

Provigil®

One Year Post Exclusivity Adverse Event Review

**Pediatric Advisory Committee Meeting
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Overview

- **OSE Reviews from Marketing-2007**
- **Pediatric Post Exclusivity Review**

OSE Provigil®
REVIEWS
FROM
12/1998-2007

Adverse Events Categories Reviewed
by OSE Since Approval

- Dermatology
- Hematology
- Hepatology
- Psychiatry
- Maternal Exposure
- Drug Abuse
- Angioedema and Anaphylaxis

OSE Provigil® Dermatology Reviews from Marketing-2007

Serious skin

- 09/2005 – 4 cases of Stevens Johnson (SJS)
- 07/2006 – no new cases
- 02/2007 – 1 case of DRESS, 1 case of SJS
- 02/2007 - EuroSCAR study – no new cases

OSE Provigil® Dermatology Reviews from Marketing-2007



7 year old male with Provigil® associated
Stevens-Johnson syndrome (SJS)

OSE Provigil® Dermatology Reviews from Marketing-2007

7



49 year old female with Provigil® associated
Stevens-Johnson syndrome (SJS)

OSE Provigil® Dermatology Reviews from Marketing-2007

8

Serious Skin - 02/2007

Epidemiology analysis of EuroSCAR study

- ✓ Drug usage too low
- ✓ Unable to identify cases of Stevens-Johnson syndrome (SJS)

OSE Provigil® Dermatology Reviews from Marketing-2007

Dermatology Labeling

Labeled (2007) for Serious Rash including SJS,
TEN, and DRESS

Labeling extended to Nuvigil® (armodafinil)

OSE Provigil® Hematology Reviews from Marketing-2007

Leukopenia and Neutropenia (all ages)

10/16/2000 – first review

8/11/2003 - update

8/8/2005 - update

Labeled (2007) for agranulocytosis

✓ No pediatric cases identified

OSE Provigil® Hepatology Reviews from Marketing-2007

10/2006 – Pediatric

1 case of hepatotoxicity

- 6 year old boy with vomiting and convulsions
- event likely related to viral etiology

✓ No recommendation for labeling change

OSE Provigil® Psychiatry Reviews from Marketing-2007

03/2006 - AERS postmarketing data

- Psychosis, mania, suicidal events, and aggression

03/2006 - Clinical trial data

✓ association with ADHD class of drugs,
including Provigil®

OSE Provigil® Psychiatry Reviews from Marketing-2007

Psychiatric Labeling

Labeled (2007) for psychiatric symptoms

Labeling extended to Nuvigil® (armodafinil)

OSE Provigil® Maternal Exposure Reviews from Marketing-2007

05/2007 - Maternal Exposure

1 fatal case of intrauterine growth
retardation

- femur length < stated gestational age
- head in 5th percentile, grew consistently

OSE Provigil® Maternal Exposure Reviews from Marketing-2007

05/2007 - Maternal Exposure, 1 fatal case of
intrauterine growth retardation (cont.)

- Cause of death - respiratory distress and severe intrauterine growth retardation related to prematurity

OSE Provigil® Maternal Exposure Reviews from Marketing-2007

Maternal Exposure Labeling

Labeled (2007) for growth retardation in the
pregnancy section

Labeling extended to Nuvigil® (armodafinil)

OSE Provigil® Drug Abuse Reviews from Marketing-2007

- **Scheduled - C-IV**
- 10/2003 - All ages

- ✓ No cases of drug abuse, misuse, or addiction

OSE Provigil® **Angioedema** and Anaphylaxis Reviews from Marketing-2007

03/2007 – all ages

- Angioedema identified in Nuvigil® (armodafinil) clinical trial data

- ✓ no cases of anaphylaxis for Provigil®

OSE Provigil® Angioedema and Anaphylaxis 2007 Review

Angioedema and Anaphylaxis Labeling

- ✓ Labeling for Angioedema and
Anaphylactoid Reactions
- ✓ Labeling extended to Nuvigil®

OSE Provigil® Pediatric Exclusivity Review

Reports Received by the FDA
from 03/21/2006-04/21/2007

Provigil® Drug Use

- Approximately 2.3 million prescriptions dispensed¹ or 594,631 patients² receiving a prescription during April 2006 – March 2007
 - Children age 17 years and less accounted for approximately 2% (50,641 prescriptions dispensed¹ or 15,415 patients²) of total use

*GP/FM/DO – General Practice, Family Medicine, Doctors of Osteopathy

¹ Verispan, Vector One®: National, Extracted June 2007.

² Verispan, Vector One®: Total Patient Tracker, Extracted June 2007.

Provigil® Drug Use

April 2006 – March 2007

- Psychiatry most common prescribers with 27% of dispensed prescriptions followed by GP/FM/DO* with 17% and Neurology at 15%¹
 - Pediatricians accounted for less than 1% of total prescribing for Provigil¹

*GP/FM/DO – General Practice, Family Medicine, Doctors of Osteopathy

¹ Verispan, Vector One®: National, Extracted June 2007.

² Verispan, Vector One®: Total Patient Tracker, Extracted June 2007.

Provigil® Drug Use

No use recorded for pediatric patients during post-exclusivity period (April 2006 – March 2007) from office-based physician survey

Source: Verispan, Physician Drug and Diagnosis Audit (PDDA), Extracted June 2007.

Provigil® Drug Use

Most common indications for use in office-based practice settings for pediatric patients (age 0-17 years) during the pre-exclusivity period (April 2005 – March 2006)

- “attention deficit disorder” (ICD-9 314.0)
- “cataplexy and narcolepsy” (ICD-9 347.0)
- “major depressive disorder, single episode” (ICD-9 296.2)

Source: Verispan, Physician Drug and Diagnosis Audit (PDDA), Extracted June 2007.

Provigil[®] Drug Use

Most common indications for use recorded for adult patients (age 18+ years) during the post-exclusivity period (April 2006 – March 2007)

- “malaise and fatigue” (ICD-9 780.7)
- “sleep disturbances” (ICD-9 780.5)
- “cataplexy and narcolepsy” (ICD-9 347.0)

Source: Verispan, Physician Drug and Diagnosis Audit (PDDA), Extracted June 2007.

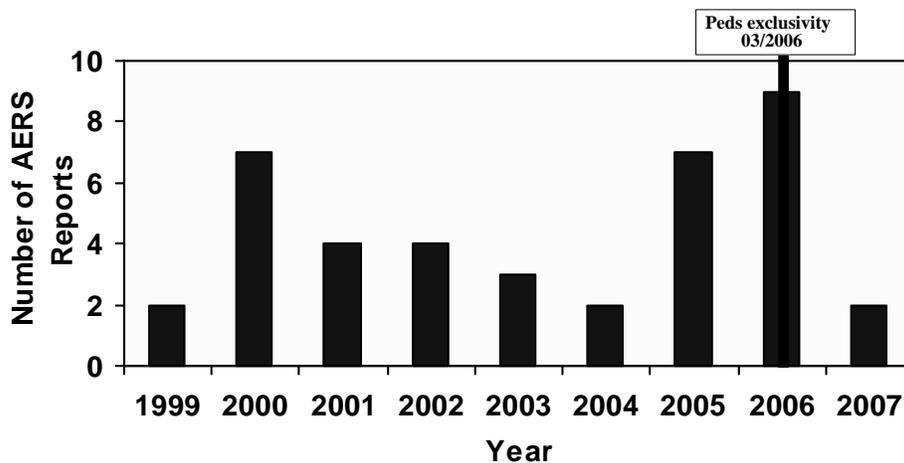
OSE Provigil[®] Post Exclusivity Review

- Review of Adverse Event Reports
 - Raw counts of adverse events from market approval (12/24/1998)
 - Raw counts of adverse events following exclusivity
 - In depth review of unduplicated reports in children 0-16 years of age during the one year post exclusivity period

Raw Counts of Provigil® Adverse Event Reports from Marketing-04/21/2007

Age	All Reports (US)	Serious (US)	Death (US)
All ages	1,122 (1,013)	364 (284)	45 (33)
> 17 years	930 (840)	291 (223)	33 (23)
<u><i>Newborn- 16 years</i></u>	<u><i>42 (40)</i></u>	<u><i>21 (19)</i></u>	<u><i>1 (1)</i></u>

Provigil® AERS Reports for Ages Newborn -16 Years from Marketing to 1st quarter 2007



Raw Counts of Provigil Domestic Adverse Event Reports from 03/21/2006-04/21/2007

Age	All Reports (US)	Serious (US)	Death (US)
All Ages	132 (105)	73 (58)	15 (12)
> 17 years	96 (78)	55 (45)	10 (8)
<u>Newborn- 16 years</u>	<u>10# (9#)</u> 1 duplicate	<u>5 (4)</u>	<u>1 (1)</u>

OSE Provigil[®] Post Exclusivity Review

OUTCOMES (report may have >1 outcome)	#
Death	1
Hospitalization	3
Life Threatening	3
Disability	1
Congenital Anomaly	1
Medically Important/Other	4

OSE Provigil® Post Exclusivity Review

INDICATIONS	#
Attention deficit hyperactivity disorder (ADHD)/bipolar	1
ADHD/anxiety	1
ADHD (study patients)	2
Narcolepsy	3
“sleep disorder”	1
Not Reported	1

OSE Provigil® Post Exclusivity Review

1 DEATH

- Completed suicide (ISR# 5059015, U.S., 2006)
- 15 year old female with history of depression

OSE Provigil® Post Exclusivity Review

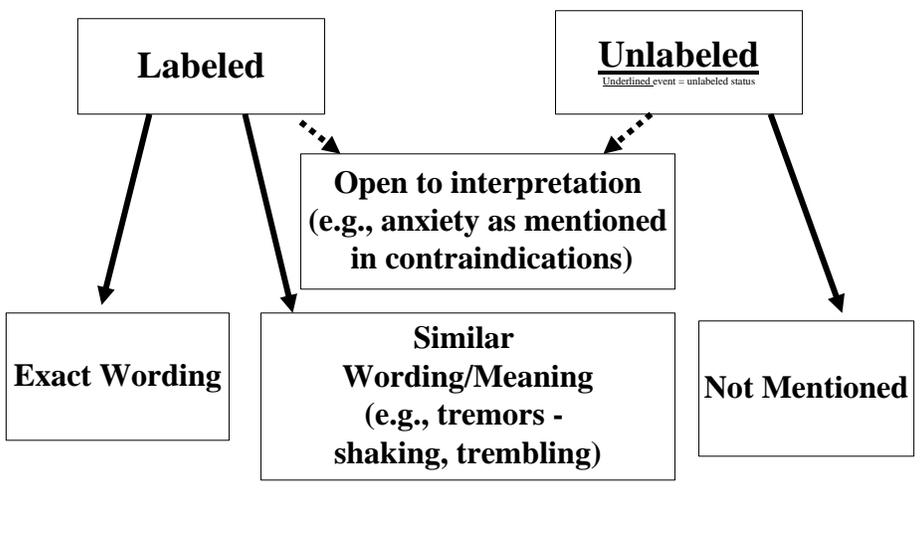
Completed Suicide (cont.)

- Unknown indication
- 50mg titrated to 100mg
- Death by strangulation 7 days after increase
- Concomitant medications: duloxetine (2005), dicyclomine (not reported)
- Described as recently upbeat

OSE Provigil® Post Exclusivity Review

AE Category	Non-fatal Events
Total	8
Psychiatry	3
Dermatology	2
Congenital Anomaly	1
Drug Interactions	1
Neurology	1

Reported Provigil® Adverse Event Signs/Symptoms Compared to Labeling



OSE Provigil® Psychiatric Post Exclusivity Review

Psychiatric, (n=3)

1. Anger, defiance, irrational behavior, and behavioral problems in school
2. Oppositional defiant behavior
3. Suicidal thoughts

Case 1 - Positive dechallenge

OSE Provigil® Psychiatric Post Exclusivity Review

Psychiatric Labeling

Label (2007) Warnings:

- ✓ **Psychiatric symptoms**

OSE Provigil® Dermatology Post Exclusivity Review

Dermatology, (n=2)

- 1 case of SJS
- 1 case of DRESS
- Both cases previously identified in 02/2007 serious skin review
- Class labeled for serious rash including SJS, TEN, and DRESS

OSE Provigil® Congenital Anomaly Post Exclusivity Review

Congenital Anomaly (n=1)

1. Phimosis

Common Event

Unlabeled

✓ No Recommendation for Labeling

OSE Provigil® Drug Interaction Post Exclusivity Review

Drug interaction, (n=1)

1. Provigil® – valproic acid

Lowered valproic acid serum levels

Unlabeled

✓ No Recommendation for Labeling

OSE Provigil[®] Neurology Post Exclusivity Review

Neurology, (n=1)

1. Seizure

No seizure with rechallenge

Unlabeled

✓ No Recommendation for Labeling

OSE Provigil[®] Post Exclusivity Review Summary

9 unduplicated pediatric reports

- Indications

4 attention deficit disorders

4 sleep disorders

1 not reported

✓ Unapproved indications in pediatric patients

OSE Provigil® Post Exclusivity Review Summary

SUMMARY (cont.)

- No serious unexpected safety signal in pediatric patients
- The FDA recommends routine monitoring of Provigil® for AEs in all populations.
- Does the Advisory Committee concur?

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OSE

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