

SPARLON™ (Provigil® / Modafinil)
Cephalon Inc.
NDA 20-717 (S-019) for ADHD

**Update from the Psychopharmacologic
Drugs Advisory Committee
held March 23, 2006**

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Division of Psychiatry Products
Center for Drug Evaluation and Research



Modafinil Agenda

- ADHD Review: Glenn Mannheim, M.D.
- Narcolepsy Review: Ronald Farkas, M.D.
- Safety Review Skin Reactions Lourdes Villalba, M.D.
- 1 Year Post Exclusivity Review: Charlene Flowers, RPh



OUTLINE

1. Background
2. Overview of Safety Database From ADHD Clinical Trials
3. Common AE's
4. Psychiatric AE's`
5. Other AE's
6. Rashes
7. Potential Public Health Impact
8. Closing Comments



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Modafinil Background

- **Drug:** Provigil® (modafinil tablets) – schedule IV
- **Therapeutic Category:** CNS stimulant
- **Sponsor:** Cephalon, Inc.
- **Indication:** Narcolepsy, Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS), and Shift Work Sleep Disorder (SWSD)
- **Original Market Approval:** December 24, 1998
- **Pediatric Exclusivity Granted:** March 21, 2006



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Modafinil Background

Approved as a wakefulness-promoting agent in adults with excessive daytime sleepiness (EDS) associated with narcolepsy [1998]

Approved for EDS associated with Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS) and Shift Work Sleep Disorder (SWSD) [2003]

Non-Approval for ADHD in children and adolescents based upon serious skin reactions [2006]



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Modafinil Background

Non-Approval for narcolepsy and OSAHS in children and adolescents under BPCA based upon lack of efficacy [2006]

Recommended Dosing:

- **200 mg once a day (2.67 mg/kg)**
Narcolepsy + OSAHS: single AM dose
SWSD: 1 hr prior to the start of work shift
- **Doses > 200 mg, no additional benefit**
- **Available Tablets: 100, 200 mg**



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Source of Data: ADHD Submission

- Not conducted under BPCA
- ADHD
 - Children (6-11 Yrs)
 - Adolescents (12-17 Yrs)
- Dosage and Administration
 - Maintenance Dose
 - < 30 kg 340 mg qd
 - 21 mg/kg, highest dose; 7.9 times higher than adult dose
 - ≥ 30 kg 425 mg qd
 - 14 mg/kg, highest dose; 5.3 times higher than adult dose
 - Titration
 - Initial dose 85 mg
 - Increase in steps of 85 mg q 2 – 7 days
- Formulation: 85, 170, 255, 340 and 425 mg Tablets



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Study Population

- 6-17 yrs with DSM-IV ADHD, in full time school
- Moderately to severely ill or greater (CGI-S ≥ 4),
- WISC-III and WIAT-II-A ≥80: Minimal LD
- Excluded:
 - Psychiatric co-morbidities
 - Psychotic disorder, suicide risk, depression, mood, anxiety disorder, substance abuse, etc.
 - Stimulant non-responders (≥ 2 courses)
 - Abnormal labs (e.g. ANC ≤ 1000/mm³)
 - Clinically significant illness ≤ 4 wks baseline



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Phase 3 Studies

– Studies 309 & 311

- Identical 9 week, double blind, flexible dose, weekly titration
 - 170 mg, 255 mg, 340 mg, 425 mg

– Study 310

- 7 week, double blind, fixed dose
 - < 30 kg; 340 mg/day
 - ≥ 30 kg: 425 mg/day
- 2 week randomized withdrawal
 - Modafinil to Modafinil or Placebo
 - Placebo to Placebo



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Extent of Modafinil Exposure by Dose in Phase 3 Studies	Number of Patients			
	≤255 mg	340 mg	425 mg	PBO
Study 309 - Flexible-dosage, parallel-group, 9 week study	31	22	78	67
Study 310 - Flexible-dosage, parallel-group, 9 week study	0	44	81	64
Study 311 - Flexible-dosage, parallel-group 9 week study	31	36	97	82
Subtotal	62	102	256	213
Total	420			



*Source: NDA 20-717 (S-019)

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PK Exposure at Therapeutic Doses: Peds vs. Adults

PK Parameter	Analyte	Adults**	Children and Adolescents*	
			WT ≥ 30 kg	WT < 30 kg
		N = 13	N = 11	N = 13
		PROVIGIL <i>Normalized to 200 mg QD x 21 D</i>	Modafinil 425 mg QD x 14 D	Modafinil 340 mg QD x 14 D
Cmax	Modafinil	6.4 ± 0.75	16.0 ± 3.00	19.5 ± 4.44
	Modafinil Acid	2.65 ± 0.5	5.4 ± 1.09	4.9 ± 1.28
	Modafinil Sulfone	1.85 ± 0.8	11.8 ± 7.25	29.0 ± 15.7
AUCtau	Modafinil	73.5 ± 13.3	177 ± 28.5	199 ± 45.4
	Modafinil Acid	26.7 ± 5.0	61.3 ± 11.4	54.7 ± 61.3
	Modafinil Sulfone	38.8 ± 1.7	251 ± 154	629 ± 349
Sulfone AUC Ratios Sub-Population : Adults		1.0	6.5	16.2
Maximum Daily Dose (MDD) (mg/kg)		2.67	14.2	21.25
MDD Ratios		1.0	5.3	8.0



• Obtained from Study C1538a/113/PK/US
 •** Obtained from Study C1538a/404/PK/US – Dose 400 mg

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Adverse Events



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**Incidence of Common Treatment-Emergent AEs
Double-Blind Placebo Controlled Studies By 2 % Subjects Treated
With Modafinil That Were More Frequent Than Placebo Group**

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%
Nervous	Insomnia	27%	4%
	Nervousness	5%	4%
	Dizziness	2%	1%
Digestive	Nausea	4%	2%
	Dry Mouth	2%	1%
	Dyspepsia	2%	1%
	Gastroenteritis	2%	1%
	Anorexia	16%	3%
Metabolic/Nutritional	Weight Loss	4%	1%
Hemic/Lymphatic	Ecchymosis	2%	0%
Skin/Appendages	Rash	4%	2%



Psychiatric AE's

- **Psychosis: 5/933 (0.5 %)**
 - 1 case formication (one day after d/cing drug)
 - 1 case command auditory hallucinations with suicidal ideation requiring hospitalization
 - 2 cases other hallucinations
 - 1 case ideas of referential control (abnormal thinking)
- **Suicidal Events 6/933 (0.6%)**
 - Placebo-Control: modafinil (4/664), placebo (0/308) *
 - 5 ideation
 - 1 attempt
 - None completed



*Source: Mosholder A: Review of Modafinil ADHD Psychiatric Adverse Events; 03/03/2006.

Other Adverse Events

SAE	Phase 3 Placebo Controlled		All Phase 2-3
	Modafinil (n= 420)	PBO (n=213)	Modafinil (n=933)
Gastric/Duodenal Ulcers ¹	1 (0.24 %)	0 (0.0 %)	2 (0.21 %)
Syncope ²	1 (0.24 %)	0 (0.0 %)	9 (1 %)
Asthma ⁴	6 (1.4 %)	1 (0.5 %)	24 (2.6 %)
Dehydration ⁵	1 (0.24 %)	0 (0.0 %)	3 (0.32 %)
Hepatocellular Injury (≥ 3 X ULN) ³	6 (1.4 %)	2 (0.9 %)	16 (1.7 %)

¹ One case associated had H. pylori associated with moderate, metabolic acidosis.
² ECG: AV dissociation with junctional rhythm, 1 wk after bradycardia, hypotensive syncopal episode
³ ALT, AST, or, GGT. No cases of jaundice or liver failure. No significant bilirubin elevation. P = 0.72.
⁴ Subject 021191 in Study 310 started modafinil (340 mg), 8 days later collapsed at school during gym, stopped breathing momentarily given an inhaler and began breathing normally, diagnosed as acute asthma, discontinuing on day 9.
⁵ Subject 058006 in Study 312 started modafinil (425 mg), hospitalized on d 147 severe dehydration, moderate ketosis, acidosis and hypoglycemia secondary to strept throat.



Overview of Rashes



RASHES, SKIN REACTIONS

RASHES

- Phase 3, Double-Blind: 4 % (Modafinil), 2 % PBO
- All subjects exposed: 49/933 (5 %) had rash
- Dropouts Phase III PC Studies:
 - Modafinil: 1/420 (0.24%); PBO: 0/213 (0%)
- Dropouts, All Studies:
 - 13/933 (1.4 %) drop-out due to rash
 - Rashes varied in spectrum of severity
 - 8 with rash also had fever
 - 2 with rash also had elevated LFT's

OTHER SKIN EVENTS

- Possible Allergic Events: 22/933 (2.4 %)
 - Hives, Urticaria, Facial Edema, Pruritus, Allergic Reactions, Red lips, Eczema with ↑ LFTs
- Miscellaneous Probable Non-Allergic Events



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Serious Skin Reactions

- **Erythema multiforme, Steven Johnson Syndrome (EM/SJS): 2 considered cases at time of PDAC**
 - **Peeling and blistering over entire body with lips and urinary tract involvement (Study 311)**
 - Drug stopped but rash progressed to peeling, blistering, mucosal involvement over days.
 - **Maculopapular, morbilliform, pruritic (Study 207)**
 - Drug stopped but rash progressed
 - Hospitalized
- **Other Rashes**
 - **Vesiculobullae cheeks with severe lip blisters (Study 207)**
 - **Unspecified rash in 7 yr. old with a positive re-challenge: day 24 onset; TX. Prednisone, Benadryl; recurred when restarted at 85 mg on day 34 (Study 312)**



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Subject ID 062338, Study 311

- 7 y.o. Asian male with ADHD
 - Titrated to modafinil 425 mg/day over 2 weeks
 - D 16: fever (101.9 °), sore throat, mild rash (red bumps)
 - D 17: received 1 single dose of amoxicillin
 - D18: modafinil stopped. Over next 4 days rash worsens and progresses
 - D 19: Multiple pruritic areas arms/stomach/face
 - D 23: Mucosal involvement in 2 areas (urethral meatus & lips)
 - Followed by extensive skin peeling
 - D 30: No new lesions, event resolved
 - D 31: Given 1 dose of modafinil, itching worsens
 - D 44: Withdrawn from Study: Event resolved



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Study 311: 7 Year Old With SJS

Photo Not Available at 03/23/2006 AC



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Subject ID 315, Study 207

- 11 y.o. Caucasian female with ADHD
 - Started modafinil 200 mg/day
 - D 4: Fever, abdominal pain, diarrhea lasting for 9 days
 - D14: Pruritic rash: face, chest. Drug stopped Treated with diphenhydramine
 - D 15: Rash worsens
 - Hospitalized for possible SJS
 - No mucosal involvement.
 - Diagnosed as moderate morbilliform rash
 - Treated with hydroxyzine
 - Rash resolved in 1 week



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Subject ID 18004, Study 213

- 8 y.o. Caucasian male with ADHD
 - Started/titrated modafinil 200 mg/day
 - D 14: Fever, moderate rash on cheeks
 - Rash Progressed
 - D 17: Severe blistering on lips
 - Vesiculobullous rash
 - D 19: Modafinil stopped
 - Recovered
 - Time Course Not Specified
 - Treatment: cephalexin (rash), acetaminophen with codeine (fever, pain)



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Cases of EM/SJS in Studies: Initial FDA Assessment

- **Definite Cases Representing EM/SJS**
 - All Studies (2/933; 0.2 %)
- **Early Prodromal EM/SJS**
 - All Studies (3/933; 0.32 %)
- **Insufficient Information But History Suggestive of Prodromal EM/SJS**
 - All Studies (7/933; 0.75 %)



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Erythema Multiforme – Stevens Johnson Syndrome

**Possible Hypersensitivity
Reactions ?**



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Possible Cross-Sensitivity with Sulfa Drugs

Subject ID's 056003-Study 311; 056180, Study 312

- 9 y.o. male
 - H/O sulfamethoxazole trimethoprim allergy
 - Normal labs and physical at baseline and during DB PBO (Study 311)
 - Rolled into open label modafinil (Study 312)
 - After 10 days: urticaria, face edema, fever (99.6°F), vomiting
 - After 14 days: increased ALT (17 X ULN), AST (10 X ULN)
 - After stopping drug and supportive treatment, recovers



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Potential Public Health Impact

SJS Background Rate: 1-2/ 1,000, 000/Yr (0.00015 %)

(Rzany B, et al. Lancet 1999; 353: 2190-94; Rzany B, et al. J Clin Epi 49: 7:769-773, 1996)

SJS Observed: 2/933 (0.214%)

• **Compatible/Suggestive of Early EM/SJS: 3/933 (0.3 %, 3/1,000)**

• **Insufficient Information, But Hx Suggesting Prodromal EM/SJS: 7/933 (0.75 %, 7/1,000)**

• **Definite + Possible Cases: 12/933 (1.3 %, 13/1,000)**

Range of Risk: 0.2% - 1.3 %



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ESTIMATED USAGE

- 2.5 million Children (4-17 Years) On ADHD Meds (CDC Study-2003)¹
- Estimated projected market share of Provigil: 10 %
 - Basis for Assumption: Atomoxetine at 16.4 % is currently at low end compared to other stimulants (dispensed prescriptions for ages < 19 years, Jan-Jun 2005)²



¹Prevalence of Diagnosis and Medication Tx for ADHD-U.S. 2003, 09/02/05, pp. 842-847
²Source: National, Dispensed Prescriptions Jan-Jun 2005, Extracted January 2006.

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Estimated Cases SJS

- **250,000 children switched to Modafinil**
 - 2.5 million children receiving medication for ADHD
 - 10% market share
- **500 – 3250 Cases SJS**
 - 0.2% - 1.3% incidence
- **25 – 162 Deaths / each 10% market share**
 - 5% mortality (Dermatol Online J 2002 Jun; 8 (1): 5)



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WILL LABELING WORK?

“There is *no satisfactory method for determining who is at greatest risk* for developing drug associated SJS and TEN and hence of preventing it, *short of avoiding drugs altogether*. There has been a single study suggesting that early withdrawal of the agent at the first sign of the illness may improve the outcome (Mittman N, et. al. Drug Safety 2004; 27 (7): 477-87). Although this intuitively makes sense, this study needs to be replicated. Even if it is proven correct, its practical application will be limited because *it is very difficult to identify the very earliest lesion in a timely manner because of the rapidly progressive nature of this illness and the non-specific features of its prodrome.*”

La Grenade L, ET. Al. Comparison of Reporting of Stevens - Johnson syndrome and Toxic Epidermal Necrolysis in Association with Selective COX-2 Inhibitors. Drug Safety 2005; 28 (10): 917-924



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Psychopharmacology Committee Recommendations

- **Rate of SJS in modafinil pediatric studies: 1/933 (+ other skin reactions and one systemic hypersensitivity reaction)**
- **Background rate of SJS reported in literature: 1-2 per million PYRs, with 10% mortality**
- **Panel voted 11 to 1 against approval**
- **Large study recommended to quantify risk of SJS in pediatric population**



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Following AC

- FDA requested updated information on all skin and multi-organ hypersensitivity reactions in all pediatric and adult clinical trials and postmarketing experience with modafinil.
- This information was combined with post-marketing data to update labeling.



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