

Provigil[®] (Modafinil)

Follow-up to Hypersensitivity Reactions in the Pediatric Population

Pediatric Advisory Committee

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Follow-up to Modafinil Hypersensitivity Reactions in the Pediatric Population

1. FDA Psychopharmacologic Drugs AC
2. Clinical Trial Data: Pediatric and Adult
3. Postmarketing data: Spontaneous AE Reports and European Epidemiologic Studies
4. FDA Actions
5. Summary



Psychopharmacologic Drugs AC March 2006

- Modafinil (N= 933)
 - 3 cases of serious rash
 - 1 multi-organ hypersensitivity reaction

As per February 2006 FDA Dermatology consultant:

- Definite cases representing EM¹ or SJS² = 2
 - Early prodromal EM or SJS= 3
 - Insufficient information but history suggestive of prodromal EM or SJS= 7
- Placebo (N= 213): No cases

¹ Erythema Multiforme



² Stevens-Johnson Syndrome

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Subject ID 062338, Study 311

**Serious rash: Case extensively discussed at 3/06 FDA PD AC.
Consensus: Stevens-Johnson syndrome¹**

- 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 - D 44: Withdrawn from Study: Event resolved



¹After AC, sponsor proposed that this is Atypical Erythema Multiforme Major

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Subject ID 315, Study 207

**Serious rash: Case discussed at previous 3/06 FDA PD AC.
Diagnosis: Controversial**

- 11 y.o. Caucasian female with ADHD
 - Started modafinil 200 mg/day
 - D 4: Fever, diarrhea, 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 mucosae involved. Diagnosed as moderate morbiliform rash. Treated with hydroxyzine
 - Rash resolved in 1 week



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Subject ID 18004, Study 213

**Serious rash: Case discussed at previous 3/06 FDA PD AC.
Diagnosis: Controversial.**

- 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, acetaminophen with codeine
 - Additional info
 - Final Dx by treating dermatologist: Erythema Multiforme



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Subject ID 056180, Study 312

Case discussed at previous FDA PD AC: Consistent with a systemic or multi-organ hypersensitivity reaction

- 9 y.o. Causasian male with ADHD
 - Hx of sulfamethoxazole trimethoprim allergy
 - Normal labs and physical at baseline and during DB placebo (Study 311)
 - Open label modafinil started (Study 312)
 - After 10 days: petechial rash, face edema, fever (99.6°F), vomiting
 - After 13 days: increased ALT (17 X ULN), AST (10 X ULN)
 - After stopping drug and supportive treatment, recovered



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Psychopharmacologic Drugs AC March 2006 (cont.)

- SJS in modafinil pediatric ADHD studies: **1/933** (plus two cases of serious rash, 1 systemic hypersensitivity reaction and several skin reactions with insufficient information). None on placebo.
- Background rate of SJS reported in literature: 1-2 per million PYRs, with 5-15% mortality.
- Panel voted 11 to 1 against approval in ADHD and recommended large study to quantify risk of SJS in pediatric population.



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After the AC - FDA Reviews

- Updated clinical trial data:
 - Skin and multi-organ hypersensitivity reactions in:
 - All pediatric & adult clinical trials of modafinil.
 - Adult clinical trials of armodafinil (R-enantiomer of modafinil).
- Postmarketing data:
 - AERS reports of serious hypersensitivity reactions with modafinil in children & adults
 - European SCAR (Severe Cutaneous Adverse Reactions) epidemiologic studies.



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Modafinil Clinical Trials Updated Exposure

Age (years)	Placebo-controlled		Modafinil
	Placebo N=1730	Modafinil N=3401	All trials N=5849
0-16 ¹	380	847	1585
≥ 17 ²	1350	2554	4264

¹ Includes all pediatric indications (ADHD, narcolepsy and obstructive sleep apnea), with doses of 100 to 425 mg/day. ² 28 patients in "legacy studies" with missing age are assumed to be adults.



Modafinil Pediatric Trials: Rash¹

	Placebo-controlled		Modafinil
	Placebo N=380	Modafinil N=847	All trials N=1585
Fatal	0	0	0
Serious	0	2 (0.2 %)	3 (0.2 %)
Led to Discontinuation ²	0	11 (1.3 %)	13 (0.8 %)

¹ Rash refers to skin reactions that may represent drug hypersensitivity reactions.

² Table excludes subjects with skin reactions that did not appear to be drug hypersensitivity reactions (e.g. fungal dermatitis, chronic eczema) and five subjects who had a skin reaction at some point during the study but discontinued for other reasons (e.g. dystonia, duodenal ulcer).



Modafinil Pediatric Trials

- Rash that led to discontinuation in modafinil-treated subjects: 13/1585 (0.8%)¹
 - 9 M/4F
 - Ages 6-12 (mean 8.6) years
 - Dose 100-425 (mean 250) mg/day
 - Onset (rel. day) 4-24 (mean 13.4) days



¹ Rash refers to skin reactions that may represent drug hypersensitivity reactions.



Modafinil Pediatric Trials Discontinuation due to Rash¹

ID	Age (years), gender, reaction (all on modafinil)	Dose mg/day	Onset (Day)
#411	10 M, mod. rash treated with DPH	200	21
#8012	9 M, moderate rash treated with DPH	200	14
#19010	11 M, moderate rash; patient withdrew consent on day 21	300	17
#020001	12 F, urticaria (IV & oral CS)	225	13
#29015 OL	7 M, mild rash, treated with MP and DPH; (+) rechallenge 5 days after re-starting drug	340	24
#34015	6 F, severe rash; small red lesions on arms and confluent large area on inner thighs, preceded by upper respiratory infection, treated with DPH and topical CS.	225	10

¹ Skin reactions that may represent drug hypersensitivity reactions. F=female, M=male, CS=corticosteroids, DPH=diphenhydramine, MP=methylprednisolone. OL: open label.



Modafinil Pediatric Trials Discontinuation due to Rash +

ID	Age (years), gender, reaction (all on modafinil)	Dose mg/day	Onset Day
#315 *	11 F, fever, diarrhea, generalized pruritic rash, hospitalized, poss. SJS but no mucosae involved	200	4
#13011	8 M, fever, leukopenia, abdominal pain, hives	100	Unk.
#18001	6 M, severe macular rash trunk & extremities, fever, vomiting, anorexia	300	3
#18004*	8 M, fever, rash on cheeks, blister on lips. Thought to be SJS; final Dx: Erythema Multiforme	200	14
#24004	8 F, fever, macular rash on trunk & extremities, leukopenia	200	13
#056180 OL*	9 M, petechial rash, fever, swollen eyes & ↑ Transaminases (<i>multi-organ hypersensitivity</i>)	340	13
#062338*	7 M, rash, sore throat, fever. [Stevens- Johnson Syndrome vs. Atypical Erythema Multiforme Major]	425	15



* Cases discussed at March 2006 AC

Adult Clinical Trials Discontinuation due to Rash¹

- **Modafinil trials**
 - Modafinil 2/2554 (0.1 %)
 - Placebo 0/1350 (0 %)
 - All modafinil patients 4/4264 (0.1 %)
- **Armodafinil trials**
 - Armodafinil 4/645 (0.6 %)
 - Placebo 2/445 (0.5 %)
 - All armodafinil patients 5/1516 (0.3 %)
 - Additionally, one case of angioedema and one anaphylactoid reaction



¹ "Rash" refers to reactions that may represent skin hypersensitivity reactions. None were serious.

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Modafinil Clinical Trials

Rate of Discontinuation due to Rash¹

- Pediatric population: Higher in the modafinil-treated group as compared to placebo. Includes 3 cases of serious rash on modafinil and none on placebo.
- Adult population: Similar for modafinil vs. placebo and for armodafinil vs. placebo. No serious rash.
- Caution needed when cross comparing trials, however, data suggest that risk of skin hypersensitivity reactions is higher in pediatric population as compared to adults.



¹ "Rash" refers to reactions that may represent skin hypersensitivity reactions.

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Modafinil Postmarketing Data: AERS (Approval through March 2007)

- **Pediatric** (0-16 years):
 - 1 case of DRESS in a 15 yo.
 - (1 case of SJS was reported but it was the 7 yo male from the pediatric ADHD clinical trial)
- **Adult** (≥17 years):
 - 4 definite cases of SJS, including one case in a 17 yo. female
 - 7 potential multi-organ hypersensitivity reactions including one fatal eosinophilic myocarditis
 - 2 cases of angioedema requiring corticosteroids



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Pediatric Postmarketing Experience in AERS - DRESS¹

- 15 yo male started modafinil on 4/13/06, titrated to 400 mg/d. After 5 weeks: maculopapular body rash + fever (38°C), myalgia, fatigue, dry cough. Treated with ibuprofen. Concomitant meds: fluvoxamine, olanzapine & aripiprazole, since 2005. All meds discontinued.
- On admission to hospital: tachycardia, eye edema, soft palate petechiae, WBC 25,000 (37% eosinophils), mild renal insufficiency. Skin Bx = eosinophilia. Dx of DRESS.
- Within 24 hours: coagulopathy, hypotension, bilateral fluffy pulmonary infiltrates. Required mechanical ventilation, dopamine, IVIG and corticosteroids. At some point also had hepatitis (ALT x 6 ULN) and pancreatitis (amylase x 2.5 ULN).
- Patient improved and was extubated on 6/2/06. WBC= 5.7 (1% eosinophils), PT/PTT normalized. All viral and bacterial cultures remained negative.



¹ DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

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Modafinil Postmarketing Data: Estimated Reporting Rate of SJS in AERS (January 2002 through December 2006)

	n ¹	Prescriptions ² (% of total)	Exposure PYRs ³	Reporting Rate per million PYRs
Pediatric 0-16 years	0 (1)	145,639 (1.8%)	12,137	0 (82.3)
Adult ≥ 17 years	4	7,827,618 (97.7%)	652,302	6.1
Overall ⁴	4 (5)	8,008,486 (100%)	667,374	5.9 (7.4)

¹ AERS reports Jan 2002 through March, 2007. ² Verispan Vector One®, National 2002-2006. Projected Number of Total Prescriptions Dispensed by Retail Pharmacies in the US. ³ PYRs: Patient years of exposure, estimated by dividing the number of prescriptions by 12. ⁴ Includes age unspecified.



Parenttheses in columns 2 and 5 indicate values when case from pediatric trial is included.

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Modafinil Postmarketing Data European SCAR¹ Epidemiologic Studies²

- Three epidemiologic studies involving ~58,000 subjects exposed to modafinil
 - 3.1 % estimated <19 years based on US usage data
- No cases of severe cutaneous adverse reactions reported with modafinil
- However, can not rule out an increased risk of SJS in pediatric population
 - Relatively small database (< 2,000 younger than 19 years)

¹SCAR: Serious Cutaneous Adverse Reactions (Erythema Multiforme Major (EMM), Acute generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) & overlap SJS/TEN). ² Includes EuroSCAR, RegiSCAR and German SCAR Registry, as of August 2006.



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Modafinil Data Summary

- **Clinical trial data:** Discontinuations due to rash¹

	All	
	Modafinil	Placebo
Pediatric (0-16)	0.8 %	0 %
1 case of SJS (vs. Atypical EMM) 12 other skin hypersensitivity reactions including 1 multi-organ hypersensitivity		
Adult (≥ 17)	0.1 %	0 %

- **Postmarketing data (AERS):** Reporting rate of SJS

Pediatric (0-16)	0 per million PYRs
Adult (≥ 17)	6.1 per million PYRs



¹“Rash” refers to reactions that may represent skin hypersensitivity reactions.

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FDA Actions for Provigil®

- Requested large study to further evaluate risk of serious skin reactions if pediatric indication is pursued.
- New labeling
- Risk Minimization Action Plan



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New Provigil® Labeling (8/17/07)*

- WARNINGS
 - **Serious rash, including Stevens-Johnson Syndrome (Bolded WARNING)**
 - Includes data from pediatric and adult clinical trials and postmarketing experience
 - Provigil is not approved for any pediatric indication
 - Angioedema and anaphylactoid reactions
 - Multi-organ hypersensitivity reactions



*Language also applies to Nuvigil® (armodafinil)

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New Provigil® Labeling (1)

WARNINGS

Serious Rash, including Stevens-Johnson Syndrome

Serious rash requiring hospitalization and discontinuation of treatment has been reported in adults and children in association with the use of modafinil.

Modafinil is not approved for use in pediatric patients for any indication.

In clinical trials of modafinil, the incidence of rash resulting in discontinuation was approximately 0.8% (13 per 1,585) in pediatric patients (age <17 years); these rashes included 1 case of possible Stevens-Johnson Syndrome (SJS) and 1 case of apparent multi-organ hypersensitivity reaction. Several of the cases were



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New Provigil® Labeling (2)

associated with fever and other abnormalities (e.g., vomiting, leukopenia).

The median time to rash that resulted in discontinuation was 13 days. No such cases were observed among 380 pediatric patients who received placebo. No serious skin rashes have been reported in adult clinical trials (0 per 4,264) of modafinil.

Rare cases of serious or life-threatening rash, including SJS, Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have been reported in adults and children in worldwide post-marketing experience. The reporting rate of TEN and SJS associated with modafinil use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate. Estimates of



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New Provigil® Labeling (3)

the background incidence rate for these serious skin reactions in the general population range between 1 to 2 cases per million-person years.

There are no factors that are known to predict the risk of occurrence or the severity of rash associated with modafinil. Nearly all cases of serious rash associated with modafinil occurred within 1 to 5 weeks after treatment initiation. However, isolated cases have been reported after prolonged treatment (e.g., 3 months). Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash.

Although benign rashes also occur with modafinil, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, modafinil should ordinarily be



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New Provigil® Labeling (4)

discontinued at the first sign of rash, unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

Angioedema and Anaphylactoid Reactions

One serious case of angioedema and one case of hypersensitivity (with rash, dysphagia, and bronchospasm), were observed among 1,595 patients treated with armodafinil, the R enantiomer of modafinil (which is the racemic mixture). No such cases were observed in modafinil clinical trials. However, angioedema has been reported in postmarketing experience with modafinil. Patients should be advised to discontinue therapy and immediately report to their physician any signs or symptoms suggesting angioedema or anaphylaxis (e.g., swelling of face, eyes, lips, tongue or larynx; difficulty in swallowing or breathing; hoarseness).



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New Provigil® Labeling (5)

Multi-organ Hypersensitivity Reactions

Multi-organ hypersensitivity reactions, including at least one fatality in postmarketing experience, have occurred in close temporal association (median time to detection 13 days: range 4-33) to the initiation of modafinil.

Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalization or be life-threatening. There are no factors that are known to predict the risk of occurrence or the severity of multi-organ hypersensitivity reactions associated with modafinil. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included



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New Provigil® Labeling (6)

myocarditis, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritis and asthenia. Because multi-organ hypersensitivity is variable in its expression, other organ system symptoms and signs, not noted here, may occur.

If a multi-organ hypersensitivity reaction is suspected, PROVIGIL should be discontinued. Although there are no case reports to indicate cross-sensitivity with other drugs that produce this syndrome, the experience with drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.



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Provigil® Risk Minimization Action Plan*

- 15-day expedited reports of serious skin and hypersensitivity reactions
- Improvement on reporting and follow-up of cases in clinical trials and postmarketing reports
- Dear Healthcare Provider letter
 - **Bolded WARNING** - Serious skin rash including SJS; angioedema; multi-organ hypersensitivity.
 - Provigil not approved in the pediatric population
 - Stop Provigil if signs of rash or hypersensitivity (unless clearly not drug related)
- Patient & physician educational materials
- Monitoring and evaluation of RiskMAP



* Similar RiskMAP for Nuvigil

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Provigil® - Safety Newsletter

- Post-marketing report of serious skin reactions with Provigil were featured in the first issue of FDA Drug Safety Newsletter (September 2007):

<http://www.fda.gov/cder/dsn/default.htm>



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Summary

- FDA identified serious skin reactions including SJS in association with the use of modafinil in pediatric clinical trials. There were no serious skin reactions in adult modafinil (and armodafinil) clinical trials.
- In post-marketing experience, overall reporting rate of SJS with modafinil is higher than the background rate. Cases of multi-organ hypersensitivity reactions have been reported in children and adults.
- To date, modafinil is not approved for any pediatric indication.
- RiskMAP and updated labeling with bolded **WARNING** for Provigil® to address serious skin reactions.

