB1 cannabinoid receptors (which rimonabant inhibits) located?

CB1 receptors are expressed in:

- Brain: Olfactory and cortical regions (neocortex and pyiform cortex), hippocampus, and amygdala, basal ganglia, thalamic and hypothalamic nuclei, cerebellar cortex, and brain stem nuclei. One of the most abundant G-protein coupled receptors in the brain.[1]
- Periphery: autonomic nervous system, liver, muscle, gastrointestinal tract, and adipose tissue,[2] pituitary gland, immune cells and reproductive tissues.[3]

Rimonabant acts:

- On all CB1 receptors, with a higher affinity for CNS cites

Broad reach of cannabinoid system:

[1] Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. *Nature reviews. Drug discovery* 2004;**3**:771–84.
[2] ibid
[3] Pertwee, RG. "The Pharmacology of Cannabinoid Receptors and Their Ligands." International Journal of Obesity 30 (2006): s13-s18. www.nature.com/ijo

- "CB system involved in diverse physiologic functions that include roles in stress recovery and the maintenance of homeostatic balance. Such roles include, for example, neuro-protection, modulation of nociception, regulation of motor activity, control of certain phases of memory, modulation of immune and inflammatory response, influence on cardiovascular and respiratory systems, and antiproliferation of tumour cells."[4]

Psychiatric Adverse Effects

Given the multiple sites in the brain with CB1 receptors, the extraordinarily broad kinds of psychiatric dysfunction caused by the drug (in addition to "statistically, significantly increased suicidality" and other depressive symptoms) are not surprising,

As seen in the following table, there are significant increases in anxiety, insomnia, panic attacks, and almost significant increases in aggression (also seen in animal studies) and agitation in patients given 20 mg of rimonabant vs. patients given a placebo. In addition, significantly more patients getting rimonabant required a sedative or tranquilizer or an anti-depressant for adverse events caused by the drug.

Psychiatric Symptoms Reported as Adverse Events – Pooled RIO Studies (Data from pp 23 and 25, FDA Briefing Document: p values calculated)			
	Placebo N= 1602 # (%)	20 mg rimonabant N=2176 # (%)	p Value
Total # of patients reporting symptoms	*226 (14.1)*	*569 (26.2)*	*<.0001*
Anxiety	40 (2.50)	131 (6.02)	<.0001
Insomnia	53 (3.31)	118 (5.42)	.0019
Required Sedative or tranquilizer for adverse event	66 (4.1)	185 (8.5)	<.0001
Required anti-depressant for adverse event	46 (2.9)	104 (4.8)	.0031
Aggression	1 (0.06)	9 (0.41)	.0516
Panic Attack	1 (0.06)	18 (0.83)	.0006
Agitation	2 (0.12)	10 (.46)	.0836

The evidence for increased suicidality and depression is of particular concern for a drug targeted towards the obese, a population that has been shown to have a significantly higher incidence of depression and eating disorders compared to non-obese individuals.[5] [6]

[4] ibid

[5] Faith, Myles S., Patty E. Matz, and Marie A. Jorge. "Obesity - Depression Associations in the Population." Journal of Psychosomatic Research 53 (2002): 935-942.

The question has been raised as to whether or not the patients studied accurately reflect the psychiatric make-up of the obese population that would be expected to seek rimonabant treatment.[7] The four studies (see table below) give information on the Hospital Anxiety and Depression Scale (HAD) data showing mean pre-treatment depression scores of approximately 3. The depression portion of this scale is out of a possible 21 points where a probable disorder is indicated by a score above 8-11.[8] The average score of 3 is well below the mean value for the general population (3.68) produced in a normative study.[9] Given that the obese population has been found to have a 20% higher incidence of depression compared to the non-obese population,[10] this number seems artificially low. Though some of this difference can be explained by the exclusion of clinically depressed patients who would have the highest scores (generally 11 or above, though this was not a specific cutoff used by the studies), the size of the discord indicates a broader cause. Regardless of the explanation for how it came about, the apparent exclusion of depressed individuals limits the capacity of the results to be generalized to clinical practice.

Baseline HADS (Hospital Anxiety and Depression Scale) scores from RIO-Trials compared with Normative HADS data from general population

	RIO-Europe	RIO-Lipids	RIO-Diabetes	RIO-North America	Normative Data for General Population
Depression	2.9 (SD=3.0)	3.1 (SD=2.8)	3.0 (SD=2.8)	3.0 (SD=2.8)	3.68 (SD=3.07)

A related concern of significant importance is the exclusion in all RIO studies of patients on anti-depressant medication. Between 2004 and 2006, "30% of all patients receiving phentermine, orlistat, sibutramine, or diethylpropion had a concurrent prescription for an anti-depressant medication."[11] This strongly suggests that patients would, if this drug is approved, end up taking anti-depressants and rimonabant in tandem, with unknown consequences.

Problems with the Clinical Studies: Discontinuation Rates and other Problems

To date, four major phase III studies have been published on rimonabant: RIO (Rimonabant In Obesity)-Europe, RIO North America, RIO-Lipids, and RIO-Diabetes.[12] There

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6 Golay, Alain, Anne Laurent-Jaccard, Frank Habicht, Jean-Pierre Gachoud, Mireille Chabloz, Anne Kammer, and Yves Schutz. "Effect of Orlistat in Obese Patients with Binge Eating Disorder." Pharmacology and Therapeutics 13 (2005): 1701-1708.

7 Gadde, Kishore M. "Effect of Rimonabant on Weight and Cardiometabolic Risk Factors." Vol. 296. John Hopkins University, 2006.

8 Herrmann, Christoph. "International Experiences with the Hospital Anxiety and Depression Scale - a Review of Validation Data and Clinical Results." Journal of Psychosomatic Research 42 (1996): 17-41.

9 Crawford, J R., J D. Henry, C Crombie, and E P. Taylor. "Normative Data for the HADS From a Large Non-Clinical Sample." British Journal of Clinical Psychology 40 (2001): 429-434.

10 Simon, Gregory E., Michael Von Korff, Kathleen Saunders, et al. "Association Between Obesity and Psychiatric Disorders in the US Adult Population." Arch Gen Psychiatry (2006): 824-830.

11 Page 14, FDA review document

12 Xie, S., M. A. Furjaniec, J. J. Ferrara, E. L. Ardino, et al. "The Endocannabinoid System and Rimonabant: a New Drug with a Novel Mechanism of Action Involving Cannabinoid CB1 Receptor Antagoinst - or Inverse Agonism - as Potential Obesity Treatement and Other Therapeutic Use." Journal of Clinical Pharmacy and Therapeutics 32 (2007): 209-231.

are serious problems with these studies, limiting the significance of their findings in the debate over the safety and efficacy of the drug.

Discontinuation rates for each treatment group by study					
	20mg	5mg	Placebo		Weight Loss Compared to Placebo
RIO-Europe	39.4%	37.3%	41.6%		5.8 kg
RIO-North America	45%	49%	49%		4.7 kg
RIO-Lipids	36.1%	39.7%	37.4%		5.4 kg
RIO-Diabetes	32%	35%	34%		3.9 kg
Discontinuation rates taken directly from the published studies (RIO-Europe, RIO-North America, RIO-Lipids, RIO-Diabetes). Weight loss numbers from Curioni and Andre (Cochrane Review, 2006).					

One major concern is the high discontinuation rates observed in these four studies (see table above). The primary method used to input data for subjects who did not complete treatment was the last observation carried forward approach.[13] [14] [15] [16] Though this is consistent with many other published weight loss papers,[17] such a large amount of missing information severely limits the validity of the data.[18]

Combined with other questions that have arisen regarding the methodological quality of the four studies with regards to method of randomization, allocation concealment, and blinding,[19] high attrition rates serve to throw conclusions on safety and efficacy into doubt. This is particularly important considering that the studies done thus far point to weight loss of around 5%, a number near the margin in terms of producing an improvement on risk factors for obesity-related diseases. Whether rimonabant use actually improves health-related quality of life or long term health outcomes is far from certain.[20] [21]

Reproductive and other pre-clinical (animal) effects

In its posted briefing document, Sanofi describes the pre-clinical animal studies as follows:

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[13] Van Gaal, Luc F., Aila M. Rissanen, Andre J. Sheen, et al. "Effects of the Cannabinoid-1 Receptor Blocker on Weight Reduction and Cardiovascular Risk Factors in Overweight Patients: 1-Year Experience From the RIO-Europe Study." Lancet 365 (2005): 1389-1397.

[14] Pi-Sunyer, F, Louis J. Aronne, and Hassan M. Heshmati. "Effect of Rimonabant, a Cannabinoid-1 Receptor Blocker, on Weight and Cardiometabolic Risk Factors in Overweight or Obese Patients (RIO-North America: a Randomized Controlled Trial)." JAMA 295.7 (2006): 761-775.

[15] Scheen, Andre J., Nick Finer, and Priscilla Hollander. "Efficacy and Tolerability of Rimonabant in Overweight or Obese Patients with Type 2 Diabetes: a Randomised Controlled Study." Lancet 368 (2006): 1660-1672.

[16] Despres, Jean-Pierre, Alain Golay, and Lars Sjostrom. "Effects of Rimonabant on Metabolic Risk Factors in Overweight Patients with Dyslipidemia." NEJM 353 (2005): 2121-34.

[17] Leung, Wilson, G. N. Thomas, Juliana Chan, et al. "Weight Management and Current Options in Pharmacotherapy: Orlistat and Sibutramine." Clinical Therapuetics (2002): 58-80.

[18] Simmons-Morton, Denise G., Eva Obarzanek, and Jeffrey A. Cutler. "Obesity Research - Limitations of Methods, Measurements, and Medications." JAMA 295.7 (2006): 826-828.

[19] Curioni, C., and C. Andre. "Rimonabant for Overweight or Obesity (Review)." Cochrane Database of Systematic Reviews (2006).

[20] Yanovski, Susan Z. "Pharmacotherapy for Obesity - Promise and Uncertainty." NEJM (2005): 2187-2189.

[21] Curioni, C., and C. Andre. "Rimonabant for Overweight or Obesity (Review)." Cochrane Database of Systematic Reviews (2006).

"In a comprehensive program of nonclinical studies, rimonabant was shown to have very limited potential to induce toxicity. No specific target organ pathology was identified in the completed animal studies. The nonclinical studies suggest a weak, proconvulsant potential for rimonabant when combined with pentylenetetrazole that alone induces convulsions under experimental procedures in some species. These data are consistent with the view that rimonabant is without proconvulsant potential in the absence of other stressors."[22]

The statement that "No specific target organ pathology was identified in the completed animal studies." is, at best, misleading and more likely simply dishonest.

Among the more worrisome findings –all included in the European label-- are:

> Rats: decrease in corpora lutea and implantations; decrease in total and viable fetuses (1.5x human dose based on BSA—body surface area); Increased pup mortality in pre-weaning period (1.5x human based on BSA); rabbits: decreased litter size, increased post-implantation loss, decreased fetal body weight and increased malformations (birth defects--anencephaly, micro-ophthalmia, widened brain ventricles and omphalocele) at (5x human based on BSA).

The following information is from the EMEA (European Medicines Agency) "Scientific Discussion."[23] Items having an asterisk are included in the current European Drug label.

- Metabolized mainly by CYP3A4*; many other drugs are metabolized by CYP3A4; competition can cause an increase in rimonabant concentration if the other drug(s) bind more tightly to this enzyme.
- Extensive tissue distribution; passes blood-brain barrier & placenta & into milk; 3-fold accumulation of drug in thyroid, spleen, plasma, thymus, liver, and brain.

Preclinical safety

1) CNS toxicity: convulsions in rats, mice, and monkeys *at exposures similar to humans;* hyperexcitability, **aggressiveness**, combative behavior (rodents and dogs); tactile hyperesthesia and hyperexcitability (rodents); proconvulsant potential when combined with physical or chemical seizure inducers or stressful conditions
2) Bone marrow:
   Fatty involution of bone marrow (rats and dogs)
   Edema of bone marrow (macaques)
3) Immunotoxicity (possibly CB2): leucopenia and lymphopenia (macaques)
4) Liver toxicity: steatosis and centrilobular necrosis (rats)
5) Genotoxicity: chromosomal aberrations in mouse lymphoma cells
6) Carcinogenicity (female rats): hepatocellular adenomas; endometrial carcinomas in uterus and squamous cell carcinomas in cervix and uterus (33x human based on BSA)
7) Reproduction toxicity (rats)*:

[22] Sanofi briefing document, page 15.

[23] http://www.emea.europa.eu/humandocs/PDFs/EPAR/acomplia/H-666-en6.pdf

a) Abnormal estrous cyclicity plus a decrease in corpora lutea and implantations; decrease in total and viable fetuses (1.5x human dose based on BSA)
b) Increased pup mortality in pre-weaning period (1.5x human based on BSA)
c) "Equivocal effects" on motor activity and auditory startle during pre- and postnatal development
d) decrease in weight of testis, prostate, seminal vesicles, epididymal fat pad, and motility of spermatozoa (>25x human based on BSA)

Reproduction toxicity (rabbit)*: decreased litter size, increased post-implantation loss, decreased fetal body weight and increased malformations (anencephaly, micro-ophthalmia, widened brain ventricles and omphalocele) at (5x human based on BSA)

8) A metabolite with a structure signifying a genotoxic alert is produced in all species (Sanofi committed to further clarify as post-approval follow-up measure)

The case of cannabinoid regulation of implantation and fetal development should also be taken as an example of how limited an understanding scientists have of the role of this widely dispersed neurotransmitter system. Rimonabant is the first drug of its class to be used in humans and there are many important questions that remain unanswered.

Questions Regarding Long Term Safety

A major issue, in addition to those discussed above, is the lack of reliable information regarding the long-term effects of rimonabant use. Of the studies performed to date, two had a duration of two years, while the other three were one year. Because rimonabant is the first drug of its class, there is no data evaluating the long term effect of antagonizing the widespread cannabinoid system. Weight lost while using rimonabant is regained after discontinuation of use,[24] [25] which means that if the drug is to be effective at all it will have to be prescribed on a long term basis. Given this fact, the complete lack of data on rimonabant use in humans over an extended period of time is cause for significant concern.

The literature on animal studies done with rimonabant contains ominous indications of issues that might arise as people continue using the drug for longer periods of time. Zimmer et al. have reported that CB1 knockout mice have significantly increased mortality due to "spontaneous" deaths of unknown causes (Figure below).[26] Zimmer, an expert in cannabinoid system research, has also noted that this same strand of CB1 deficient mice exhibit increased loss of neurons with aging.[27] Though this does not generalize directly to rimonabant use in humans, it is still cause for concern in the absence of studies evaluating the effects of long term CB1 antagonism.

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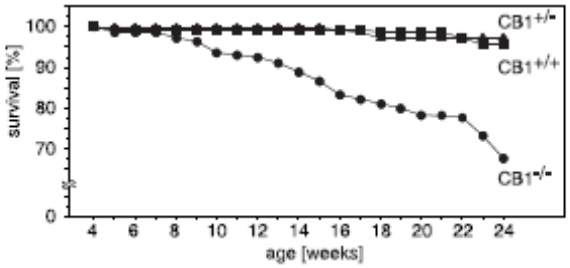
[24] Pi-Sunyer, F, Louis J. Aronne, and Hassan M. Heshmati. "Effect of Rimonabant, a Cannabinoid-1 Receptor Blocker, on Weight and Cardiometabolic Risk Factors in Overweight or Obese Patients (RIO-North America: a Randomized Controlled Trial)." JAMA 295.7 (2006): 761-775.

[25] Prescrire Editorial Staff. "Rimonabant." Prescrire International 15 (2006): 123-126.

[26] Zimmer, Andreas, Anne M. Zimmer, and Andrea G. Hohmann. "Increased Mortality, Hypoactivity, and Hypoalgesia in Cannabinoid CB1 Receptor Knockout Mice." PNAS 96 (1999): 5780-5785.

[27] German Press.



From Zimmer et al., 1999: Mortality rate in CB1 knockout mice (-/-), wild type (+/+) and heterozygous.

Other studies have shown clear effects of the CB1 receptor on the cardiovascular system in producing hypotension and bradycardia.[28] [29] It is unclear whether rimonabant, by blocking the regulatory effects of endogenous agonists or through an inverse agonist mechanism,[30] could alter cardiovascular system functioning in a way that might prove detrimental over the long run.

Conclusion

A recent thorough review of rimonabant by the Cochrane database of systematic reviews concluded that 1) that average weight loss is "modest" and 2) more rigorous studies of efficacy and safety are required to "fully evaluate the benefit risk ratio of this new drug."[31] We strongly agree with this statement that clearly requires the rejection of the approval of rimonabant because of a lack of ability to "fully evaluate the benefit risk ratio of this new drug."

[28] Varga, Karoly, Kristy Lake, Billy Martin, and George Kunos. "Novel Antagonist Implicates the CB1 Cannabinoid Receptor in the Hypotensive Action of Anandamide." European Journal of Pharmacology 278 (1995): 297-283.

[29] Lake, Kristy D., David R. Compton, Karoly Varga, Billy R. Martin, and George Kunos. "Cannabinoid-Induced Hypotension and Bradycardia in RAts is Mediated by CB1-Like Cannabinoid Receptors." Journal of Pharmacology an Experimental Therapeutics 281 (1997): 1030-1037.

[30] Pertwee, RG. "Inverse Agonism At Cannabinoid Receptors." International Congress Series 1249 (2003): 75-86.

[31] http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006162/frame.html