

Modafinil for the Treatment of ADHD

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Acknowledgments

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Safety Work-up

- Deaths
- Serious Adverse Events
- Adverse Dropouts
- Potentially Clinically Significant Labs/ECG/Vitals
- Common and Drug Related Adverse Events
- Special Searches-Psychiatric Adverse Events, SJS, Neutropenia, Blood Pressure-Pulse
- Safety Update



Modafinil-marketed with extensive exposure

Verispan, LLC Projected Unique Patients

Total Number of Unique Patients That Have Filled Prescriptions at a Retail Pharmacy in the US from 2002-2005.

Age Group	Patient Count	Percent
0-12	10,944	1.01%
13-17	25,769	2.37%
All Ages	1,087,677	100%



Extent of ADHD Data

2.7.4 Summary of Clinical Safety Page 2-3

	Number of patients who received modafinil				
	Open-label study C1538d/312/AD/US				
Study number	Double-blind	Modafinil-modafinil	Placebo-modafinil	Open-label total	Total Phase 3 exposure
C1538d/309/AD/US	131	112	57	169	188 a
C1538d/310/AD/US	125	84	49	133	174 a
C1538d/311/AD/US	164	131	72	203	236 a
Other open-label patients b	.	.	.	28 b	28 b
Total Phase 3				533	626
Total All Studies					933

a Number of patients who received modafinil in the respective Phase 3 double-blind study + number of patients who switched from placebo (double-blind) to modafinil (open-label).

b Patients who entered study 312 from Phase 1 or Phase 2 studies: C1538d/113/BA/US (n=13) and C1538a/213/AD/US (n=15).



Phase 2 Exposure

2.7.4 Summary of Clinical Safety-Page-3

Study number	Study design	Duration a	Modafinil dosage	N b
C1538d/113/BA/US	Open-label, crossover	Single dose	170 or 200 mg/day	24
	Open-label, multiple dose	14 days	340 or 425 mg/day	(24)
C1538a/206/PK/US	Open-label, dose-ranging	12 weeks	100 to 400 mg/day	20
C1538a/207/AD/US	Double-blind, crossover (4-period)	4 weeks	100 to 400 mg/day	47
	Open-label, treatment extension	8 weeks	100 to 400 mg/day	(30)
C1538a/213/AD/US	Double-blind, parallel-group	4 weeks	300 to 400 mg/day	197
	Open-label, treatment extension	8 weeks	100 to 400 mg/day	220[47]
Total				335c

a Maximum duration of modafinil treatment.

b Number of patients who received modafinil as of the clinical cutoff date (5 October 2004).

c Numbers in parentheses are not included in the total since these patients were already exposed to modafinil in a prior period of study; the number in brackets indicates patients who switched from placebo (double-blind) to modafinil (open-label) in study 213 and are included in the total.



Exposure by Dose in Phase 3 Studies			Modafinil (mg/day)			
			≤255	340	425	PBO
Study	Design	Duration				
309	Flexible-dosage, parallel-group	9 weeks	31	22	78	67
310	Fixed-dosage, parallel-group	9 weeks	0	44	81	64
311	Flexible-dosage, parallel-group	9 weeks	31	36	97	82
Total	Pool of studies for Common AE Table		62	102	256	213



Body System	Preferred Term	Modafinil (n = 420)	Placebo (n = 213)
Body as a Whole	Headache	20%	13%
	Abdominal Pain	10%	8%
	Fever	5%	3%
	Pain	3%	2%
Digestive	<i>Anorexia</i>	16%	3%
	Nausea	4%	2%
	Dry Mouth	2%	1%
	Dyspepsia	2%	1%
	Gastroenteritis	2%	1%
Hemic/Lymphatic	Ecchymosis	2%	0%
Metabolic/Nutritional	Weight Loss	4%	1%
Nervous	<i>Insomnia</i>	27%	4%
	Nervousness	5%	4%
	Dizziness	2%	1%
Skin/Appendages	Rash	4%	2%



Safety Results from Controlled Trials

- **No Deaths**
- **Adverse Events of Note**
 - **SJS/EM: Modafinil N=2; PBO=0**
 - **Leukopenia: No new cases in AERS Safety Update**
 - **Psychiatric Adverse Events**
 - **SRAE Modafinil N=4; PBO=0**
 - **Mean Blood Pressure: Modafinil –slight decrease compared to PBO; 9/420 Modafinil vs 1/213 with BP systolic \geq 130 and increase of \geq 20-mmHG**
 - **Pulse no mean difference from placebo; 6/420 vs 2/213 outliers \geq 120 bpm and increase of \geq 15 bpm**
 - **Weight: Modafinil 0.7-Kg loss; PBO 1.0-Kg gain**

Psychiatric Adverse Events ADHD Children Only

A Mosholder Appendix Table D; Page 29 for study sample

Study Design	Rx	N	Pt-years Exposure	Psychosis/ Mania	SRAE	Aggression/Pt -100 year corrected	
DB	PBO	308	32.6	0	0	5	15.4
DB	MOD	664	75.1	2	4	9	12.0
Open	MOD	799	369.4	2	0	14	3.8



Fishers Exact Test for Suicide Related Adverse Events

– 2-tailed

$p=0.31$

– 1-tailed

$p=0.22$

	SRAE	No SRAE
MOD	4	660
PBO	0	308

Sponsor Proposes WARNINGS section language

- Sparlon

- 4/664 vs. 0/308
- Not statistically significant (p=0.22 1-tailed Fisher's Exact Test)
- All cases of ideation
- 3 cases resolved without discontinuation

- Stratтера

- 6/1357 vs. 0/851 (FDA Criteria) p=0.01
- 7/1357 vs. 1/851 (Lilly Criteria) p=0.07
- Statistically significant
- 5 cases ideation and 1 attempt (FDA defined cases)
- Boxed Warning

Cases of Severe Rash EM/SJS

- 2 Children in Controlled Trial Database
 - 062338 and 315 (no histopathology)
- No Children in Post-Marketing AERS
- 4 Adults in AERS Post-Marketing Database
 - US016653, Triage #202048, Triage # 163459, and US011480 (3 with confirmatory histopathology one the is EM-without histopathology)
- No Adults in Controlled Trial Database

Rash

- 2 serious (1-admitted to the hospital-not ICU or burn unit)/0 PBO
- 10 dropouts due to rash/ 0 PBO
- Spontaneous Adverse Events in Controlled Trials: 4% Modafinil vs. 1% Placebo
- No other Childhood SJS/EM in Post-Marketing AERS Database with >36K children exposed

Verispan, LLC Projected Patients Exposed to Modafinil

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the US from 2002-2005.

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Labeling

- Sponsor Proposes WARNINGS section language-
 - no deaths
 - child cases were not severe enough to require burn unit or ICU
 - 2/933 EM/SJS in Sparlon RCT no biopsy confirmation
 - No other child cases in AERS with >36K exposures
 - 3 confirmed adult SJS cases in post-marketing AERS database with >1,050,000 unique adult patients exposed.
- Lamictal Boxed Warning-
 - SJS death of child in a prospective registry study of 1,983 patients
 - 8/1000 in children; 3/1000 adults; 1.3/1000 in adult adjunctive therapy Bipolar Disorder patients.

Questions

- Has modafinil been shown to be effective for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents?
- Has modafinil been shown to be acceptably safe in the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents?
- If modafinil were to be considered for approval:
 - What kind of a risk management plan should be implemented with regard to the signal for serious skin rashes with this drug in the ADHD program?
 - How should the concern about serious skin rashes be addressed in product labeling (you have been provided our labeling proposal in the approvable letter and also the sponsor's currently proposed labeling)?
 - Should there be a requirement for a post-marketing study(ies) to better understand the serious skin rashes, and what type of study(ies) might be considered?