

Provigil[®] (Modafinil) Pediatric Exclusivity Studies

Pediatric Advisory Committee

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Pediatric Exclusivity Studies: Modafinil

- **Narcolepsy Efficacy and Safety** study in patients age 5-17 years: 165 pediatric patients with narcolepsy used modafinil or placebo for 6 weeks, plus 12-month open-label extension.
- **Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) Efficacy and Safety** Study Aborted due to low enrollment: 26 patients with OSAHS used modafinil or placebo for 6 weeks, plus 12-month open-label extension
- **12-month open label extension**: 148 patients from narcolepsy (n=132) or OSAHS (n=16) controlled studies.
- **6-month Open Label Study** 91 patients with narcolepsy (n=46) or OSAHS (n=45).



Pediatric Exclusivity Study: Narcolepsy

- Design: Multi-center, double-blind, placebo-controlled, randomized study of modafinil (100, 200, 400 mg/day)
 - modafinil n=123
 - placebo n=42



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Narcolepsy Exclusivity Study: Efficacy Results

- Co-Primary Efficacy Endpoints:
 - Change from Baseline to Final visit in Multiple Sleep Latency Test (MSLT)
 - Proportion of patients with improvement on a 7-point Clinical Global Impression of Change (CGI-C)
- No statistically significant differences favoring modafinil in prolonging sleep latency (MSLT), or in perceptions of sleepiness (CGI-C)



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OSAHS Exclusivity Study

- Design: Multi-center, double-blind, placebo-controlled, randomized, parallel group study of modafinil (100, 200, 400 mg/day)
- Study aborted
 - Sponsor demonstrated enough patients could not reasonably be enrolled
 - Modafinil N=19, Placebo N=7
 - Study not in final WR, patients evaluated for safety only and results were included in supplement



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Efficacy Labeling: Exclusivity Studies

- **INDICATIONS AND USAGE**
 - No pediatric indications
- **Pediatric Use**
 - ‘Safety and effectiveness in pediatric patients, below age 16, have not been established...’
 - ‘In a controlled 6-week study, 165 pediatric patients (aged 5-17 years) with narcolepsy were treated with modafinil (n=123), or placebo (n=42). There were no statistically significant differences favoring modafinil over placebo in prolonging sleep latency as measured by MSLT, or in perceptions of sleepiness as determined by the clinical global impression-clinician scale (CGI-C).’



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Exclusivity Studies: Safety Results

- N= 270 exposed patients
- No deaths
- Serious Adverse Events
 - Controlled Trial (Narcolepsy)
 - viral encephalitis (400 mg/day)
 - appendicitis (placebo)
 - Open-label (Narcolepsy and OSAHS)
 - Suicide gesture (400 mg/day)
 - Weight loss (100 mg/day)



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Controlled Studies: Common AEs

	<u>Drug(%)</u>	<u>Placebo (%)</u>
Insomnia	6	2
Abdominal pain	7	0
Pharyngitis/Sinusitis	3-4	0
Dysmenorrhea	5	0
Hostility/irritability	5	5



N= 165 (123 Modafinil, 42 placebo)

Pediatric Exclusivity Studies: Safety Results (n= 270 total exposed patients)

- More open-label cases of irritability/hostility (13), than might be expected in this population, but difficult to clearly ascribe to drug
- Other psychiatric AEs
 - Abnormal thinking (1)
 - Hypnagogic hallucinations (2), hallucinations (1)
 - Agitation (1)
 - Emotional lability (1)
 - Hypomania (1)



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Hostility Case Report

- 8 year old girl with narcolepsy
- 200 mg/day titrated up to 400 mg/day by day 22.
- On day 55, 'behavior outbursts' coded as hostility.
- Modafinil dose halved on day 56 and eliminated on day 69.
- Event resolved on day 88.



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Suicidal Ideation Case Report

- 10 year old girl with narcolepsy
- 100 mg/day, titrated to 400 mg/day due to continued sleepiness
- Threatened to cut her wrists after reprimanded for arguing, day 75
- No psychiatric treatment given
- Modafinil continued at first, then withdrawn on day 144



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Safety Concerns in Modafinil Label Pediatric Use Section

- Psychiatric and nervous system
 - Tourettes' syndrome
 - Insomnia
 - Hostility
 - Increased cataplexy
 - Increased hypnagogic hallucinations
 - Suicidal ideation



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Safety Concerns in Modafinil Label Pediatric Use Section

Pediatric Use

Safety and effectiveness in pediatric patients, below age 16, have not been established. Serious skin rashes, including erythema multiforme major (EMM) and Stevens-Johnson Syndrome (SJS) have been associated with modafinil use in pediatric patients (see **WARNINGS, Serious Rash, including Stevens-Johnson Syndrome**).



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Safety Concerns in Modafinil Label Pediatric Use Section

Pediatric Use

In the controlled and open-label clinical studies, treatment emergent adverse events of the psychiatric and nervous system included Tourettes' syndrome, insomnia, hostility, increased cataplexy, increased hypnagogic hallucinations and suicidal ideation. Transient leukopenia, which resolved without medical intervention, was also observed. In the controlled clinical study, 3 of 38 girls, ages 12 or older, treated with modafinil experienced dysmenorrhea compared to 0 of 10 girls who received placebo.



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