

Food and Drug Administration Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Paul M. Kirsch Senior Director, Regulatory Affairs Cephalon Inc. 145 Brandywine Parkway West Chester, PA 19380-4245

RE: NDA # 20-717

Provigil (modafinil) Tablets

MACMIS ID # 10183

Dear Mr. Kirsch:

This letter objects to Cephalon Inc's (Cephalon) dissemination of false or misleading promotional materials¹ for Provigil (modafanil) Tablets. As a part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these materials for Provigil and has concluded that they are false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act (Act), and applicable regulations. Our specific objections follow:

Promotion of Unapproved Uses

Promotional materials are false, lacking in fair balance, or otherwise misleading if they contain representations or suggestions that a drug is better, more safe, more effective, or useful in a broader range of conditions or patients than has been demonstrated by substantial evidence. Provigil is indicated in a select group of patients. Specifically, the "Indications and Usage" section of the approved product labeling (PI) for Provigil states, "Provigil is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy."

The claims contained in your promotional materials suggest that Provigil is safe and effective for a variety of unapproved uses. For example, your journal advertisements² prominently present the following misleading claims under the header "Consider PROVIGIL to improve wakefulness:"

[&]quot;When patients complain of FATIGUE or TIREDNESS"

[&]quot;When patients present with SLEEPINESS"

[&]quot;When patients complain of SLEEPINESS"

¹ The promotional materials include, but are not limited to the following sales aids (PRO214, PRO215, PRO212, PRO227, PRO221, PRO197, PRO198 and PRO164), journal advertisements (PRO230, PRO231, PRO228, PRO229, PRO225, PRO224, PRO223, and PRO222), and Provigil website (http://www.provigil.com) PRO264.

² PRO222, PRO223, PRO224, PRO225, PRO228, PRO229, PRO230, and PRO231

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- "When patients present with FATIGUE or TIREDNESS"
- "When patients complain of feeling FATIGUED or TIRED"
- "When patients present with sleepiness and Decreased ACTIVITY"
- "When patients complain of sleepiness and Decreased ACTIVITY"
- "When patients present with Lack of ENERGY"
- "When patients complain of Lack of ENERGY"

The claims are misleading because Provigil is not approved to treat such symptoms as sleepiness, tiredness, decreased activity, lack of energy, and fatigue. Therefore, the claims promote Provigil for unapproved uses.

Similarly, your sales aids³ prominently present the claim "[a] wake-promoting alternative for your psychiatry practice..." on the front cover, followed by the claim "PROVIGIL: A prescription for daytime wakefulness," on the inside front cover. These claims are misleading because they suggest that Provigil is a safe and effective treatment for anyone with daytime sleepiness. Provigil is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy. Provigil is not approved for use as a daytime stimulant. Furthermore, presenting the indication for Provigil in small print at the bottom of the sales aids and journal advertisements does not correct the overwhelming misleading impression that Provigil can be used to improve wakefulness in all patients presenting with symptoms of daytime sleepiness, characteristic of generalized sleep disorders, whether or not they have narcolepsy.

The Provigil website⁴ also prominently presents the claim, "Provigil, a prescription for daytime wakefulness," along with a questionnaire with the headline, "Do you suffer from excessive daytime sleepiness?" Thus, the Provigil website is misleading because, like your sales aids and journal advertisements, the website does not adequately communicate the indication for Provigil. Additionally, the website promotes Provigil for unapproved uses by suggesting that Provigil is useful for anyone with excessive daytime sleepiness.

Minimization of CNS Effects and Abuse Potential

Your promotional materials⁵ present claims that "Provigil promotes wakefulness without widespread CNS stimulation in preclinical models" and "Low abuse potential" to suggest that Provigil does not have CNS properties that may lead to abuse and are common to other scheduled stimulants or stimulant-like drugs. The claim is misleading because it is inconsistent with the PI. "[t]he abuse potential of modafanil (200, 400, and 800mg) was assessed relative to methylphenidate (45 and 90mg) in an inpatient study in individuals experienced with drugs of abuse. Results from this clinical study demonstrated that modafanil produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate)." Furthermore, presenting data from pre-clinical models is not considered substantial evidence to support efficacy claims.

³ PRO197, PRO198, PRO214, and PRO215
⁴ PRO264, http://provigil.com/patient/ess/default.asp

⁵ PRO222, PRO223, PRO224, PRO225, PRO228, PRO229, PRO230, and PRO231

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Misleading Mechanism of Action Claims

Claims contained in your promotional materials⁶ suggest that the mechanism of action of Provigil is understood. For example, your sales aids, journal advertisements, and Provigil website present the following misleading claims:

"PROVIGIL works differently from stimulants in preclinical models."
"PROVIGIL promotes wakefulness without widespread CNS stimulation."
"PROVIGIL acts selectively in areas of the brain to regulate normal wakefulness."
"Unlike stimulants, PROVIGIL is not mediated by a dopaminergic mechanism."
"The highly selective CNS activity of PROVIGIL is distinct from amphetamine and methylphenidate in pre-clinical models."

The claims are presented with pictures that illustrate selective sites of action in the brain where Provigil is purported to have activity based on animal studies. Moreover, the claims and pictures are presented in comparison to amphetamine and methylphenidate. These presentations are misleading because they imply that the mechanism of action of Provigil is fully understood when such is not the case. The PI specifically states that "the precise mechanism(s) of action through which modafanil promotes wakefulness is unknown." Additionally, it is misleading to make claims based on data from animal studies to suggest clinical significance when, in fact, no clinical significance has been demonstrated. Furthermore, placement of statements in small print that "the relationship of these findings in animals to the effects of Provigil in humans has not been established" or "the precise mechanism of action is unknown" does not correct the overwhelming misleading impression presented by the claims and pictures.

Misleading Switch Protocol

Your sales aids⁷ and Provigil website⁸ state or suggest that patients should be switched from traditional stimulants (e.g., methylphenidate) to Provigil, along with other claims such as "switching to Provigil is easy" and "switch to Provigil for all the right reasons." Additionally, a protocol for switching from methylphenidate to Provigil is provided in the promotional materials. The claims and switch protocol are misleading because they imply that the efficacy of Provigil and methylphenidate, for example, are equivalent when such has not been demonstrated by substantial evidence.

Unsubstantiated Superiority Claims

Your sales aids⁹ present claims that patients dissatisfied with stimulants and patients seeking a well-tolerated agent are candidates for Provigil. Your sales aids also claim that patients should be switched to Provigil because Provigil has more selective activity in the brain and improves sleep latency compared to traditional stimulants. These claims are misleading because they suggest that Provigil is superior to other agents when such has not been demonstrated by substantial evidence i.e., head-to-

⁶ PRO197, PRO198, PRO212, PRO214, PRO215, PRO222, PRO223, PRO224, PRO225, PRO228, PRO229, PRO230, PRO231, and PRO264, http://www.provigil.com/patient/ess/default.asp

⁷ PRO197, PRO198, PRO212, PRO214, and PRO215

⁸ PRO264, http://www.provigil.com/physician/materials/dosing.asp PRO164, and PRO212

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head clinical studies. In fact, data used to support the improved sleep latency claim was derived from a post-hoc analysis of sleep latency. Data from post-hoc analyses are not adequate evidence to support superiority or comparative efficacy claims.

Additionally, your sales aid ¹⁰ presents the misleading claim "Provigil significantly improved daytime wakefulness in patients unsatisfactorily treated with traditional stimulants" followed by a graph entitled "Provigil improved wakefulness." The claim and accompanying graph are misleading because they suggest superiority for Provigil versus dextroamphetamine, methylphenidate, and pemoline, when such has not been demonstrated by substantial evidence.

Requested Action

We request that you immediately cease the dissemination of sales aids, journal advertisements, websites and all other promotional materials and activities for Provigil that contain the same or similar violations outlined in this letter. Your written response to the above request should be received no later than January 17, 2002. Your response should include a list of all promotional materials that are discontinued and the date that they were discontinued. If you have any questions or comments, please contact James Rogers, Pharm.D., by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm 17-B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 10183 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

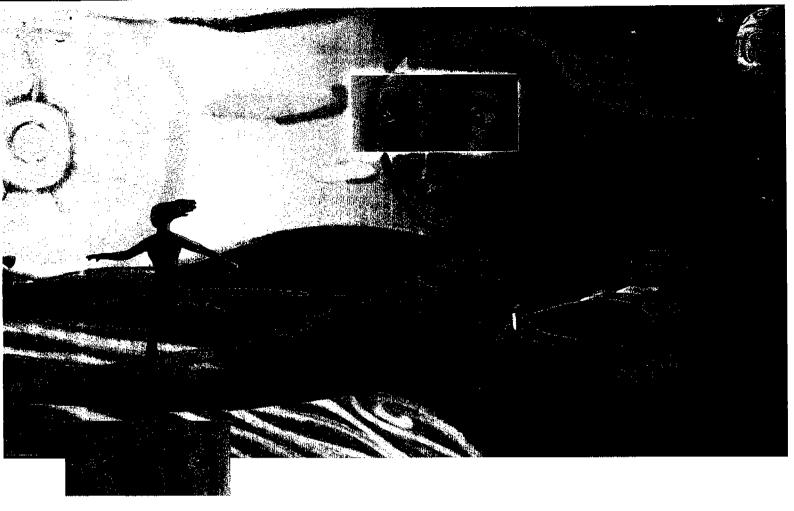
James R. Rogers, Pharm.D. Regulatory Review Officer Division of Drug Marketing, Advertising, and Communications

¹⁰ PRO164

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/s/ --**----**

James Rogers 1/3/02 03:40:29 PM



Which patients are candidates for PROVIGIL?

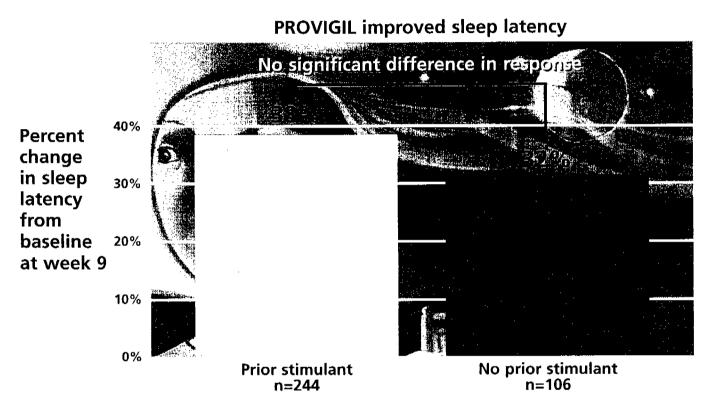


For excessive daytime sleepiness associated with narcolepsy

The only agent indicated to improve wakefulness in patients with excessive daytime

Patients dissatisfied with

Prior stimulant users and newly diagnosed patients both stayed awake longer with PROVIGIL as compared to placebo¹



Results of two 9-week double-blind, placebo-contolled clinical trials in 530 patients with EDS due to narcolepsy.

There were no statistical differences in response to PROVIGIL between newly diagnosed patients and patients previously treated with stimulants! sleepiness associated with narcolepsy

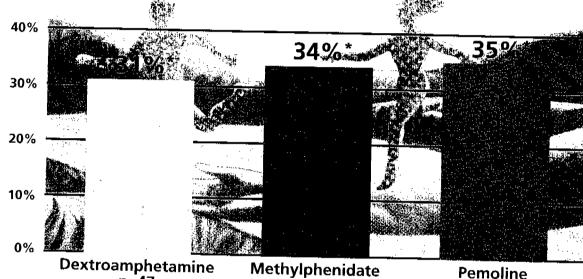
stimulants.



PROVIGIL significantly improved daytime wakefulness in patients unsatisfactorily treated with traditional stimulants¹

PROVIGIL improved wakefulness

Percent improvement 30% in ESS score from baseline at week 6 20%



n=63
Previous therapy

*P<0.0001 vs baseline.

Results of a 6-week, open-label, multicenter study involving 151 patients with narcolepsy who had been unsatisfactorily treated for EDS with stimulants.

n=47

PROVIGIL (MODAFINIL) @

n=35

A prescription for daytime wakefulness™

Please see full prescribing information on last pages.

The only agent indicated to improve wakefulness in patients with excessive daytim

Patients seeking a well-t

PROVIGIL was well tolerated for up to 88 weeks in open-label extensions¹

The acute effects of PROVIGIL on mood were not significantly different from placebo as measured by Profile of Mood States²:

- Anger/hostility
- Confusion/bewilderment
- Tension/anxiety

Vigor/activity increased with PROVIGIL

Convenient for you and your patients

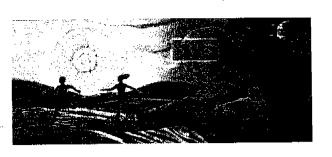
- Fewer prescribing restrictions than methylphenidate or dextroamphetamine
 - Phone-in prescriptions permitted
 - Phone-in refills permitted
 - No triplicate Rxs required

Proven safety profile

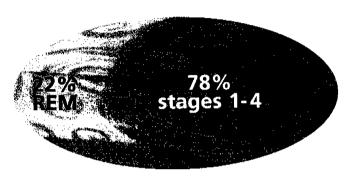
- PROVIGIL is generally well tolerated
- Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection, and insomnia (most adverse events were mild to moderate)
- No specific symptoms of withdrawal were observed during 14 days of observation in a 21-center study³
- May interact with drugs that inhibit, induce, or are metabolized by cytochrome P450 isoenzymes

epiness associated with narcolepsy

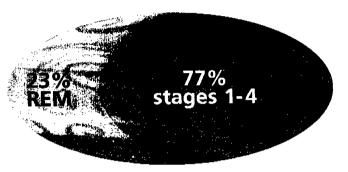
lerated agent.



PROVIGIL did not interfere with nighttime sleep architecture after 9 weeks of treatment^{1*}

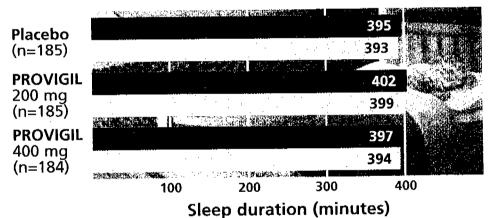


Placebo (n=185)



PROVIGIL 200 mg and 400 mg (n=369)

PROVIGIL did not affect sleep duration1*



*In two 9-week, randomized, double-blind, placebo-controlled, multicenter trials (n=554), nocturnal polysomnography data were collected to determine the effect of modafinil on nighttime sleep parameters in patients with narcolepsy.

Please see full prescribing information on last pages.

Baseline
Week 9



A prescription for daytime wakefulness™

Alert Aware. Awake.™

PROVIGIL: For patients dissatisfied with stimulants

- Effective in both previously treated and newly diagnosed patients
- Acute effects on mood not different from placebo
- No disruption of nighttime sleep architecture
- Incidence of insomnia comparable to placebo
- Phone-in Rxs and refills, no triplicate Rxs
- Recommended dose: 200 mg every morning
- 200 mg and 400 mg doses are effective and generally well tolerated
- Once-a-day dosing may enhance compliance

Please see full prescribing information inside.





References: 1. Data on file. Cephalon, Inc. 2. Broughton RJ, Fleming JAE, George CFP, et al. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology. 1997;49:444-451. 3. US Modafinil in Narcolepsy Multicenter Study Group. Modafinil administration and withdrawal in narcolepsy patients with excessive daytime somnolence. Neurology. In press.

For more information about PROVIGIL, please visit our Website at **www.PROVIGIL.com** or call Cephalon Professional Services at 1-800-896-5855. © 2000 Cephalon, Inc. PRO164 Feb 2000 All rights reserved. Printed in USA.

Switch to PROME!L from traditional sumulants for all the right reasons.



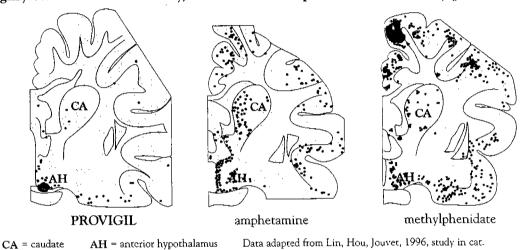
For excessive daytime sleepiness associated with narcolepsy

PROVIGIL works differently.



PROVIGIL promotes wakefulness without generalized stimulation in preclinical models.^{1,2}

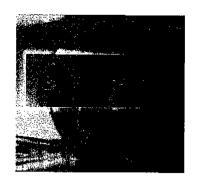
Highly selective CNS activity, distinct from amphetamine and methylphenidate*



- PROVIGIL acts selectively in areas of the brain believed to regulate normal wakefulness
- PROVIGIL is not a direct- or indirect-acting dopamine receptor agonist
- Unlike traditional stimulants, PROVIGIL does not mediate wakefulness by a dopaminergic mechanism

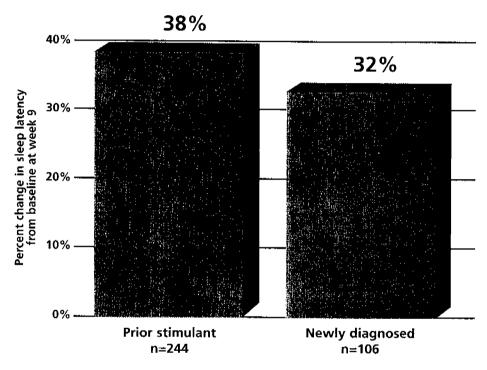
^{*}The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.

Switch to PROVIGIL for proven efficacy.



Prior stimulant users and newly diagnosed patients both stayed awake longer with PROVIGIL.³

PROVIGIL improved sleep latency*



There were no statistical differences in response to PROVIGIL between newly diagnosed patients and patients previously treated with stimulants.³

* Results of post hoc analysis from two 9-week double-blind, placebo-contolled clinical trials in 530 patients with EDS due to narcolepsy.

Please see full prescribing information on last pages.



A prescription for daytime wakefulness™

Switch to PROVIGIL for safety and convenience.



Proven safety profile.

- PROVIGIL did not affect sleep duration or interfere with nighttime sleep architecture^{4,5}
- PROVIGIL is generally well tolerated.
 Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection and insomnia. Most adverse events were transient and mild to moderate in severity
- Discontinuation rate of 5% in clinical trials4,5
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes

PROVIGIL was proven to be well tolerated for up to 88 weeks in open-label extensions.^{3,6}

The acute effects of PROVIGIL on mood were not significantly different from placebo as measured by Profile of Mood States⁷:

- Anger/hostility
- Confusion/bewilderment
- Tension/anxiety

Vigor/activity increased with PROVIGIL.

Convenient for you and your patients.

- Once-a-day dosing
- Fewer prescribing restrictions than methylphenidate or dextroamphetamine
 - Phone-in prescriptions permitted
 - Phone-in refills permitted
 - No triplicate Rxs required

Switching to PROVIGIL is easy.



Select the approach that works best for your patients.*

		•	,
	Day 1	Day 3	
	Stop methylphenidate at 4 PM	Continue PROVIGIL 200 mg/day	
	Stop methylphenidate at 4 _{PM}	No drug	
	Reduce methylphenidate dose by 20%-40%	Reduce methylphenidate dose by an additional 20%-40%; continue PROVIGIL 200 mg/day	
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- Switching approach and dosage should be determined at physician's discretion
- Recommended dose: 200 mg taken once daily in the morning
- 200 mg and 400 mg doses are effective and generally well tolerated



* There were no significant differences found in safety profile and tolerability among the 3 approaches in a randomized study of 35 patients.³ Please see full prescribing information on last pages.

A prescription for daytime wakefulnessTM

Alert Aware. Awake."

Switch to PROVIGIL for all the right reasons.



- Proven efficacy as confirmed by objective and subjective measures of wakefulness
- Effective in both previously treated and newly diagnosed patients
- Generally well tolerated; adverse events were mild to moderate
- Long-term safety established for up to 88 weeks
- No adverse effect on sleep duration or sleep architecture
- Acute effects on mood not different from placebo
- No black box warning
- Phone-in Rxs and refills permitted, no triplicate Rxs required
- Recommended dose: 200 mg taken once daily in the morning
- 200 mg and 400 mg doses are effective and generally well tolerated

References: 1. Lin JS, Hou Y, Jouvet M. Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-fos immunocytochemistry in the cat. Proc Natl Acad Sci USA. 1996;93:14128-14133.

2. Edgar DM, Seidel WF. Modafinil induces wakefulness without intensifying motor activity or subsequent rebound hypersom-nolence in the rat. J Pharmacol Exp Ther. 1997;283:757-769.

3. Data on file. Cephalon, Inc. 4. US Modafinil in Narcolepsy Multicenter Study Group. Modafinil administration and withdrawal in narcolepsy patients with excessive daytime somnolence. Neurology. In press.

5. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol. 1998;43:88-97.

6. Mitler MM, Harsh J, Hirshkowitz M, Guilleminault C. Long-term efficacy and safety of modafinil (PROVIGIL®) for the treatment of excessive daytime sleepiness associated with narcolepsy. Sleep Med. 2000;1:231-243.

7. Broughton RJ, Fleming JAE, George CFP, et al. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology. 1997;49:444-451.

Please see full prescribing information on preceding pages.

For more information about PROVIGIL, please visit our Website at **www.PROVIGIL.com** or call Cephalon Professional Services at 1-800-896-5855.

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Promotes wakefulness all day long – and still lets them sleep at night



A wake-promoting alternative for your psychiatry practice...

(MODAFINIL)®

Alert. Aware. Awake."

PROVIGIL: A prescription for daytime wakefulness"





PROVIGIL has proven efficacy.

- PROVIGIL improved patients' ability to remain awake during the day by 33%-39% after 9 weeks as measured by MWT.^{1,2,*}
- PROVIGIL improved patients' ability to participate in daily activities by 20%-32% as measured by ESS.^{12†}
- PROVIGIL improved the clinical conditions of 64%-72% of patients after 9 weeks as measured by CGI-C.^{1,2†}

PROVIGIL is convenient for you and your patients.

- No triplicate Rxs required.
- Phone-in prescriptions and refills permitted
- Once-a-day dosing.

PROVIGIL has proven safety.

- PROVIGIL was generally well tolerated. Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection and insomnia (most adverse events were mild to moderate).
- Well tolerated for up to 88 weeks in open-label extensions.^{3,4}
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.



for excessive daytime sleepiness associated with narcolepsy™

*MWT: Maintenance of Wakefulness Test, an objective assessment of sleepiness that measures patients' ability to remain awake. *ESS: Epworth Sleepiness Scale, a validated patient self-questionnaire that provides a subjective measurement of sleepiness. *CGI-C: Clinical Global Impression-Change over time, a validated independent physician rating assessment.

Prescribing PROVIGIL is easy.

For you...PROVIGIL has fewer prescribing restrictions than Schedule II agents.

LIVONICE LIGO ICARCI PICOCIONIO	23012013			
	Schedule	Triplicate Forms	Refills	Phone-In Rxs
PROVIGIL ^{5,6}	V	NO	YES*	YES
Methylphenidate ^{6,7}	=	Yes	No	No
Dextroamphetamine ^{6,8}	II	Yes	No	No

For your patients.	nts.	For your patients. Once-a-day dosing is convenient and may enhance patient compliance.	
	Dosing Frequency	Recommended Dose	Middle-of-the-Day Dosing
PROVIGIL ⁵	QĐ	200 mg QD	NO
Methylphenidate ⁷	BID-TID	10-60 mg BID to TID Dose must be individually adjusted	Yes (TID)
Dextroamphetamine ^a	BID-TID	5-60 mg BID to TID Dose must be individually adjusted	Yes (TID)



 $\star \mathsf{Up}$ to 5 refills permitted within 6 months.

Please see full prescribing information in pocket.

Switching to PROVIGIL is easy.

Select the approach that works best for your patients.

Reduce methylphenidate dose by 20%-40%	Stop methylphenidate at 4 PM	Stop methylphenidate at 4 PM	Day 1
Reduce methylphenidate dose by an additional 20%-40%; continue PROVIGIL 200 mg/day	No drug	Continue PROVIGIL 200 mg/day	Day 3

- Tolerability and safety were similar with all 3 approaches.⁴
- Switching approach and dose should be determined at physician's discretion.
- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated.



A prescription for daytime wakefulness™

Switch to PROVIGIL for all the right reasons

- Proven efficacy as confirmed by objective and subjective measures of wakefulness
- Long-term safety established for up to 88 weeks
- PROVIGIL has fewer prescribing restrictions than Schedule II agents
- Once-a-day dosing is convenient and may enhance compliance
- No black box warning
- Phone-in Rxs and refills permitted, no triplicate Rxs required

Switching to PROVIGIL is easy. Request your free samples and discover for yourselt.

Simply complete and return the sample request card enclosed

Medical Economics Co; 2000:345, 7. Ritalin* (methylphenidate HCl) prrescribing information. East Hanover, NJ: Novartis Pharmaceuticals; 2000. 8. Dexedrine* (dextroamphetamine sulfate) prescribing information. Philadelphia, Pa: SmithKline Beecham Pharmaceuticals; 2000. narcolepsy. Ann Neurol. 1998;43:88-97. 2. US Modafinil in Narcolepsy Multicenter Study Group. Modafinil administration and withdrawal in narcolepsy patients with excessive daytime somnolence. Neurology: In press. 3. Mitler MM, Haish 1, Hirshkowitz M, Guilleminault C. Long-term efficacy and safety of References: 1. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in Inc. **5.** PROVIGIL full prescribing information. **6.** Key to controlled substances categories. In: *Physicians' Desk Reference*. 54th ed. Montvale, NJ: modafinil (PROVIGIL®) for the treatment of excessive daytime sleepiness associated with narcolepsy. Sleep Med. 2000;1:231-243. 4. Data on file. Cephalon

Please see full prescribing information in pocket.

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For excessive daytime sleepiness

associated with narcolepsym



A wake-promoting alternative for your psychiatry practice...

PRODAFINIL) ® Tablets



PROVIGIL: A prescription for daytime wakefulness"



PROVIGIL has proven efficacy.

- PROVIGIL improved patients' ability to remain awake during the day by 33%-39% after 9 weeks as measured by MWT 1.2*
- PROVIGIL improved patients' ability to participate in daily activities by 20%-32% as measured by ESS.^{1,2†}
- PROVIGIL improved the clinical conditions of 64%-72% of patients after 9 weeks as measured by CGI-C.^{1,2}*

PROVIGIL has proven safety.

- PROVIGIL was generally well tolerated. Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection and insomnia (most adverse events were mild to moderate).
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.

PROVIGIL is convenient for you and your patients.

- No triplicate Rxs required
- Phone-in prescriptions and refills permitted.
- Once-a-day dosing.

PROVIGIL:

For excessive daytime sleepiness associated with narcolepsy

*MWT: Maintenance of Wakefulness Test, an objective assessment of sleepiness that measures patients' ability to remain awake.
†ESS: Epworth Sleepiness Scale, a validated patient self-questionnaire that provides a subjective measurement of sleepiness.
†CGFC: Clinical Global Impression-Change over time, a validated independent physician rating assessment.

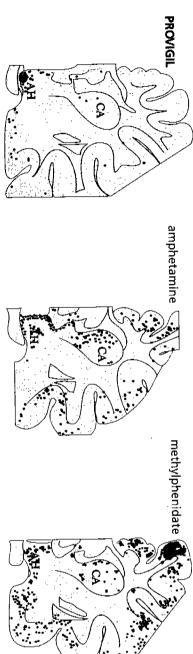
PROVIGIL has a proven safety profile.

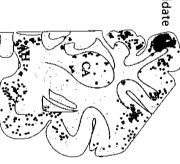
- PROVIGIL is a C-IV agent. As a class, C-IV agents have lower potential for abuse than C-II agents.3
- The acute effects of PROVIGIL on mood were not significantly different from placebo as measured by Profile of Mood States.4
- Long-term safety established for up to 88 weeks in open-label extensions.
- PROVIGIL did not interfere with nighttime sleep architecture. 1.2*
- Adverse events with PROVIGIL were generally mild to moderate in severity.



A prescription for

In pre-clinical models.7.81 The highly selective CNS activity of PROVIGIL is distinct from amphetamine and methylphenidate





CA = caudate AH = anterior hypothalamus Data adapted from Lin, Hou, Jouvet, 1996, study in cat

 ${}^{\intercal}$ The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established. parameters in patients with narcolepsy.

Please see full prescribing information in pocket

^{*}In two 9-week, randomized, double-blind, placebo-controlled, multicenter trials (n=554), nocturnal polysomnography data were collected to determine the effect of modalfail on nighttlme sleep

Switching to PROVIGIL is easy.

Select the approach that works best for your patients.

	Day 1	Day 2	Day 3	Day 4
No washout	Stop	Next AM Start	Continue PROVIGII	Continue
	at 4 PM	200 mg/day	200 mg/day	200 mg/day
With washout	Stop methylphenidate at 4 PM	No drug	No drug	Start PROVIGIL 200 mg/day
Step down	Reduce methylphenidate dose by 20%-40%	Maintain methylphenidate dose; start PROVIGIL 200 mg/day	Reduce methylphenidate dose by an additional 20%-40%; continue PROVIGIL 200 mg/day	Stop methylphenidate, continue PROVIGIL 200 mg/day

- Tolerability and safety were similar with all 3 approaches.^{5*}
- Switching approach and dose should be determined at physician's discretion.
- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated.

PROVIGIL:

*Randomized study of 35 patients

A prescription for daytime wakefulness[™]

Switch to PROVIGIL for all the right reasons.

- Proven efficacy as confirmed by objective and subjective measures of wakefulness
- Long-term safety established for up to 88 weeks
- PROVIGIL does not adversely affect sleep architecture or Profile of Mood States
- No black box warning
- Phone-in Rxs and refills permitted, no triplicate Rxs required

Switching to PROVIGIL is easy. Request your free samples and discover for yourself.

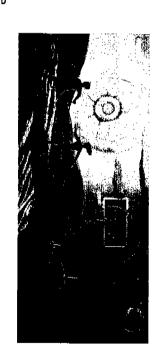
Simply complete and return the sample request card enclosed

References: 1. U.S. Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol. 1938;43:38-97. Z. U.S. Modafinil in Narcolepsy Multicenter Study Group. Modafinil administration and withdrawal in narcolepsy patients with excessive daytime somnolence. Neurology, 2000;54:1166-1173. 3. Key to controlled substances categories. Physicians: Desk Reference. Softh et A. Montade, IN: Medical Economics Co; 2000;345. 4. Broughton RJ. Flehring JAE, George CFP et al. Randomized, double-bind placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology. 1997;49:444-451. 5. Data on file. Cephalon, Inc. 6. Mitter NMA, Harsh. J. Hisrikowitz M. Guilleminault C. Long-term efficacy and safety of modafinil PROVIGE! for the treatment of excessive daytime sleepiness associated with narcolepsy. Sleep. Med. 2009;12:31-243. T. Lin 1-5; Hou Y, Jouvet M. Potential brain neuronal targets for amphetamine, methylphenidate, and modafinil-induced wakefulness evidenced by c-fos immunocytochemistry in the cet. Proc Natl Acad Sci U.S.A. 1995;35:14128-14133. B. Edgar DMI, Scield VIII. Modafinil induces wakefulness without intensifying motor activity or subsequent rebound hypersormolence in the rat. J Pharmacol Exp Ther. 1997;283:757-769.

Please see full prescribing information in pocket.

For more information about PROVIGIL, please visit our Website at www.PROVIGIL.com or call Cephalon Professional Services at 1-800-896-5855

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For excessive daytime sleepiness associated with narcolepsy



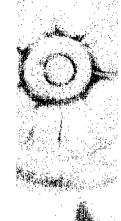
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A wake-promoting alternative for your psychiatry practice...

PRODAFINIL) © Tablets



PROVIGIL: A prescription for daytime wakefulness





PROVIGIL has proven efficacy.

- PROVIGIL improved patients' ability to remain awake during the day by 33%-39% after 9 weeks as measured by MWT.^{1,2*}
- PROVIGIL improved patients' ability to participate in daily activities by 20%-32% as measured by ESS.^{1,2†}
- PROVIGIL improved the clinical conditions of 64%-72% of patients after 9 weeks as measured by CGI-C.^{1,2†}

PROVIGIL has proven safety.

- PROVIGIL was generally well tolerated. Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection and insomnia (most adverse events were mild to moderate).
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.

PROVIGIL is convenient for you and your patients.

- No triplicate Rxs required
- Phone-in prescriptions and refills permitted
- Once-a-day dosing

PROVIGIL:

*MWT: Maintenance of Wakefulness Test, an objective assessment of sleepiness that measures patients' ability to remain awake.
†ESS: Epworth Sleepiness Scale, a validated patient self-questionnaire that provides a subjective measurement of sleepiness.
†CGI-C: Clinical Global Impression-Change over time, a validated independent physician rating assessment.

For excessive daytime sleepiness associated with narcolepsy

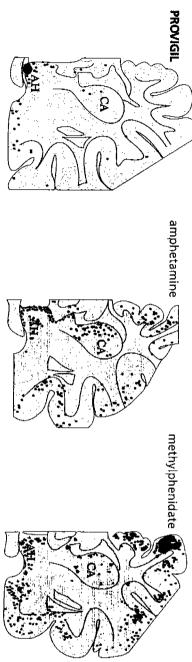
PROVIGIL has a proven safety profile.

- PROVIGIL is a C-IV agent. As a class, C-IV agents have lower potential for abuse than C-II agents.3
- The acute effects of PROVIGIL on mood were not significantly different from placebo as measured by Profile of Mood States.⁴
- Long-term safety established for up to 88 weeks in open-label extensions.
- PROVIGIL did not interfere with nighttime sleep architecture. 1.2*
- Adverse events with PROVIGIL were generally mild to moderate in severity.



A prescription for daytime wakefulness[™]

In pre-clinical models.7,81 The highly selective CNS activity of PROVIGIL is distinct from amphetamine and methylphenidate



CA = caudate AH = anterior hypothalamus Data adapted from Lin, Hou, Jouvet, 1996, study in cat.

The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.

Please see full prescribing information in pocket

^{*}In two 9-week, randomized, double-blind, placebo-controlled, multicenter trials (n=554), nocturnal polysomnography data were collected to determine the effect of modafinil on nighttime sleep

Switching to PROVIGIL is easy.

Select the approach that works best for your patients.

	Day 1	Day 2	Day 3	Day 4
No washout	Stop	Next am start PROVIGIL	Continue PROVIGIL	Continue PROVIGIL
	at 4 PM	200 mg/day	200 mg/day	200 mg/day
With washout	Stop methylphenidate at 4 PM	No drug	No drug	Start PROVIGIL 200 mg/day
Step down	Reduce methylphenidate dose by 20%-40%	Maintain methylphenidate dose; start PROVIGIL 200 mg/day	Reduce methylphenidate dose by an additional 20%-40%; continue PROVIGIL 200 mg/day	Stop methylphenidate; continue PROVIGIL 200 mg/day

- Tolerability and safety were similar with all 3 approaches.5*
- Switching approach and dose should be determined at physician's discretion.
- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated.

PROVIGIL:

A prescription for daytime wakefulness^{IM}

*Randomized study of 35 patients

Switch to PROVIGIL for all the right reasons.

- Proven efficacy as confirmed by objective and subjective measures of wakefulness
- Long-term safety established for up to 88 weeks
- PROVIGIL does not adversely affect sleep architecture or Profile of Mood States
- No black box warning
- Phone-in Rxs and refills permitted, no triplicate Rxs required

about PROVIGIL. Send for more information

Simply complete and return the reply card enclosed

References: 1, U.S. Modafinil in Narcolepsy Multicenter Study Group, Randomized trial of modafinil for the treatment of pathological summolence in narcolepsy, Ann Neurol. 1998;43:88-97. 2, U.S. Modafinil in Narcolepsy Multicenter Study Group, Modafinil administration and withdrawal in narcolepsy patients with excessive daytime sommolence. Neurology, 2000;54:1166-1175. 3, Key to controlled substances categories, in Physicians' Deak Reference. 54th ed. Monthale, Ity. Medical Economics Co. 2000;345. 4. Brouphton RJ. Fleming JAE, George CFP et al. Randomized, double-blind, Jacebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy, Neurology, 1997;49:44-51. 5. Data on file. Cephalon, Inc. 6. Miller MM, Hasth. J. Hirsikowitz M, Guillerminault C. Long-term efficacy and safety of modafinil PROVIGIT for the treatment of excessive daytime sleepiness associated with narcolepsy. Sizep. Medi. 2000;1:231-243. 7. Lin J-S., Hou Y, Jouvet M. Potential brain neuronal trigets for amphetamine-, methylpheniotate, and modafinil-induced wakefulness, evidenced by c-fos immunocytochemistry in the cat. Proc Nath Acad Sci U.A. 1996;9:141(28-14133). 8. Edgar DM, Scield WR. Modafinil induces wakefulness without intensifying motor activity or subsequent rebound hypersomnolence in the rat. J Pharmacol Exp Ther. 1997;283:757-769.



For excessive daytime sleepiness associated with narcolepsy

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For more information about PROVIGIL, please visit our Website at www.PROVIGIL.com or call Cephalon Professional Services at 1-800-896-5855 Please see full prescribing information in pocket.

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Cephalon

A wake-promoting alternative for your psychiatry practice...

PRODAFINIL) © Tablets

Alert. Aware. Awake.

PROVIGIL: A prescription for daytime wakefulness



PROVIGIL has proven efficacy.

- PROVIGIL improved patients' ability to remain awake during the day by 33%-39% after 9 weeks as measured by MWT.1.2*
- PROVIGIL improved patients' ability to participate in daily activities by 20%-32% as measured by ESS.¹²¹
- PROVIGIL improved the clinical conditions of 64%-72% of patients after 9 weeks as measured by CGI-C.^{1,2+}

PROVIGIL is convenient for you and your patients.

- No triplicate Rxs required
- Phone-in prescriptions and refills permitted.
- Once-a-day dosing.

PROVIGIL has proven safety.

- PROVIGIL was generally well tolerated. Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection and insomnia (most adverse events were mild to moderate).
- Well tolerated for up to 88 weeks in open-label extensions,^{3,4}
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.



For excessive daytime sleepiness associated with narcolepsy

*MWT. Maintenance of Wakefulness Test, an objective assessment of sleepiness that measures patients' ability to remain awake. †ESS: Epworth Sleepiness Scale, a validated patient self-questionnaire that provides a subjective measurement of sleepiness. †CGI-C: Clinical Global Impression-Change over time, a validated independent physician rating assessment.

Prescribing PROVIGIL is easy.

For you...PROVIGIL has fewer prescribing restrictions than Schedule II agents.

	Schedule	Triplicate Forms	Refills	Phone-In Rxs
PROVIGIL ^{5,6}	M	NO	YES*	YES
Methylphenidate ^{6,7}		Yes	No	No
Dextroamphetamine ^{6,8}	=	Yes	No	No
-				

For your patients.

Once-a-day dosing is convenient and may enhance patient compliance.

Unce-a-day dosing is o	Convenient and may	Unce-a-day dosing is convenient and may enhance patient compilaries.	
	Dosing Frequency	Recommended Dose	Middle-of-the-Day Dosing
PROVIGIL ⁵	QĐ	200 mg QD	NO
Methylphenidate ⁷	BID-TID	10-60 mg BID to TID Dose must be individually adjusted	Yes (TID)
Dextroamphetamine®	8ID-TID	5-60 mg BID to TID Dose must be individually adjusted	Yes (TID)

A prescription for daytime walkefulnessTM

 $^\star \cup p$ to 5 refills permitted within 6 months.

Please see full prescribing information in pocket.

Switching to PROVIGIL is easy.

Select the approach that works best for your patients.

Reduce methylphenidate dose by 20%-40%	Stop methylphenidate at 4 PM	Stop methylphenidate at 4 PM	Day 1
Red dc 20 PR			
Reduce methylphenidate dose by an additional 20%-40%; continue PROVIGIL 200 mg/day	No drug	Continue PROVIGIL 200 mg/day	Day 3

- Tolerability and safety were similar with all 3 approaches.⁴
- Switching approach and dose should be determined at physician's discretion.
- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated.



A prescription for daytime wakefulness^{1M}

Switch to PROVIGIL for all the right reasons.

- Proven efficacy as confirmed by objective and subjective measures of wakefulness
- Long-term safety established for up to 88 weeks
- PROVIGIL has fewer prescribing restrictions than Schedule II agents
- Once-a-day dosing is convenient and may enhance compliance
- No black box warning
- Phone-in Rxs and refills permitted, no triplicate Rxs required

Send for more information about PROVIGIL.

Simply complete and return the reply card enclosed.

References: 1. US Modafini in Narcolepsy Multicenter Study Group, Randomized trial of modafinii for the treatment of pathological somnolence in narcolepsy. Ann Neurol. 1998;43:88-97. 2. US Modafini in Naticelepsy Multicenter Study Group, Modafini administration and withdrawal in narcolepsy patients with excessive daytime somnolence. Neurology. In press. 3. Miller MM, Haria J, Hishkowstr, M, Gullenninault C, Long-term efficacy and safety of modafini (PROMGL®) for the treatment of excessive daytime sleepiness associated with narcolepsy. Sleep Med. 2000;1:231:243. 4. Data on file. Cephalon, Inc. 5. PROVIGIL full prescribing information. 6. Key to controlled substances categories. In: Physicians' Desk Reference. 54th ed. Montvale, NJ: Medical Economics Co. 2000;245. 7. Ritaliam' (methyphenidate Hol) prescribing information. East Hanover, NJ: Novartis Pharmaceuticals; 2000.

8. Dexedrine* (dextroamphetamine sulfate) prescribing information. Philadelphia, Pa: SmithKline Beecham Pharmaceuticals; 2000.

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For excessive daytime sleepiness associated with narcolepsy^{IM}



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Prescribing PROVIGIL is easy.

For you...PROVIGIL has fewer prescribing restrictions than Schedule II agents.

	Schedule	Triplicate Forms	Refills	Phone-In Rxs
PROVIGIL ^{5,6}	N	NO	YES*	YES
Methylphenidate ^{6,7}	11.	Yes	No	No
Dextroamphetamine ^{6,8}		Yes	No	No

For your patients.

Once-a-day dosing is convenient and may enhance patient compliance.

Dextroamphetamine®	Methylphenidate ⁷	PROVIGIL ⁵		
BID-TID	BID-TID	QD	Dosing Frequency	
5-60 mg BID to TID Dose must be individually adjusted	10-60 mg BID to TID Dose must be individually adjusted	200 mg QD	Recommended Dose	
Yes (TID)	Yes (TID)	NO	Middle-of-the-Day Dosing	

PROVIGIL:
(MODAFINIL)®
Tablets

A prescription for daytime wakefulness³⁶

*Up to 5 refills permitted within 6 months.

Please see full prescribing information in pocket.

PROVIGIL: A prescription for daytime wakefulness"



PROVIGIL has proven efficacy.

- PROVIGIL improved patients' ability to remain awake during the day by 33%-39% after 9 weeks as measured by MWT.^{1,2}*
- PROVIGIL improved patients' ability to participate in daily activities by 20%-32% as measured by ESS.^{1,2†}
- PROVIGIL improved the clinical conditions of 64%-72% of patients after 9 weeks as measured by CGI-C.^{1,2*}

PROVIGIL is convenient for you and your patients.

- No triplicate Rxs required
- Phone-in prescriptions and refills permitted.
- Once-a-day dosing.

PROVIGIL has proven safety.

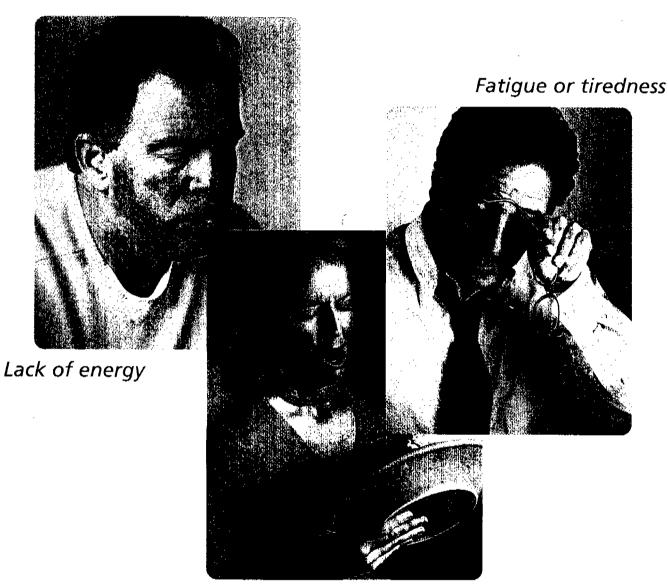
- PROVIGIL was generally well tolerated. Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection and insomnia (most adverse events were mild to moderate).
- Well tolerated for up to 88 weeks in open-label extensions.^{3,4}
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.



For excessive daytime sleepiness associated with narcolepsy

*MWVT: Maintenance of Wakefulness Test, an objective assessment of sleepiness that measures patients' ability to remain awake. †ESS: Epworth Sleepiness Scale, a validated patient self-questionnaire that provides a subjective measurement of sleepiness. †CGI-C; Clinical Global impression-Change over time, a validated independent physician rating assessment.

What would you prescribe to improve wakefulness in patients who present with these Complaints?

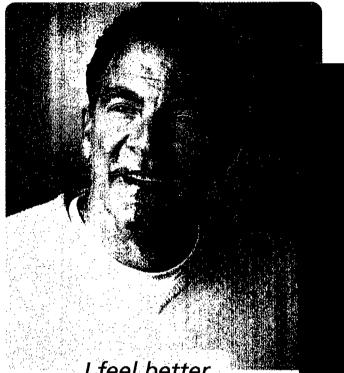


Sleepiness

To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy



Consider PROVIGIL, a unique wake-promoting agent.



I feel better.

58%-72% of narcolepsy patients showed overall improvement in CGI-C with PROVIGIL.1.2*

I'm able to be more active during the day.

PROVIGIL improved narcolepsy patients' ability to participate in daily activities by 20%-32% based on **ESS**.1,2t

References: 1. US Modafinil in Narcolepsy Multicenter Study Group. Ann Neurol. 1998;43:88-97. 2. US Modafinil in Narcolepsy Multicenter Study Group. Neurology. 2000;54:1166-1175. 3. Lin JS, Hou Y, Jouvet M. Proc Natl Acad Sci USA. 1996;93:14128-14133. 4. Edgar DM. Seidal WF. J Pharmacol Exp Ther. 1997; 283:757-769. 5. Data on file, Cephalon, Inc. 6. Physician's Desk Reference, current edition

Please see brief summary of prescribing information at the end of this advertisement.

^{*} CGI-C: Clinical Global Impression-Change over time, a validated independent physician

rating assessment.
† ESS: Epworth Sleepiness Scale, a validated patient self-questionnaire that provides a subjective

 ^{**}MWT: Maintenance of Wakefulness Test, an objective assessment of sleepiness that measures patients' ability to remain awake.

 **The relationship of these findings in animals to the effects of PROVIGIL in humans has not

been established.



PROVIGIL improved narcolepsy patients' ability to remain awake during the day by 33%–39% in **MWT**.^{1,2†}

For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at www.PROVIGIL.com



To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy

PROVIGIL keeps patients Alert, Aware, Awake all day. And still lets them sleep at night.

PROVIGIL works differently from stimulants in preclinical models.34

- PROVIGIL promotes wakefulness without widespread CNS stimulation.
- Unlike stimulants, PROVIGIL does not mediate wakefulness by a dopaminergic mechanism.

Pharmacologic activities in preclinical models.45

	PROVIGIL	Åmphetamine	Methylphenidate
Wakefulness	++	++	++
Locomotor activity	-/ +	++	++
Stereotypy	-	++	++
Anxiety	_	++	++
Intense NREM rebound	-	++	++
Blood pressure	_	+	+
Heart rate	-	+	+
	– ≂ no activity	-/+ = minimal activit	y ++ marked activity

PROVIGIL offers proven efficacy as confirmed by objective and subjective measures of wakefulness.

• Both prior stimulant users and newly diagnosed patients stayed awake longer with PROVIGIL.

PROVIGIL does not disrupt nighttime sleep patterns.12

- Won't interfere with the architecture of nighttime sleep or with patients' ability to fall asleep when needed.
- No statistical difference vs placebo in nighttime sleep duration.
- Incidence of insomnia comparable to placebo (5% vs 3%).5

PROVIGIL has a proven safety profile.

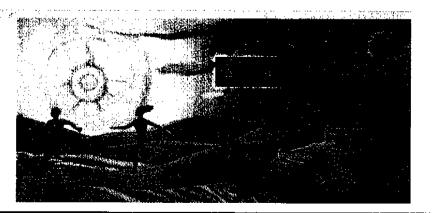
- PROVIGIL is generally well tolerated. Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection and insomnia. Most adverse events were mild to moderate.
- Long-term safety has been established for up to 136 weeks.5
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.

PROVIGIL is easy to prescribe.

- PROVIGIL, a @ agent, has few prescribing restrictions and low abuse potential compared to @ agents such as methylphenidate or dextroamphetamine.
 - Phone-in prescriptions and refills permitted.
 - No triplicate/multiple prescriptions required.

PROVIGIL offers convenient once-a-day dosing.

- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated.







PROVIGIL* (modafinii) TABLETS

BRIEF SUMMARY: Co sult Package Insert for Complete Prescribing Information

INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated

CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL

PRECAUTIONS: General: Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities

Cardiovascular System: In clinical studies of PROVIGIL, signs and symptoms including chest pain, papilations, dyspnea, and transient ischemic T-wave changes on EGG were observed in 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic EGG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic monitoring of hypertensive patients taking PROVIGIL may be appropriate.

Central Nervous System: Caution should be exercised when PROVIGIL is given to patients with a history of psychosis.

Patients with Severe Renal Impairment: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modafinil acid, but not PROVIGIL itself.

Patients with Severe Henatic Impairment: PROVIGIL should be administered at a reduced dose because its clearance is decreased.

Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Alternative or concomitant methods of contraception are recommended during and for 1 month after treatment.

Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL: Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing fetus were not conducted so as to ensure a comprehensive evaluation of the potential of PROVIGIL to adversely affect lertility, or cause embryolethality or teratogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation. *Nursing*: Patients should notify their physician if they are breast feeding. *Concomitant Medication*: Patients should inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, because of the potential for drug interactions. Alcehai: It is prudent to avoid alcohol while taking PROVIGIL. Allergic Reactions: Patients should notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Orug Interactions: CNS Active Drugs: In a single-dose study, coadministration of PROVIGIL 200 mg with

methylphenidate 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single dose of clomipramine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of

either drug. One incident of increased levels of *clomipramine* and its active metabolite desmethylclomipramine has been reported. In a single-dose study with PROVIGIL (50, 100 or 200 mg) and *triazolam* 0.25 mg, no clinically important alterations in the safety profile of either drug were noted. In the absence of interaction studies with monoamine oxidase (MAO) inhibitors, caution should be exercised. Potential Interactions with Drugs That Inhibit, Induce. exercised. Potential Interactions with Drugs That Inhibit, Induce, or Are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes: Chronic dosing of PROVIGIL 400 mg/day resulted in -20% mean decrease in PROVIGIL plasma trough concentration suggesting that PROVIGIL, may have caused induction of its metabolism. Coadministration of potent inducers of CYP3A4 (eg. carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg. ketoconazole, could after the levels of PROVIGIL Caution needs to be exercised when PROVIGIL is coadministration with drugs that depend on hepatic enzymes for their clearance; some disease adjustment may be

istered with drugs that depend on hepatic enzymes for their clearance; some dosage adjustment may be required. Potentially relevant in vivo effects of PROVIGIL based on in vitro data are:

A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4 substrates (eg, cyclosporine, steroidal contraceptives, theophylline).

An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels

of CYP2C9 substrates (eq. warfarin, phenytoin)

A reversible inhibition of CYP2C19 may result in higher levels of CYP2C19 substrates (eg. diazepam, propranoiol phenytoin, S-mephenytoin)

In some patients deficient in CYP2D6, the amount of metabolism via CYP2C19 may be substantially larger. Co-therapy with PROVIGIL may increase levels of some tricyclic antidepressants (eq. clomipramine,

Carcinogenésis, Mutapenesis, Impairment of Fertility

enesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rat) the maximum recommended human daily dose of 200 mg on a mg/m- basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the carcinogenic potential in that species has not been fully evaluated. *Mutagenesis*: There was no evidence of mutagenic or clastogenic potential of PROVIGIL. *Impairment of Fertility*: When PROVIGIL was administered orally to male and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/ms basis) no effects on fertility were seen. This study did not use sufficiently high doses or large enough sample size to adequately assess effects

cy: Pregnancy Calegory C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVIGIL throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m² basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day um recommended daily human dose on a mg/m² basis). When rabbits received oral PROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended daily human dose on a mg/m^2 basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been opinital uses for the evaluation of entity-toxicity. Although a threshold gose for empryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL, should be used during pregnancy only if the potential benefit outweighs the potential risk.

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received PROVIGIL during pregnancy.

Nursing Mothers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution should be exercised when PROVIGIL is administered to nursing woman.

PEDIATRIC USE: Safely and effectiveness in individuals below 16 years of age have not been established.

GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established.

ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersonnia were given at least 1 dose of PROVIGIL. In controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (25%) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, ban pacebo-treated patients in controlled to any other first studies were freatdacte, milection, hatevore nervousness, anxiety, and insomnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (≥1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narcolepsy patients at a rate of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse events.

Body as a whole: Headache, chest pain, neck pain, chills, rigid neck, fever/chills

Dioestive: Nausea.\ diarrhea.\ dry mouth.\ anorexia.\ abnormal liver function.\ yomiting, mouth ulcer, gingivitis, thirst Digestive: Nausea, 'diarmea, 'dry moutil, 'arotexia, automiai ivea nuncion,' vorniung, moutil occi, yingivea, amo Respiratory system: Rhinitis,' pharyngitis,' lung disorder, dyspnea, asthma, epistaxis Nervous system: Nervousness,' dizziness, depression, anxiety, cataplaxy, insomnia, paresthesia,

dyskinesia,3 hypertonia, confusion, amnesia, emotional lability, ataxia, tremor

Cardiovascular: Hypotension, hypertension, vasodilation, arrhythmia, syncone

Hemic/Lymphatic: Eosinophilia

Special senses: Ambiyooja abnormal vision Metabolic/Nutritional: Hyperglycemia, albuminuria Musculo-skeletal: Joint disorder

Skin/Appendages: Herpes simplex, dry skin

Urogenital: Abnormal urine, urinary retention, abnormal ejaculation

Incidence ≥5%,2 Elevated liver enzymes,3 Oro-facial dyskinesias,4 Incidence adjusted for gender.

Dose Dependency: In US trials, the only adverse experience more frequent (≥5% difference) with PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.

Vital Signs Changes: There were no consistent effects or patterns of change in vital signs for patients treated with PROVIGIL in the US trials

Weight Changes: There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo.

Laboratory Changes: Mean plasma levels of gamma-glutamyl transferase (GGT) were higher following

administration of PROVIGIL but not placebo. Few subjects (1%) had GGT elevations outside the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the differences were not clinically significant.

ECG Changes: No treatment-emergent pattern of ECG abnormalities was found in US studies following administration of PROVIGIL.

DRUG ABUSE and DEPENDENCE: Abuse Potential and Dependence: In addition to wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. In vitro, PROVIGIL binds to the dopamine reuptake site and causes an increase in extracellular dopamine but no increase in doparnine release. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies PROVIGIL was also partially discriminated as stimulantlike. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (eg, methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (eg, incrementation of doses or drug-seeking behavior). In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). Patients should be observed for signs of misuse or abuse.

Withdrawal: Following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.

OYERDOSAGE: Human Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day, including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. **Overdose Management:** No specific antidote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or unnary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

Manufactured for: Cephalon, Inc., West Chester, PA 19380



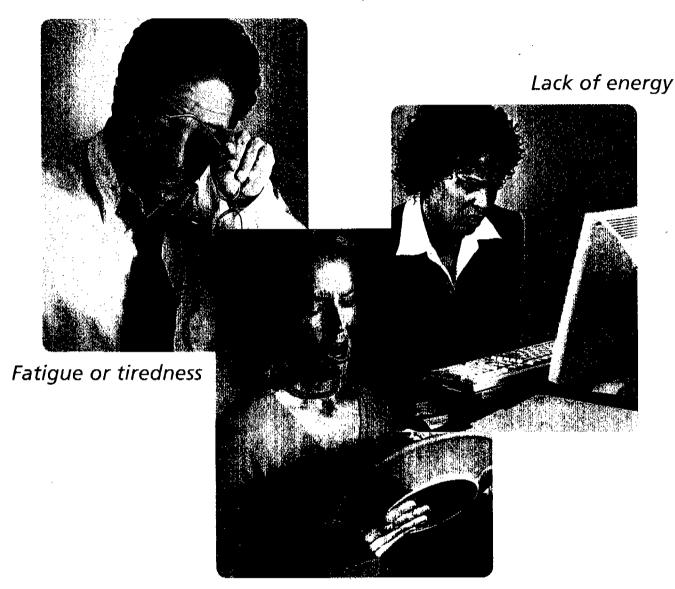
For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at www.PROVIGIL.com

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Printed in USA

What would you prescribe to improve wakefulness in patients who present with these complaints?

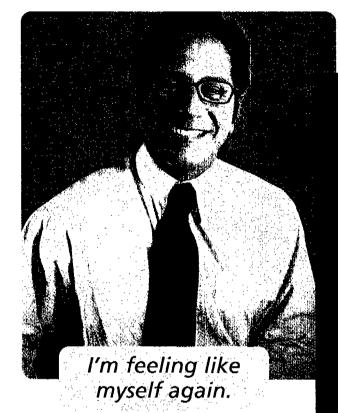


Sleepiness

To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy



Consider PROVIGIL, a unique wake-promoting agent.



58%-72% of narcolepsy patients showed improvement in CGI-C with PROVIGIL.1.2*

Now I'm not dozing off all the time.

PROVIGIL improved narcolepsy patients' ability to remain awake during the day as measured by MWT.1,2t

* CGI-C: Clinical Global Impression-Change over time, a validated independent physician

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rating assessment.

† MWT: Maintenance of Wakefulness Test, an objective assessment of sleepiness that measures

atients' ability to remain awake

ESS: Epworth Sleepiness Scale, a validated patient self-questionnaire that provides a subjective measurement of sleepiness.
 The relationship of these findings in animals to the effects of PROVIGIL in humans has not

been established

References: 1. US Modafinii in Narcolepsy Multicenter Study Group. Ann Neurol. 1998;43:88-97.
2. US Modafinii in Narcolepsy Multicenter Study Group. Neurology. 2000;54:1166-1175.
3. Schwartz JR. et al. [Abstract 1189.K2]. Sleep. 2000;23(suppl 2):A306. 4. Data on file. Cephalon, Inc. 5. Lin IS, Hou Y, Jouvet M. Proc Natl Acad Sci USA. 1996;93:14128-14133.
6. Edgar DM, Seidal Wr. J Pharmacol Exp Ther. 1997;283:757-769. 7. Physician's Desk Reference.

Please see brief summary of prescribing information at the end of this advertisement.



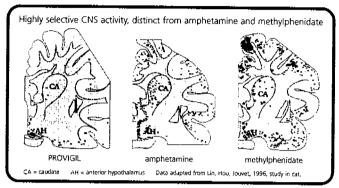
I'm able to be more active during the day.

ESS scores of narcolepsy patients significantly improved vs baseline in just one week with PROVIGIL (*P*<0.001).^{3,4‡}

For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at www.PROVIGIL.com

PROVIGIL keeps patients Alert, Aware, Awake all day. And still lets them sleep at night.

PROVIGIL works differently from stimulants in preclinical models. 5,65



- PROVIGIL promotes wakefulness without widespread CNS stimulation.
- PROVIGIL acts selectively in areas of the brain believed to regulate normal wakefulness.
- Unlike stimulants, PROVIGIL does not mediate wakefulness by a dopaminergic mechanism.

PROVIGIL does not disrupt nighttime sleep patterns. 1.2

- Won't interfere with the architecture of nighttime sleep or with patients' ability to fall asleep when needed.
- No statistical difference vs placebo in nighttime sleep duration.

PROVIGIL has a proven safety profile.

- PROVIGIL is generally well tolerated. Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection and insomnia. Most adverse events were mild to moderate.
- Long-term safety has been established for up to 136 weeks.⁴
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.

PROVIGIL has low abuse potential.7

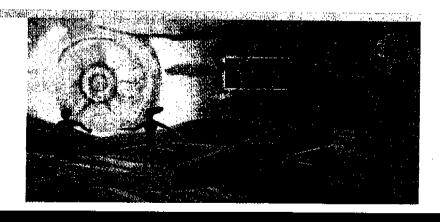
- PROVIGIL, a (V) agent, has fewer prescribing restrictions than (I) agents such as methylphenidate or dextroamphetamine.
- Phone-in prescriptions and refills permitted.
- No triplicate/multiple prescriptions required.

PROVIGIL offers convenient once-a-day dosing.

- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated.



To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy







PROVIGIL® (modafinii) TABLETS

BRIEF SUMMARY: Consult Package Insert for Complete Prescribing Information
INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated

CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL

PRECAUTIONS: General: Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to

Cardiovascular System. In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on ECG were observed in 3 subje palptations, dyspinea, and transient ischemic. I-wave changes on EUG were observed in 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIAL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic monitoring of hypertensive patients taking PROVIGIL may be appropriate.

Central Nervous System: Caution should be exercised when PROVIGIL is given to patients with a history of psychosis.

Patients with Severe Renal Impairment: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modalinil acid, but not PROVIGIL itself.

Patients with Severe Hepatic Impairment: PROVIGIL should be administered at a reduced dose because

Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Alternative or concomitant methods of contraception are recommended during and for 1 month after treatment.

Information for Palients: Physicians are advised to discuss the following with patients taking PROVIGIL: Pregnancy: Animal studies to assess the effects of PROVICIL on reproduction and the developing fetus were not conducted so as to ensure a comprehensive evaluation of the potential of PROVIGIL to adversely affect fertility, or cause embryolethality or teratogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased pregnant or means to become pregnant ourning merapy. They strout be carbonized or the potential indicates in tisk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation. *Nursing:* Patients should notify their physician if they are breast feeding. Concomitant Medication: Patients should inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, because of the potential for drug interactions. Alcohol: It is

prudent to avoid alcohol while taking PROVIGIL. Allergic Reactions: Patients should notify their physician if they develop a rash, hives, or a related allergic phenomenon,

Drug Interactions: CNS Active Drugs: In a single-dose study, coadministration of PROVIGIL 200 mg with methylphenidate 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single dose of clomipramine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of either drug. One incident of increased levels of clomipramine and its

active metabolite desmethylclomipramine has been reported. In a single-dose study with PROVIGIL (50, 100 or 200 mg) and triazolam 5 mg, no clinically important alterations in the safety profile of either drug were noted. In the absence of interaction studies with monoamine oxidase (MAO) inhibitors, caution should be exercised. Potential Interactions with Drugs That Inhibit, In or Are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes: Chronic dosing of PROVIGIL 400 mg/day resulted in -20% mean decrease in PROVIGIL plasma trough

concentration suggesting that PROVIGIL plasma trought concentration suggesting that PROVIGIL may have caused induction of its metabolism. Coadministration of potent inducers of CYP3A4 (eg., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg., ketoconazole, itraconazole), could alter the levels of PROVIGIL Caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on hepatic enzymes for their clearance; some dosage adjustment may be required. Provided the produced of the provided the produced of required. Potentially relevant in vivo effects of PROVIGIL based on in vitro data are:

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A slight Induction of CYP3A2 and CYP2B6 in a concentration-dependent manner has been observed.

A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4.

substrates (eg. cyclosporine, steroidal contraceptives, theophylline).

An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels

of CYP2C9 substrates (eg, warfarin, phenytoin).

A reversible inhibition of CYP2C19 may result in higher levels of CYP2C19 substrates (eg, diazepam, propranolol,

phenyloin, S-mephenyloin).
In some patients deficient in CYP2D6, the amount of metabolism via CYP2C19 may be substantially larger.

Co-therapy with PROVIGIL may increase levels of some tricyclic antidepressants (eg. clomipramine,

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rat) the maximum recommended human daily dose of 200 mg on a mg/m basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the the mouse study used an inadequate high dose below that representative or a maximum tolerated dose, use carrinogenic potential in that species has not been fully evaluated. *Mutagenesis*: There was no evidence of mutagenic or clastogenic potential of PROVIGIL. *Impairment of Fertility*: When PROVIGIL and administered orally to male and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/m; basis) no effects on fertility were n. This study did not use sufficiently high doses or large enough sample size to adequately assess effects

Pregnancy: Pregnancy Category C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVICIL throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m² basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was followed (5 times the maximum recommended daily human dose on a mg/m² basis). When rabbits received oral PROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended daily human dose on a mg/m² basis), no embryotoxicity was seen. Noither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweighs the potential risk

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically normal births occurred in patients who had received PROVIGIL during pregnancy. Nursing Mothers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution should be exercised when PROVIGIL is administered to nursing woman.

PEDIATRIC USE: Safety and effectiveness in individuals below 16 years of age have not been established. GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established. AOVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersomnia were given at least 1 dose of PROVIGIL. In controlled clinical trials. PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (£5%) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, nervousness, anxiety, and insomnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (≥1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narcolepsy patients at a rate of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse events.

controlled trials are listed below. Consult full prescribing information on adverse events.

Body as a whole: Headache, 'chest pain, neck pain, chills, rigid neck, fever/chills

Digestive: Nausea, 'diarrhea,' dry mouth,' anorexia, 'ahormal liver function,' vorniting, mouth ulcer, gingivitis, thirst

Respiratory system: Rhinitis,' pharyngitis,' lung disorder, dyspnea, asthma, epistaxis

Nervous system: Nervousness,' dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,' hypertonia, confusion, amnesia, emotional lability, ataxia, tremor

Cardiovascular: Hypotension, hypertension, vasodilation, arrhythmia, syncope

Hemic/Lymphatic: Eosinophilia

Special senses: Amblyopia, abnormal vision Metabolic/Nutritional: Hyperglycemia, albuminuria

Musculo-skeletal: Joint disorder

Skin/Appendages: Herpes simplex, dry skin

Urogenital: Abnormal urine, urinary retention, abnormal ejaculation

Incidence ≥5%,² Elevated liver enzymes,³ Oro-facial dyskinesias,⁴ Incidence adjusted for gender.

Dose Dependency: In US trials, the only adverse experience more frequent (£5% difference) with PROVIGIL 400 mg/day than PROVIGIL, 200 mg/day and placebo was headache.

Vital Signs Changes: There were no consistent effects or patterns of change in vital signs for patients vith PROVIGIL in the US trials.

Weight Changes: There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo.

Laboratory Changes: Mean plasma levels of gamma-glutamyl transferase (GGT) were higher following

ninistration of PROVIGIL but not placebo. Few subjects (1%) had GGT elevations outside the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the differences were not clinically significant

ECG Changes: No treatment-emergent pattern of ECG abnormalities

was found in US studies following administration of PROVIGIL.

DRUG ABUSE and DEPENDENCE: Abuse Potential and
Dependence: In addition to wakefulness-promoting effect and
accreased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects,

alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. *In vitro*, PROVIGIL binds to the dopamine reuptake site and causes an increase in extracellular dopamine but no increase in dopamine release. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies PROVIGIL was also partially discriminated as stimulantlike. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (eg, methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or

methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (eg. incrementation of doses or drug-seeking behavior). In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). Patients should be observed for signs of misuse or abuse. Withdrawal: Following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients. DVERDOSAGE: Human Experience: A total of 151 doses of \$1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or aditation, insomnia, and slight or moderate following day. The adverse experiences included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day, including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diamhea, and decreased prothrombin time. **Overdose Management**: No specific antidote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or urinary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

Manufactured for: Cephalon, Inc., West Chester, PA 19380 --



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PROVIGIL® (modafinil) TABLETS

olt Package Insert for Complete Prescribing Infor

INDICATIONS and IISAGE: To improve wakefulness in natients with excessive daytime sleeniness associated

CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL

PRECAUTIONS: General: Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activitie

Cardiovascular System: In clinical studies of PROVIGIL, signs, and symptoms including chest pain, papilitations, dyspinea, and granient stoches or Province, signs and symptotis including these papilitations, dyspinea, and granient stochemic T-wave changes on EGG were observed in 3 subjects in association with mitral valve prolapse or left ventricular hypertrephy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS lant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic

Surrious trace. Patients with a recent instruction on the distractive ariginal should be deared with caution. Periodic monitoring of hypertensive patients taking PROVIGIL may be appropriate.

Central Manuess Systems: Caution should be exercised when PROVIGIL is given to patients with a history of psychosis.
Patients with Severe Renal Impairment: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modafinil acid, but not PROVIGIL itself.

Patients with Severe Hepatic Impairment: PROVIGIL should be administered at a reduced dose because its clearance is decreased.

Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Alternative or concomitant methods of contraception are recommended during and for 1 month after treatment.

Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL: Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing fetus were not conducted so as to ensure a comprehensive evaluation of the potential of PROVIGIL to adversely fertility, or cause embryolethality or teratogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation. *Nursing:* Patients should notify their physician if they are breast feeding. *Concomitant Medication*: Patients should inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, because of the potential for drug interactions. Alcohol: It is prudent to avoid alcohol while taking PROVIGIL. Allergis Reactions: Patients should notify their physician if they develop a rash, hives, or a related altergic phenomenon.

beractions: CNS Active Drugs: In a single-dose study, coadministration of PROVIGIL 200 mg with methylphenidate 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single dose of clomipramine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of

either drug. One incident of increased levels of clomioramine and its active metabolite desmethylclomipramine has been reported. In a single-dose study with PROVIGIL (50, 100 or 200 mg) and triazolam 0.25 mg, no clinically important alterations in the safety profile of either drug were noted. In the absence of interaction studies with ne oxidase (MAO) inhibitors, caution should be exercised. Potential Interactions with Druns That Inhibit. Induce. or Are Metabolized by Cytochrome P-450 Isoenzymes and Other the metabolized by Cylicitions P-430 isolarity may and other Hepatis Enzymes: Chronic dosing of PROVIGIL 400 mg/day resulted in -20% mean decrease in PROVIGIL plasma trough concentration suggesting that PROVIGIL may have caused induction of its metabolism. Coadministration of potent inducers of CYP3A4 (eg. carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg. ketoconazole,

CTF344 (eg., caroamazepine, pnenoparonal, mampin) or knownors or CYPS44 (eg., ketoconazole, traconazole) could after the levels of PROVIGIL. Caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on hepatic enzymes for their clearance; some dosage adjustment may be required. Potentially relevant in vivo effects of PROVIGIL based on in vitro data are:

A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed.

A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4 substrates (eg., cyclosporine, steroidal contraceptives, theophylline).

An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels of CYP2C9 substrates (eg, warfarin, phenytoin).

A reversible inhibition of CYP2C19 may result in higher levels of CYP2C19 substrates (eg. diazepam, propranolol, phenytoin, S-mephenytoin).

In some patients deficient in CYP2D6, the amount of metabolism via CYP2C19 may be substantially larger Co-therapy with PROVIGIL may increase levels of some tricyclic antidepressants (eg., clomipramine,

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rat) the maximum recommended human daily dose of 200 mg on a mg/m basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the carcinogenic potential in that species has not been fully evaluated. Mutagenesis: There was no evidence of mutagenic or clastogenic potential of PROVIGIL Impairment of Fertility: When PROVIGIL was administered orally to male and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/m² basis) no effects on fertility were seen. This study did not use sufficiently high doses or large enough sample size to adequately ass

per Category C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVIGIL throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m² basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day (5 times the maximum recommended daily human dose on a mg/m² basis). When rabbits received oral ROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommend daily human dose on a mg/m² basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweighs the potential risk

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically d. Seven normal births occurred in patients who had received PROVIGIL during pregnancy. Nursing Mothers: It is not known whether PROVIGIL or its metabolite are excreted in human milk Caution should be exercised when PROVIGIL is administered to nursing woman.

PEDIATRIC USE: Safety and effectiveness in individuals below 16 years of age have not been established.

GEFIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established.

ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersomnia were given at least 1 dose of PROVIGIL. In controlled clinical trials, PROVIGIL, was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (25%) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea. nervousness, anxiety, and insomnia, in US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (≥1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narcolepsy patients at a rate of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse events.

Body as a whole: Headache, chest pain, neck pain, chills, rigid neck, fever/chilts Digestive: Nausea, diarrhea, dry mouth, anorexia, abnormal liver function, vomiting, mouth ulcer, gingivitis, thirst

briggsaver, reassa; carrinea; cry mount, ancienza; abnormal intertrunction; vormang, mount uncer gingvins, miss. Respiratory system: Rhinitis, phanyngitis, lung disorder, dyspnea, asthma, epistaxis Nervous system: Nervousness, i dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia, hypotension, amnesia, emotional lability, ataxia, tremor Cardlevascular: Hypotension, hypertension, vasodilation, arrhythmia, syncope

nic/Lymphatic: Eosinophilia

Special senses: Ambivopia abnormal vision Metabelic/Nutritional: Hyperglycemia, albuminuria Musculo-skoletal: Joint disorder

Skin/Appendages: Herpes simplex, dry skin Urogenital: Abnormal urine, urinary retention, abnormal ejaculation

Incidence ≥5%, Elevated liver enzymes, Oro-facial dyskinesias, Incidence adjusted for

Dose Dependency: In US trials, the only adverse experience more frequent (25% difference) with PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.

Vital Signs Changes: There were no consistent effects or patterns of change in vital signs for patients vith PROVIGIL in the US trials.

Weight Changes: There were no clinically significant differences in body weight change in patients

treated with PROVIGIL compared to placebo Laboratory Changes: Mean plasma levels of gamma-glutarmyl transferase (GGT) were higher following

administration of PROVIGIL but not placebo. Few subjects (1%) had GGT elevations outside the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase total protein, albumin, or total bilirubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the differences were not clinically significant.

ECG Changes: No treatment-emergent pattern of ECG abnormalities was found in US studies following administration of PROVIGIL. DRUG ABUSE and DEPENDENCE: Abuse Potential and Dependence: In addition to wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects,

alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. In vitro, PROVIGIL binds to the donamine reuptake site and causes an increase in extracellular donamine but no increase in dopamine release. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies PROVIGIL was also partially discriminated as stimulantlike. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (eg, methylohenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (eg. incrementation of doses or drug-seeking behavior). In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). Patients should be observed for signs of misuse or abuse.

Withdrawat: Following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawal were

observed during 14 days of observation, although skepiness returned in narroleptic patients. **QVERDOSABE:** Heman Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia, and stight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day, including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. **Overdose Management:** No specific antidote to the toxic refrects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or urinary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

Manufactured for: Cephalon, Inc., West Chester, PA 19380



For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at www.PROVIGIL.com

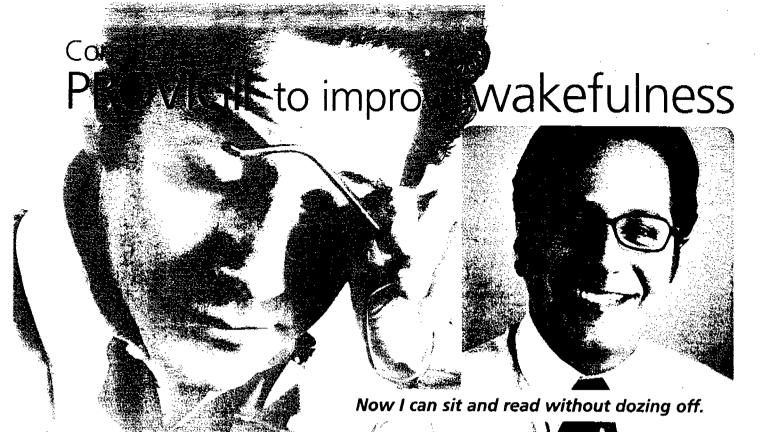
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When patients present with

FATIGUE or TIREDNESS

Patients with sleep disorders present with various symptoms. PROVIGIL, a unique wakepromoting agent, keeps patients Alert, Aware, Awake all day. And lets them sleep at night.12

Efficacy confirmed by objective and subjective measures of wakefulness in narcolepsy patients.

- PROVIGIL improved patients' ability to remain awake during the day by 33%-39% in MWT.12*
- · Prior stimulant users and newly diagnosed patients both stayed awake longer.

Works differently.451

- PROVIGIL promotes wakefulness without widespread CNS stimulation in preclinical models.*
- Unlike stimulants, PROVIGIL does not mediate wakefulness by a dopaminergic mechanism.

Proven safety profile.

- PROVIGIL is generally well tolerated. Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection and insomnia. Most adverse events were mild to moderate.
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.

Easy to prescribe.

- PROVIGIL, a (iv agent, has few prescribing restrictions and low abuse potential compared to (agents such as methylphenidate or dextroamphetamine.6
- Phone-in prescriptions and refills permitted.
- No triplicate/multiple prescriptions required.

Convenient once-a-day dosing may enhance compliance.

- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated.

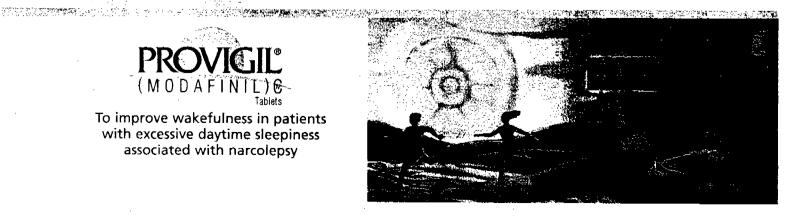
For more information about PROVIGIL, please call 1-800-896-5855 or visit our Website at www.PROVIGIL.com

- MWT: Maintenance of Wakefulness Test; an objective assessment of sleepiness that measures patients' ability to remain awake.
 The precise mechanism of action is unknown.
 The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.

References: 1. US Modafinii in Narcolepsy Multicenter: Study Group. Ann Neurol. 1998;43:88-97. 2. US Modafinii in Narcolepsy Multicenter Study Group. Neurology. 2000;54:1166-1175. 3. Data on file, Cephalon, Inc. 4. Lin JS, Hou Y, Jouvet M. Proc. Natl Acad. Sci. USA. 1996;93:14128-14133. 5. Edgar DM, Seidal WF. J Pharmacol Exp. Ther. 1997;283:757-769. 6. Physician's Desk Reference, current edition. Please see brief summary of prescribing information on the adjacent page.



To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy







PROVIGIL® (modafinii) TABLETS

PROFILE (INVARY: Consult Package Insert for Complete Prescribing Information INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated

CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL

PRECAUTIONS: General: Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to

Cardiovascular System: In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on ECG were observed in 3 subjects in perplantists, by spikes, and transfer is continuous in the average of the perpendicular typerforphy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic EGG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic

sumular use. Patients with a recent nestory or will or unstable angina should be treated with caution. Periodic monitoring of hypertensive patients taking PROVIGIL may be appropriate.
Central Hernous System: Caution should be exercised when PROVIGIL is given to patients with a history of psychosis.
Patients with Severe Renal Impairment: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modafinil acid, but not PROVIGIL itself.

Patients with Severe Hepatic Impairment: PROVIGIL should be administered at a reducits clearance is decreased.

Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation, Alternative or concomitant methods of contraception are recommended during and for 1 month after treatment.

Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL: Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing fetus were not conducted so as to ensure a comprehensive evaluation of the potential of PROVIGIL to adversely affect fertility, or cause embryolethality or teratogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation. *Marsing:* Patients should notify their physician if they are breast feeding. Concomitant Medication: Patients should inform their physician if they are lating or plan to take any prescription or over-the-counter drugs, because of the potential for drug interactions. Alcohol: It is prudent to avoid alcohol while taking PROVIGIL. Allergic Reactions: Patients should notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Drug Interactions: CNS Active Drugs: In a single-dose study, coadministration of PROVIGIL 200 mg with methylphenidate 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single dose of ctomipramine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of either drug. One incident of increased levels of ctomipramine and its

active metabolite desmethylclomipramine has been reported. In a ingle-dose study with PROVIGIL (50, 100 or 200 mg) and triazolam 0.25 mg, no clinically important alterations in the safety profile of either drug were noted. In the absence of interaction studies with monoamine oxidase (MAO) inhibitors, caution should be exercised. Potential Interactions with Drugs That Inhibit, Indu or Are Metabolized by Cytochrome P-450 isoenzymes and Other Hepatic Enzymes: Chronic desing of PROVIGIL 400 mg/day resulted in -20% mean decrease in PROVIGIL plasma trough concentration suggesting that PROVIGIL may have caused induction of its metabolism. Coadministration of potent inducers of

CYP3A4 (eg. carbamazepine, phenobarbital, rffampin) or inhibitors of CYP3A4 (eg., ketoconazole itraconazole) could after the levels of PROVIGIL. Caution needs to be exercised when PROVIGIL is coadmin istered with drugs that depend on hepatic enzymes for their clearance, some dosage adjustment may be required. Potentially relevant *in vivo* effects of PROVIGIL based on *in vitro* data are:

A slight induction of CYP1A2 and CYP286 in a concentration-dependent manner has been observed. A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4.

substrates (eg, cyclosporine, steroidal contraceptives, theophylline).

An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels of CYP2C9 substrates (eg, warfarin, phenytoin). A reversible inhibition of CYP2C19 may result in higher levels of CYP2C19 substrates (eg, diazepam, propranolol,

phenytoin, S-mephenytoin).
In some patients deficient in CYP2D6, the amount of metabolism via CYP2C19 may be substantially larger.

Co-therapy with PROVIGIL may increase levels of some tricyclic antidepressants (eg. clomipramine,

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rat) the maximum recommended human daily dose of 200 mg on a mg/mr basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the mouse study used an inadequate bigh dose below that representative of a maximum tolerated dose the carcinogenic potential in that species has not been fully evaluated. Mestagenesis: There was no evidence of mutagenic or classogenic potential of PROVIGIL. Impairment of Fertility: When PROVIGIL was administered orally to male and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/m² basis) no effects on fertility were seen. This study did not use sufficiently high doses or large enough sample size to adequately assess effects

Pregnancy: Pregnancy Category C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVIGIL throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m² basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day the maximum recommended daily human dose on a mg/m² basis). When rabbits received oral PROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended daily human dose on a mg/m basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweight

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received PROVIGIL during pregnancy. Nursing Mothers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution should be exercised when PROVIGIL is administered to nursing woman.

PEDIATRIC USE: Safely and effectiveness in individuals below 16 years of age have not been established. GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established. ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersomnia were given at least 1 dose of PROVIGIL. In controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (>5%) associated with the use of PROVIGIL more frequently The first community observed adverse events (core) associated when the use of movement man inequation, than placebo-heated patients in controlled US and foreign studies were headed; infection, nausea, nervousness, anxiety, and insomnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (>1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narcolepsy patients at a rate of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse events. Body as a whole: Headache, chest pain, neck pain, chills, rigid neck, fever/chills

body as a winder neadctive, curest pain, next pain, mins, injud next, revercines pilgestive: Nausea, 'diarrhea,' dry mouth,' anorexia,' abnormal liver function,' vorniting, mouth ulcer gingivitis, thirst Respiratory system: Ninitis,' pharyngitis,' lung disorder, dyspnea, asthma, epistaxis Nervous system: Nervousness,' dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,' hypertonia, confusion, amnesia, emotional lability, ataxia, tremor

ardiovascular: Hypotension, hypertension, vasodilation, arrhythmia, syncope

Hemic/Lymphatic: Eosinoonilia

Special senses: Amblyopia, abnormal vision Metabolic/Nutritional: Hyperglycemia, albuminuria

Muscule-skeletal: Joint disord

Skin/Appendages: Hernes simplex dry skin.

Urogenital: Abnormal urine, urinary retention, abnormal ejaculation

'Incidence ≥5%,'Elevated liver enzymes,'Oro-facial dyskinesias, 'Incidence adjusted for gender.

Dese Dependency: In US trials, the only adverse experience more frequent (≥5% difference) with

PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.

Vital Signs Changes: There were no consistent effects or patterns of change in vital signs for patients treated with PROVIGIL in the US trials.

Weight Changes: There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo.

Laboratory Changes: Mean plasma levels of gamma-glutamyl transferase (GGT) were higher following

administration of PROVIGIL but not placebo, Few subjects (1%) had GGT elevations outside the normal range. Shift to higher, but not clinically significantly abnormal. GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilimbin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the differences were not clinically significant.

ECG Changes: No treatment-emergent pattern of ECG abnormalities found in US studies following administration of PROVIGI)

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OVERDOSAGE: Human Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day, including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. Overdese Management: No specific antidote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or urinary acidification or attainization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

Manufactured for: Cephalon, Inc., West Chester, PA 19380



For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at www.PROVIGE..com

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Jan 2001

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IL to im Nove wakefulness الت



I'm able to be more active during the day.

When patients present with

SLEEPINESS

Patients with sleep disorders present with various symptoms. PROVIGIL, a unique wake-promoting agent, keeps patients Alert, Aware, Awake all day. And lets them sleep at night.¹²

Efficacy confirmed by objective and subjective measures of wakefulness in narcolepsy patients.

- In the ESS, PROVIGIL improved patients' ability to participate in daily activities by 20%–32%!²³
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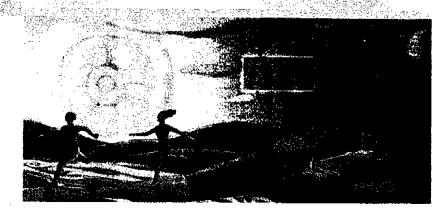
- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerand

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PROVIGIE (MODAFINIL) @ Tablets

To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy







PROVIGIL* (modafinii) TABLETS

BRIEF SUMMARY: Consult Package Insert for Complete Prescribing Information

INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated

CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL

PRECAUTIONS: General: Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities

Cartiforascular System: In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspinea, and transient ischemic T-wave changes on ECG were observed in 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolanse in association with CNS stimulant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic monitoring of hypertensive patients taking PROVIGIL may be appropriate.

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they develop a rash, hives, or a related allergic phenomenon.

Drug Interactions: CNS Active Drugs: In a single-dose study, coadministration of PROVIGIL 200 mg with methylphenidate 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single-dose of clampipamine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with page 100 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with page 100 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with page 100 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with page 100 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with page 100 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with page 100 mg/day did not affect the pharmacokinatics of a single dose of clampipamine 50 mg with page 100 mg/day did not affect the pharmacokinatics of a single dose 100 mg/day did not affect the pharmacokinatics of a single dose 100 mg/day did not affect the pharmacokinatics of a single dose 100 mg/day did not affect the pharmacokinatics of a single dose 100 mg/day did not affect the pharmacokinatics of a single dose 100 mg/day did not affect the pharmacokinatics of a single dose 100 mg/day did not affect the pharmacokinatics of a single dose 100 mg/day did not affect the pharmacokinatics of a single dose 100 mg/day did not affect the pharmacokin

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A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed. A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4 substrates (eg. cyclosporine, steroidal contraceptives, theophylline).

An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher lev

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Carcinogenesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rat) the maximum recommended human daily dose of 200 mg on a mg/m² basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the carcinogenic potential in that species has not been fully evaluated. Matagenesis: There was no evidence of mutagenic or clastogenic potential of PROVIGIL Impairment of Fertility: When PROVIGIL was administered orally to male and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/m² basis) no effects on fertility were seen. This study did not use sufficiently high doses or large enough sample size to adequately assess effects

Pregnancy: Preg y Category C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVIGER throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day maximum recommended daily human dose on a mg/m² basis). When rabbits received oral PROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended PROVIGIL Inroughout organizations at ouses up to 100 mg/mg/mg/mg/ (10 times the studies, however, used daily human dose on a mg/m² basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweights the potential risk.

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received PROVIGIL during pregnancy.

Nursing Mothers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution should be exercised when PROVIGIL is administered to nursing woman.

PEDIATRIC USE: Safety and effectiveness in individuals below 16 years of age have not been established.

GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established.

ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersomnia were given at least 1 dose of PROVIGIL. In controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (25%) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, nervousness, arouety, and insornnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (≥1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narcolepsy patients at a rate of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse events

Body as a whole: Headache,' chest pain, neck pain, chills, rigid neck, fever/chills

Digestive: Nausea, 'darnea,' dry mouth,' anorexia, 'abnormal liver function,' vorniting, mouth ulcer, gingivitis, thirst Respiratory system: Rhinitis,' pharyngitis,' lung disorder, dyspnea, asthma, epistaxis Nervous system: Nervousness,' dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,' hypertonia, confusion, arnnesia, emotional lability, ataxia, tremor

Cardiovascular: Hypotension, hypertension, vasodilation, arrhythmia, syncope

Hemic/Lymohatie: Eosinophilia

Special senses: Amblyopia, abnormal vision Metabolic/Netritional: Hyperglycemia, albuminuria Musculo-skeletal: Joint disord

Skin/Appendages: Herpes simpley dry skin

Urogenital: Abnormal urine, urinary retention, abnormal ejaculation

"Incidence 25%,? Elevated liver enzymes,*Oro-facial dyskinesias,* Incidence adjusted for gender, Dose Dependency: In US trials, the only adverse experience more frequent (25% difference) with PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.

Vital Signs Changes: There were no treated with PROVIGIL in the US trials. est: There were no consistent effects or patterns of change in vital signs-for patients

Weight Changes: There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo.

Laboratory Changes: Mean plasma levels of gamma-glutamyl transferase (GGT) were higher following

administration of PROVIGIL but not placebo. Few subjects (1%) had GGT elevations outside the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies, the ices were not clinically significant.

ECG Changes: No treatment-emergent pattern of ECG abnormalities vas found in US studies following administration of PROVIGIL

DRUG ABUSE and DEPENDENCE: Abuse Potential and Dependence: In addition to wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and suphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. In vitro, PROVIGIL binds to the dopamine reuptake site and causes an increase in extracellular dopamine but no increase in dopamine release. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies PROVIGIL was also partially discriminated as stimulantlike. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (eg, methylphenidate, amphetamine, or cocalne) abuse. Patients should be observed for signs of misuse or abuse (eg., incrementation of doses or drug-seeking behavior). In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). Patients should be observed for signs of misuse or abuse. Withdrawat: Following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawal were

observed during 14 days of observation, although sleepiness returned in narcoleptic patients.

OVERDOSASE: Human Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse taken intertuoliary by 2 powers participating in foreign depression stitutes. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day, including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, initiability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. **Overdose Management:** No specific antidote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarity supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or urinary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

Manufactured for: Caphalon, Inc., West Chester, PA 19380



For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 visit our Website at www.PROVIGIL.com

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PR0229

Jan 2001

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IL to impowerwake fulness



Now I'm not dozing off all the time.

When patients complain of

SLEEPINESS

Patients with sleep disorders present with various symptoms. PROVIGIL, a unique wakepromoting agent, keeps patients Alert, Aware, Awake all day. And lets them sleep at night.¹²

Efficacy confirmed by objective and subjective measures of wakefulness in narcolepsy patients.¹²

- PROVIGIL improved patients' ability to remain awake during the day as measured by NAVICE
- Does not interfere with a different section of the different secti

Works differently.3.41

- PROVIGIL promotes wakefulness without widespread CNS stimulation in preclinical models.
- PROVIGIL acts see in areas of the believes and the believes are normal.

Proven safety profile.

- PROV Gil. is generally well tolerated. Most frequently replaced adverse events and beadache, haused topper apport.
 - events to moderate.
- interact with drugs Linhibit, induce or re metabolized by cytochrome P450 isoenzymes

Low abuse potential.5

- PROVIGIL, a (v agent, has fewer prescribing restrictions than (l agents such as methylphenidate or dextroamphetamine.
 - Phone-in prescriptions and refills permitted.
- No triplicate/multiple prescriptions required.

Convenient once-a-day dosing may enhance compliance.

- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated

For more information about PROVIGIL, please call 1-800-896-5855 or visit out

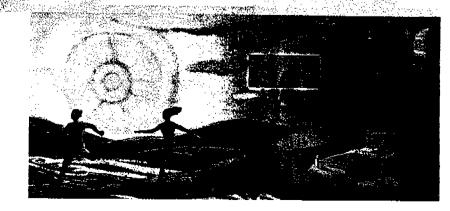
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Group. Ann Neurol. 1998 31,3897. 2. US Modafinii in Narcolepsy Multicenter Study Group. Neurology. 2000;54:1166-1175: 3. Lin 15. Hour V. Cidoar DM, Seidal W. Brisiniacol Exp Ther. 1997;283:757-769. 5. Physician's Desk Reference, current edition.

PROVIGIL (MODAFINIL) 6

To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy







PROVIGIL* (modaflail) TABLETS

BRIEF SUMMARY: Consult Package Insert for Complete Prescribing Information

INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated

CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL

PRECAUTIONS: General: Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities.

Cardiovascular System: In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspinea, and transient ischemic T-wave changes on ECG were observed in 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic

aminism use, if a verifies with a recent mission or million unstagned ariginal structure to exceed with causion. For occur, monitoring of hypertensive patients taking PROVIGIL may be appropriate.

**Central Nerviews Systems: Caution should be exercised when PROVIGIL is given to patients with a history of psychosis. Patients with Severe Renal Impairment: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modafinil acid, but not PROVIGIL itself,

Patients with Severe Hepatic Impairment: PROVIGIL should be administered at a reduced dose because its clearance is decreased

Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Alternative or concomitant methods of contraception with Prioritical and for 1 month after treatment.

Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL:

Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing fetus were Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing fetus were not conducted so as to ensure a comprehensive evaluation of the potential of PROVIGIL to adversely affect fertility, or cause embryolethality or leartogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation. Nursing: Patients should notify their physician if they are breast feeding. Concomitant Medication: Patients should inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, because of the potential for drug interactions. Alcohol: It is prudent to avoid alcohol while taking PROVIGIL. Allergie Reactions: Patients should notify their physician if they develon a rash hives or a related allernic phenomenon. ey develop a rash, hives, or a related altergic phenomenon.

Drug Interactions: CNS Active Drugs: In a single-dose study, coadministration of PROVIGIL 200 mg with methylphenidate 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single dose of ciomipramine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of either drug. One incident of increased levels of ciomipramine and its

active metabolite desmethylclomipramine has been reported. In a single-dose study with PROVIGIL (50, 100 or 200 mg) and triazolam 0.25 mg, no clinically important atterations in the safety profile of U.25 mg, no clinicary important afterations in the satery profile or either drug were noted. In the absence of interaction studies with monoamine oxidase (MAO) inhibitors, caution should be exercised. Patential Interactions with Drugs That Inhibit, Induce, or Are Metabolized by Cytochrome P-450 Isoenzymes and Other of the meta-onized by Lymberrolling 1-4-by isbencymes and union Hepatic Enzymes: Chronic dosing of PROVIGIL 400 mg/day resulted in ~20% mean decrease in PROVIGIL plasma trough concentration suggesting that PROVIGIL may have caused induction of its metabolism. Coadministration of potent inducers of

CYP3A4 (eg. carbamazepine, phenobarbital, ritamplin) or inhibitors of CYP3A4 (eg. ketoconazole, itraconazole) could after the levels of PROVIGIL. Caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on hepatic enzymes for their clearance; some dosage adjustment may be required. Potentially relevant in vivo effects of PROVIGIL based on in vitro data are:

A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4 substrates (eg. cyclosporine, steroidal contraceptives, theophylline).

An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels.

of CYP2C9 substrates (eg, warfarin, phenytoin).

A reversible inhibition of CYP2C19 may result in higher levels of CYP2C19 substrates (eg, diazepam, propranolol,

phenyloin, S-mephenyloin). In some patients deficient in CYP206, the amount of metabolism via CYP2C19 may be substantially larger. Co-therapy with PROVIGIL may increase levels of some tricyclic antidepressants (eg. clomipramine,

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rat) the maximum recommended human daily dose of 200 mg on a mg/m² basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because no evidence or turnorigenesis associated with PHOVIGIL administration in these studies, but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the carcinogenic potential in that species has not been fully evaluated. Mutagenesis: There was no evidence of mutagenic or clastogenic potential of PROVIGIL. Impairment of Fertility: When PROVIGIL was administered orally to male and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day. (4.8 times the maximum recommended daily dose of 200 mg on a mg/m² basis) no effects of retility were seen. This study did not use sufficiently high doses or large enough sample size to adequately assess effects

ory C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVIGIL throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/mr basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day (5 times the maximum recommended daily human dose on a mg/m² basis). When rabbits received oral PROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended daily human dose on a mg/m² basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweights the potential risk.

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received PROVIGIL during pregnancy. Nursing Methers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution should be exercised when PROVIGIL is administered to nursing woman.

PEDIATRIC USE: Safety and effectiveness in individuals below 16 years of age have not been established. GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established. ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersomnia were given at least 1 dose of PROVIGIL. In controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (25%) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, nervousness, amoiety, and insomnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (21%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), decression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narcolepsy patients at a rate of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse events Body as a whele: Headache, 'chest pain, neck pain, chills, rigid neck, fever/chills

as a mover, measure, west point, neur pain, willis, right neur, reversiones silver Nausea, diarrhea, dry mouth, anorexia, abnormal liver function, vomiting, mouth ulcer, gingivitis, thirst Iratory systems: Rhinitis, pharyngitis, lung disorder, dyspnea, asthma, epistaxis

Nervous system: Nervousness.' dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia, hypertonia, confusion, amnesia, emotional lability, ataxia, tremor

artievascular: Hypotension, hypertension, vasodilation, arrhythmia, syncope nic/Lymohatic: Eosinoohilia

Special senses: Amblyopia, abnormal vision Metabolic/Nutritional: Hyperglycemia, albuminuria de-skeletal: Joint disorder

indages: Herpes simplex, dry skin

Uregenital: Abnormal urine, urinary retention, abnormal ejaculation*
¹incidence ≥5%. Elevated liver enzymes,³ Oro-facial dyskinesias. ¹Incidence adjusted for gender.

Dese Dependency: In US trials, the only adverse experience more frequent (25% difference) with PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.

Vital Slows Cha ages: There were no consistent effects or patterns of change in vital signs for patients treated with PROVIGIL in the US trials.

Weight Changes: There were no clinically significant differences in body weight change in patients ted with PROVIGIL compared to placebo.

Laboratory Changes: Mean plasma levels of gamma-glutarmyl transferase (GGT) were higher following administration of PROVIGIL but not placebo. Few subjects (1%) had

GGT elevations outside the normal range. Shift to higher, but not cool everations outside the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the differences were not clinically significant.

ECG Changes: No treatment-emergent pattern of ECG abnormalities

was found in US studies following administration of PROVIGIL

was found in Us studies following administration of PROVIGIL.

DRUG ABUSE and DEPENDENCE: Abuse Potential and

Dependence: In addition to wakefulness-promoting effect and
increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects,
alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. In vitro, PROVIGIL binds to the dopamine reuptake site and causes an increase in extracellular dopamine but no increase in dopamine release. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer occaine. In some studies PROVIGIL was also partially discriminated as stimulant-like. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (eg, methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (eg, incrementation of doses or drug-seeking behavior). In individuals experienced with drugs of

abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). Patients should be observed for signs of misuse or abuse.

withdrawal: following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.

OVERDOSAGE: Numan Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day. inctuding experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. Overdose Management: No specific articlote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or urinary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

Manufactured for: Conhaion, Inc., West Chester, PA 19380



For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at we w.PROVIGIL.

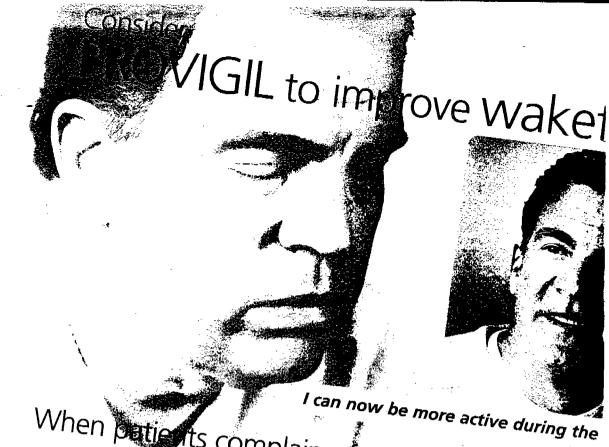
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PR0230

Jan 2001

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When patients complain of

Lack of ENERGY Patients with sleep disorders present with various symptoms. PROVIGIL, a uniq promoting agent, keeps patients Alert, Aware, Awake all day. And lets them ske Efficacy confirmed

by objective and subjective measures of wakefulness in narcolepsy patients.

- ESS scores of patients significantly improved vs baseline in just one week with PROVIGIL (P<0.001),3,4
- Does not interfere with nighttime sleep architecture or sleep duration.12

- wakefulness without widespread CNS stimulation in preclinical models.*
- PROVIGIL acts selectively in areas of the brain believed to regulate normal wakefulness.
- Unlike stimulants; PROVIGIL does not mediate wakefulness by a dopaminergic mechanism.

- PROVIGIL is generally well tolerated. Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection and insomnia Möst adverse events were mild to moderate.
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.

Low abuse potential.

- PROVIGIL, a @ agent, has fewer prescribing restrictions than @agents such as methylphenidate or dextroamphetamine.
- Phone-in prescriptions and refills permitted
- No triplicate/multiple prescriptions required.

Conven. Once-a-c may ent compliar • Recomm

- 200 mg : daily in th • 200 mg a:
- doses are . generally v

For more inform PROVIGIL, pleas 1-800-896-5855

* ESS: Epworth Sleepiness Scale; a validated patient self-questionnaire that provides a subjective measurement of sleepiness.

† The precise mechanism of action is unknown.

† The relationship of these findings in animals to the effects of PROVIGIT. In humans has not been established.

*Reference: 1. LIC Mortalinii in Narrolanov Adulticantor Chiefe Grain. And Narrolanov 1 1000-13-08.07 2 11C Mortalinii in Narrolanov Adulticantor Chiefe Grain.

* The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.

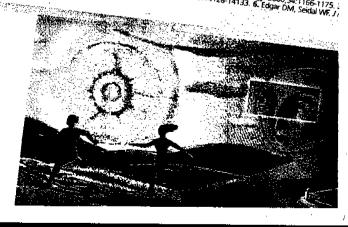
References: 1. US Modafinil in Narcolepsy Multicenter Study Group. Ann Neurol. 1998;43:88-97.

Ann. 1997;283:757-769. 7. Physician's Dest. Reference, current edition.

Please see brief summary of prescribing information on the adjacent page. The second of th



To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy







PROVIGIL® (modafinil) TABLETS

SUMMARY: Consult Package Insert for Complete Prescribing Information

INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated

CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL

PRECAUTIONS: General: Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities

vascular System: In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspinea, and transient ischemic T-wave changes on ECG were observed in 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic monitoring of humaniculus described in the properties.

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Patients with Severe Hepatic Impair Next: PROVIGIL should be administered at a reduced dose because its clearance is decreased.

Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Alternative or concumitant methods of contraception with Froversit, and the Thomas alles inscommindation. Americance of concomment inscribes or commenced are recommended during and for 1 month after treatment.

Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL:

Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing fetus were not conducted so as to ensure a comprehensive evaluation of the potential of PROVIGIL to adversely affect fertility, or cause embryolethality or teratogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased pregnant of finent to become pregnant during interapy. They should be cautooned or me potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation, *Numering:* Patients should notify their physician if they are breast feeding. *Concomitant Medication:* Patients should inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, because of the potential for drug interactions. *Alcohol:* It is proudent to avoid alcohol while taking PROVIGIL. *Allergis: Reactions:*: Patients should notify their physician if ney develop a rash, hives, or a related allergic phenomenon.

Drug Interactions: CNS Active Drugs: In a single-dose study, coadministration of PROVIGIL 200 mg with methylphenidate 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single dose of clomipramine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of either drug. One incident of increased levels of clomipramine and its

active metabolite desmethylclomipramine has been reported. In a single-dose study with PROVIGIE \$\infty\$ 50, 100 or 200 mg) and triazolam 0.25 mg, no clinically important alterations in the safety profile of either drug were noted. In the absence of interaction studies with monoamine oxidase (MAO) inhibitors, caution should be exercised. Potential Interactions with Drugs That Inhibit, Induce, or Are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes: Chronic dosing of PROVIGIL 400 mg/day resulted in -20% mean decrease in PROVIGIL plasma trough concentration suggesting that PROVIGIL may have caused induction of its metabolism. Coadministration of potent inducers of

CYP3A4 (eg., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg., ketoconazole, itraconazole) could after the levels of PROVIGIL. Caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on hepatic enzymes for their clearance; some dosage adjustment may be required. Potentially relevant in vivo effects of PROVIGIL based on in vitro data are:

A slight induction of CYP1A2 and CYP286 in a concentration-dependent manner has been observed. A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4 substrates (eg. cyclosporine, steroidal contraceptives, theophylline).

An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels.

of CYP2C9 substrates (eg, warfarin, phemytoin).

A reversible inhibition of CYP2C19 may result in higher levels of CYP2C19 substrates (eg, diazepam, propranolol,

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In some patients deficient in CYP2D6, the amount of metabolism via CYP2C19 may be substantially larger. Co-therapy with PROVIGIL may increase levels of some tricyclic articlepressants (eg. clomipramine,

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rat) the maximum recommended human daily dose of 200 mg on a mg/m basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the carcinogenic potential in that species has not been fully evaluated. Mutagenesis: There was no evidence of mutagenic or clastogenic potential of PROVIGIL. Impairment of Fertility: When PROVIGIL was administered orally to male and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/m² basis) no effects on fertility seen. This study did not use sufficiently high doses or large enough sample size to adequately assess effects

y Category C: Embryotoxicity was observed in the absence of maternal toxicity when resortion, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day. es the maximum recommended daily human dose on a mg/m² basis). When rabbits received oral PROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended daily human dose on a mg/m² basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been optimal goses for the evaluation or empryotoxicity, authority in a threshold gose for empryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized sever dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and welf-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweighs the potential risk

Labor and Delivery. The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received PROVIGIL during pregr Nursing Methers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution

should be exercised when PROVIGIL is administered to nursing woman.

PEDIATRIC USE: Safety and effectiveness in individuals below 16 years of age have not been established.

GEFIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established. ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than ts with narcolepsy or narcolepsy/hypersomnia were given at least 1 dose of PROVIGIL. In 300 students with inactionary or hat companying sortina were given a reast i doze or innovation. controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (≥5%) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, nervousness, anxiety, and insomnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (≥1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression occurred in a large of the feet of the feet processor patients were reasonable (1.7%), housed (1.7%), uppressions (1.7%). The incidence of adverse experiences that occurred in narcolepsy patients at a rate of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse e Body as a whole: Headache, chest pain, neck pain, chills, rigid neck, fever/chilts

Digestive: Nausea, 'diarrhea,' dny mouth,' aronexia,' abnormal liver function,' vorniting, mouth ulcer, gingivitis, thirst Respiratory system: Rhinitis,' pharyngitis,' lung disorder, dyspnea, asthma, epistaxis Nervous system: Nervousness,' dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,' hypertonia, confusion, amnesia, emotional lability, ataxia, tremor Cardiovascutar: Hypotension, hypertension, vasodilation, arrhythmia, syncope

Hemic/Lymphatie: Eosinophilia

Special senses: Amblyonia abnormal vision Metabolic/Nutritional: Hyperplycemia, albuminuria

Musculo-skeletal: Joint disorder

Skin/Appendages: Herpes simplex, dry skin

Urogenitat: Abnormal urine, urinary retention, abnormal ejaculation*
"Incidence ≥5%," Elevated liver enzymes," Oro-facial dyskinesias, *Incidence adjusted for gender

Dose Dependency: In US trials, the only adverse experience more frequent (25% difference) with PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.

Vital Signs Changes: There were no consistent effects or patterns of change in vital signs for patients treated with PROVIGIL in the US trials.

Weight Changes: There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo.

Laboratory Changes: Mean plasma levels of gamma-glutamyl transferase (GGT) were higher tollowing administration of PROVIGIL but not placebo. Few subjects (1%) had GGT elevations outside the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspertate aminotransferase. total protein, albumin, or total bilirubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the

differences were not clinically significant.

ECG Changes: No treatment-ernergent pattern of ECG abnormalities was found in US studies following administration of PROVIGIL.

DRUG ABUSE and DEPENDENCE: Abuse Potential and Dependence: In addition to wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. In vitro, PROVIGIL binds to the doparnine reuptake site and causes an increase in extracellular doparnine but no increase in doparnine release. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously oppanies recessor. Provincia is removing, as executives by its semi-autimissations is inclined as stimulant-trained to self-administer occarine. In some studies PROVIGIL was also partially discriminated as stimulant-like. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (eg, like, Physicians should follow patients closely, especially those with a history of drug and/or stimulant (eg, methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (eg, incrementation of doses or drug-seeking behavior). In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). Patients should be observed for signs of misuse or abuse. Withdrawal: Following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients. OVERDOSAGE: Human Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were abused.

taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day, including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. Overdese Management: No specific antidote to the toxic nausea, diarrhea, and decreased prothrombin time. Overdoses Management: No specific anticide to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarity supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or unnary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

Manufactured for: Cephalon, Inc., West Chester, PA 19380



For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at www.PROVIGIL.com

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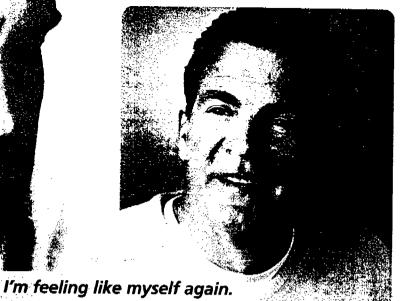
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/IGIL to improve wakefulness



When pure its present with

Lack of ENERGY

Patients with sleep disorders present with various symptoms. PROVIGIL, a unique wakepromoting agent, keeps patients Alert, Aware, Awake all day. And lets them sleep at night.12

Efficacy confirmed by objective and subjective measures of wakefulness in narcolepsy patients.

- 58%-72% of patients showed improvement in CGI-C with PROVIGIL 12*
- Prior stimulant users and newly diagnosed patients both stayed awake longer.3

Works differently.4.51

- PROVIGIL promotes wakefulness without: widespread CNS stimulation in preclinical models.*
- Unlike stimulants. PROVIGIL does not mediate wakefulness by a dopaminergic. mechanism.

Proven safety profile.

- PROMGIL is generally well tolerated. Most frequently reported adverse events weije headache, nausea, negrousness, anxiety, infection and insomnia. Most adverse events were mild to moderate.
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.

Easy to prescribe.

- PROVIGIL, a (V agent, has few prescribing restrictions and low abuse: potential compared to (agents such as methylphenidate or dextroamphetamine.5
- Phone-in prescriptions and refills permitted.
- No triplicate/multiple prescriptions required.

Convenient once-a-day dosing may enhance compliance.

- Recommended dose 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated.

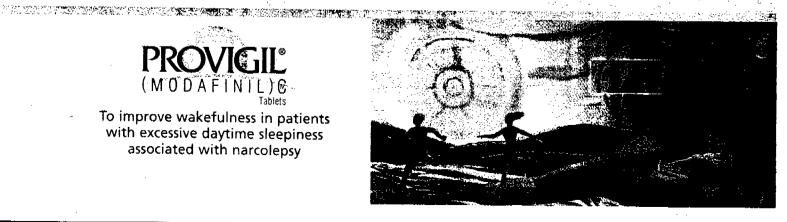
For more information about . PROVIGIL, please call 1-800-896-5855 or visit our Website at www.PROVIGIL.com

- CGI-C: Clinical Global Impression-Change over time, a validated independent physician rating assessment.
 The precise mechanism of action is unknown.
 The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.

References: 1. US Modafinii in Narcolepsy Multicenter Study Group. Ann Neurol. 1998;43:88-97. 2. US Modafinii in Narcolepsy Multicenter Study Group. Neurolo Cephalon, Inc. 4. Lin JS, Hou Y, Jouvet M. Proc Natl Acad Sci USA. 1996;93:14128-14133. 5. Edgar DM, Seidal WF. J Pharmacol Exp Ther. 1997;283:757-769. 6. Phys. Please see brief summary of prescribing information on the adjacent page



To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy







PROVIGIL® (modaffeil) TABLETS

BRIEF SUMMARY: CORE all Package Insert for Complete Prescribing Information

INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated

CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL

PRECAUTIONS: General: Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to

vascular Systems: In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on ECG were observed in 3 s palpitations, dyspinea, and transient ischemic T-wave changes on ECG were observed in 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, armythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic

simulatin user. Fatterits with a recent history of Mi of unstable anglina should be treated with caution. Periodic monitoring of hypertensive patients taking PROVIGIL may be appropriate.

Central Nervous Systems Caution should be exercised when PROVIGIL is given to patients with a history of psychosis.
Patients with Severe Read Impairment: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modafinil acid, but not PROVIGIL itself.

Patients with Severe Hepatic Imp ent: PROVIGIL should be administered at a reduced dose because its clearance is decreased.

Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Atternative or concomitant methods of contraception are recommended during and for 1 month after treatment.

Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL: Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing tetus were not conducted so as to ensure a comprehensive evaluation of the potential of PROVIGIL to adversely affect fertility, or cause embryolethality or teratogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation. **Mustage**. Patients should notify their physician if they are breast feeding. **Concernitant Medications**. Patients should inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, because of the potential for drug interactions. **Alcohot**: It is prudent to avoid alcohol while taking PROVIGIL. **Allergic Reactions**. Patients should notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Drug Interactions**: CNS **Active Drugs**: In a single-dose study, coadministration of PROVIGIL 200 mg with methylphenidate** 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single dose of clomipramine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of either drug. One incident of increased levels of comipramine and its active metabolite desimethylcomipramine has been reported. In a fertility, or cause embryolethality or teratogenicity. Patients should notify their physician if they become

active metabolite desmethylclomipramine has been reported. In a single-dose study with PROVIGIL (50, 100 or 200 mg) and triazolam single-dose study with PHOVIGIL (50, 100 or 200 mg) and triazolam 0.25 mg, no clinically important afterations in the safety profile of either drug were noted. In the absence of interaction studies with monoamine oxidasa (MAO) inhibitors, caution should be exercised. Potential Interactions with Drugs That Inhibit, Induce, or Are Metabolized by Optoberone P-40b Isoenzymes and Other Hepatis Enzymes. Chronic dosing of PROVIGIL 400 mg/day resulted in -20% mean decrease in PROVIGIL plasma trough concentration superstices the DROVIGIL plasma trough concentration suggesting that PHOVIGIL may have caused induction of its metabolism. Coadministration of potent inducers of

CYP3A4 (eg. carbamazepine, phenobarbital, rifampln) or inhibitors of CYP3A4 (eg. ketoconazole, itraconazole) could after the levels of PROVIGIL. Caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on hepatic enzymes for their clearance; some dosage adjustment may be required. Potentially relevant in vivo effects of PROVIGIL based on in vitro data are:

A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed. A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4

substrates (eg. cyclosporine, steroidal contraceptives, theophylline).

An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels of CYP2C9 bubstrates (eg. warfarin, herrytoin).

A reversible inhibition of CYP2C19 may result in higher tevels of CYP2C19 substrates (eg. diazepam, propranolol,

phenytoin, S-mephenytoin).
In some patients deficient in CYP206, the amount of metabolism via CYP2C19 may be substantially larger.
Co-therapy with PROVIGIL may increase levels of some tricyclic antidepressants (eg. clomipramine, designamine).

nasis. Mutapenesis, impairment of Fertility Carcinoge

nests: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rat) the maximum recommended human daily dose of 200 mg on a mg/m² basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the carcinogenic potential in that species has not been fully evaluated. *Mutagenesia*: There was no evidence of mutagenic or clastogenic potential of PROVIGIL. Impairment of Fertility: When PROVIGIL was administered orally to male and fernale rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/mt basis) no effects on fertility were seen. This study did not use sufficiently high doses or large enough sample size to adequately asset

Pregnancy: Pregnancy Category C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVIGIL throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m² basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day (5 times the maximum recommended daily human dose on a mg/m² basis). When rabbits received oral PROVIGIL throughout organogenesis at doses up to 100 mg/kg/dw/ (10 times the maximum recommended daily human dose on a mg/m² basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity, Athrough a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity were oused introduction and section at 10000 up to 200 ingregorary, no decompliance toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweighs the potential risk.

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received PROVIGIL during pregnancy.

Nursing Methers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution should be exercised when PROVIGIL is administered to nursing woman.

PEDIATRIC USE: Safely and effectiveness in individuals below 16 years of age have not been established. GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established.

ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersomnia were given at least 1 dose of PROVIGIL In controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (25%) associated with the use of PRCVIGIL mount frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, nervousness, arraiety, and insomnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (≥1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narcollepsy patients at a rate of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse events.

controlled triass are insted below. Consult till prescribing information on adverse events.

Body as a whole; Headache; chest pain, neck pain, chills, rigid neck, fever/chills

Digestive; Nausea; diarrhea; dry mouth; anorexia; abnormal liver function; vomiting, mouth ulcer, gingivitis, thirst

Respiratory systems: Nervousness; dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia; hypertonia, confusion, anniesia, emotional lability, ataxia, tremor

r. Hypotension, hypertension, vasodilation, arrhythmia, syncope Hemic/Lymphatic: Eosinophilia

Special senses: Amblyopia, abnormal vision Special senses. Anterprepa, autorina disconsiderationals. Hyperglycemia, albuminuria Musculo-skeletal: Joint disorder

1985: Heroes simplex, dry skin Uregenital: Abnormal urine, urinary retention, abnormal ejaculation

"Incidence 25%, 'Elevated liver enzymes,' Oro-facial dyskinesias,' Incidence adjusted for gender.
Dose Dependency: In US trials, the only adverse experience more frequent (25% difference) with PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.

Vital Signs Changes: There were no consistent effects or patterns of change in vital signs for patients treated with PROVIGIL in the US trials.

Weight Changes: There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo.

Laboratory Champes: Mean plasma levels of gamma-glutamyl transferase (GGT) were higher following

administration of PROVIGIL but not placebo. Few subjects (1%) had GGT elevations outside the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the nces were not clinically significant

nges: No treatment-emergent pattern of ECG abnormalities was found in US studies following administration of PROVIGIL.

DRUG ABUSE and DEPENDENCE: Abese Potential and
Dependence: In addition to wakefulness-promoting effect and

increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphonic effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimularits. In vitro, PROVIGIL binds to the dopamine reuptake site and causes an increase in extracellular dopamine but no increase in dopamline release. PROVICIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies PROVIGIL was also partially discriminated as stimulantlike. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (eg, methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (eg. incrementation of doses or drug-sesting behavior). In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled

CRS stimulars (methylenidate), Patients should be observed for signs of misuse or abuse.

Withdrawait: Following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawai were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.

OVERDOSAGE: Human Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum OVENDOSAGE: Hamman Experimental: A total on 131 doses of ≥1000 mg/day to times me maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia, and slight or moderate. evations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day, including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, termor, palpatations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. **Dverdose Management:** No specific arridote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or uniary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

Manufactured for: Cophalon, Inc., West Chester, PA 19380



For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at www.PROVIGIL.com

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Jan 2001

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ove wakefulness



I can participate in more activities during the day.

When patie

Efficacy confirmeds by objective and subjective measures of wakefulness in tarcolepsy (

sleepiness and

ecreased ACTIV

various symptoms. PROVIGIL, a unique wakeare, Awake all day. And lets them sleep at night.12

safety profile.

GIL is generally well ited. Most frequently ted adverse events headache, nausea, usness, anxiety, tion and insomnia. adverse events ild to moderate.

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Low abuse potential.

- PROVIGIL, a (V agent, has fewer prescribing restrictions than @agents such as methylphenidate or dextroamphetamine.
 - Phone-in prescriptions and refills permitted.
- No triplicate/multiple prescriptions required.

Convenient once-a-day dosing may enhance compliance.

- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated.

For more information about. PROVIGIL, please call 1-800-896-5855 or visit our. Website at www.PROVIGIL.com

ESS: Epworth Sleepiness Scale, a validated patient self-questionnaire that provides a subjective measurement of sleepiness.

† The precise mechanism of action is unknown.

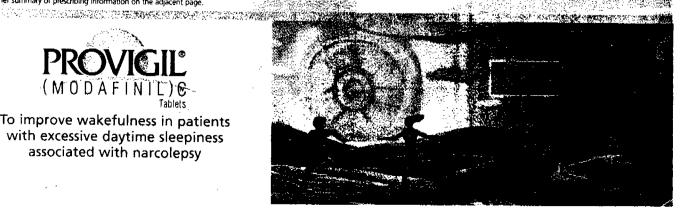
† The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.

References: 1. U.S. Modalinil in Narcolepsy Multicenter Study Group. Ann Neurol. 1998;43:88-97: 2. U.S. Modalinil in Narcolepsy Multicenter Study Group. Neurology. 2000;54:1166-1178. 3. Schwarts 1189 K.Z.J. Sleep. 2000;23(suppl 2):A306. 4. Data on file, Cephalon, Inc. 5. Lin J.S. Hou Y. Jouwet M. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M.F. Philipself Acad Sci U.S.A. 1996;93:14128-14133. 6. Edgar DM. Seidal M

Pléase see brief summary of prescribing information on the adjacent page



To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy







PROVIGIL® (modafinii) TABLETS

BRIEF SUMMARY: Consult Package insert for Complete Prescribing information INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.

CONTRAINORCATIONS: Known hypersensitivity to PROVIGIL

PRECAUTIONS: General: Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to

Cardiovascular System: In clinical studies of PROVIGIL, signs and symptoms including chest pain Cardiovascular System: In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on ECG were observed in 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic monitoring of hypertensive patients taking PROVIGIL may be appropriate.

Central Nervous System: Caution should be exercised when PROVIGIL is given to patients with a history of psychosis. Patients with Server Renal Impairment: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modafinil acid, but not PROVIGIL itself.

Patients with Servery Necessite Impairment. Treatment (2007)

Patients with Severy Heartic Importunent: PROVIGIL should be administered at a reduced dose because

Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Alternative or concomitant methods of contraception are recommended during and for 1 month after treatment.

Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL: Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing fetus were not conducted so as to ensure a comprehensive evaluation of the potential of PROVIGIL to adversely affect fertility, or cause embryolethality or teratogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased pregnant or intent to become pregnant during ineraby. They should be cautioned or the potential increase risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation. *Nursing:* Patients should notify their physician if they are breast feeding. *Concomitant Medication:* Patients should inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, because of the potential for drug interactions. *Aleaber*: It is prudent to avoid alcohol while taking PROVIGIL. *Allengic Reactions:* Patients should notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Drug interactions: CNIS Active Drugs: In a single-dose study, coadministration of PROVIGIL 200 mg with the properties of the properties

methylphenidate 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single dose of comipramine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of

either drug. One incident of increased levels of ctomipramine and its active metabolite desmethylclomipramine has been reported. In a single-dose study with PROVIGIL (50, 100 or 200 mg) and triazolam 0.25 mg, no clinically important alterations in the safety profile of either drug were noted. In the absence of interaction studies with monoamine oxidase (MAO) inhibitors, caution should be evercised Potential Interactions with Druce That Inhibit Induce exercised. Potential Interactions with Drugs That Inhibit, Induce, or Are Metabolized by Cytochrone P-456 Isoenzymes and Other Hepatie Enzymes: Chronic dosing of PROVIGIL 400 myday resulted in -20% mean decrease in PROVIGIL plasma trough concentration suggesting that PROVIGIL may have caused induction of its metabolism. Coadministration of potent inducers of

CYP3A4 (eg., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg., ketoconazole, itraconazole) could after the levels of PROVIGIL. Caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on hepatic enzymes for their clearance; some dosage adjustment may be required. Potentially relevant in vivo effects of PROVIGIL based on in vitro data are: A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed.

A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4

substrates (eq. cyclosporine, steroidal contraceptives, theophylline). An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher in of CYP2C9 substrates (eg. warfarin, phenytoin).

A reversible inhibition of CYP2C19 may result in higher levels of CYP2C19 substrates (eg. diazepam, propranolol,

phenytoin, S-mephenytoin). In some patients deficient in CYP2D6, the amount of metabolism via CYP2C19 may be substantially larger Co-therapy with PROVIGIL may increase levels of some tricyclic antidepressants (eg. clomipramine,

irment of Fortility

Carcinogenesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rai) the maximum recommended human daily dose of 200 mg on a mg/m² basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the carcinogenic potential in that species has not been fully evaluated. **Mutagements*: There was no evidence mutagenic or classogenic potential of PROVIGIL. **Impalment of FertiMity*: When PROVIGIL was admir subt: There was no evidence of tered orally to make and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/mp basis) no effects on fertility were en. This study did not use sufficiently high doses or large enough sample size to adequately assess effects

Preparatory: Pregnancy Category C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVIGIL throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m² basks) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day (5 times the maximum recommended daily human dose on a mg/m² basis). When rabbits received oral PROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended daily human dose on a mg/m² basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential loxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweights the potential risk.

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received PROVIGIL during pregnancy.

Nersing Methers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution exercised when PROVIGIL is administered to nursing woman.

PEDIATRIC USE: Salely and effectiveness in individuals below 16 years of age have not been established GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established. ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersorinnia were given at least 1 dose of PROVIGIL. In controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (>5%) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea. than paceborheated patients in controlled to 3 and notes were resident, nection, necrousness, anxiety, and insomnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (≥1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narcolepsy patients at a of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse events.

Body as a whele: Headache,' chest pain, neck pain, chills, rigid neck, fever/chills Digestive: Nausea' diarrhea,' dry mouth,' anorexia, 'abnormal liver function,' vorniting, mouth ulcer, gingivitis, thirst Respiratory system: Rhinitis, pharyngitis, lung disorder, dyspinea, asthma, epistavis Nervous system: Nervousness, dizziness, depression, anxiety, cataplexy, insomnia, paresthesia,

dyskinesia, hypertonia, confusion, amnesia, emotional lability, ataxia, tremor Cardievascular: Hypotension, hypertension, vasodilation, arrhythmia, syncope nekatic: Eosinophilia

Special senses: Ambivopia, abnormal vision nat: Hyperglycemia, albuminuria

sente chatetat: Joint disorder

endages: Herpes simplex, dry skin

Uropenitat: Abnormal urine, urinary retention, abnormal ejaculation⁴ ¹Incidence ≥5%,³Elevated liver enzymes,³Oro-facial dyskinesias,⁴Incidence adju

Desa Dependency: In US trials, the only adverse experience more frequent (≥5% difference) with PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.

Vital Shanes Changes: There were no consistent effects or patterns of change in vital signs for patients.

with PROVIGIL in the US trials.

Weight Changes: There were no clinically significant differences in body weight change in patients ed with PROVIGIL compared to placebo Laboratory Changes: Mean plasma levels of gamma-olutarnyl transferase (GGT) were higher following

administration of PROVIGIL but not placebo. Few subjects (1%) had GGT elevations outside the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the rences were not clinically significant.

ECG Changes: No treatment-emergent pattern of ECG abnormalities was found in US studies following administration of PROVIGIL.

DRUG ABUSE and DEPENDENCE: Abuse Potential and Dependence: In addition to wakefulness-promoting effect and

increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. *In vitro*, PROVIGIL binds to the doparnine reuptake site and causes an increase in extracellular doparnine but no increase in doparnine release. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies PROVIGIL was also partially discriminated as stimulantunied to serradininster counter. In solins acutes province, was also put to be understanding as suit interests of the service abuse (eg. incrementation of doses or drug-seeking behavior). In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenicidale). Patients should be observed for signs of nisuse or abuse.

Withdrawal: Following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawal were abused to the observed for attention of the observed for signs of nisuse or abuse. incrementation of doses or drug-seeking behavior). In individuals experienced with drugs of

observed during 14 days of observation, although sleepiness returned in narcoleptic patients.

OVERDOSAGE: Humae Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or apitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses >1000 mg/day, including apperience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep distructiones, nausea, diarrhea, and decreased prothrombin time. Overdose Management: No specific antidote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or urinary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

Manufactured for: Cephalon, Inc., West Chester, PA 19380



For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at www.PROVIGIL.com

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PR0225

Jan 2001

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ove wakefulness



I am able to be more active during the day.

en patie

Effects confirmed to by objective and subjective measures vakefulne

- Prior stanulant users and newly diagnosed patients both stayed awake longer

n sleepiness and

ecreased ACTIVI

various symptoms. PROVIGIL, a unique wakeare, Awake all day. And lets them sleep at night.12

safety profile.

GIL is generally well ited. Most frequently ted adverse events headache, nausea, usness, anxiety, ion and insomnia

description and the second sec are inletabolized by cytochrome P450 isoenzymes.

Easy to prescribe.

- has few prescribing restrictions and low abuse potential compared to (ii agents such as methylphenidate or dextroamphetamine.7
 - -- Phone-in prescriptions and refills permitted.
- No triplicate/multiple prescriptions required.

Convenient once-a-day dosing may enhance compliance.

- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated.

For more information about PROVIGIL, please call 1-800-896-5855 or visit our Website at www.PROVIGIL.com

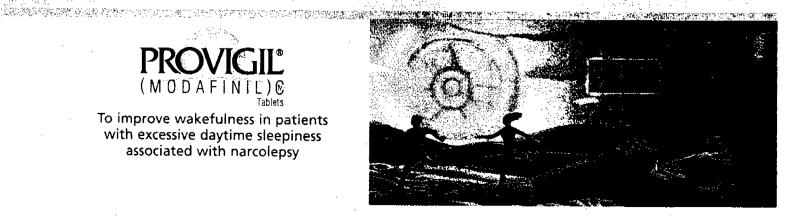
- * ESS. Epworth Sleepiness Scale; a validated patient self-questionnaire that provides a subjective measurement of sleepiness.
 † The precise mechanism of action is unknown.
 ‡ The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.

References: 1. US Modafinil in Narcolepsy Multicenter Study Group. Ann Neurol. 1998;43:88-97. 2. US Modafinil in Narcolepsy Multicenter Study Group. Neurology. 2000;54:1166-1175. 3. Schwartz JR, et al. [Abstract 1189.K2]. Sieep. 2000;23(suppl 2):A306. 4. Data on file, Cephalon, Inc. 5. Un JS, Hou Y, Jouvet M. Proc Natl Acad Sci USA. 1996;93:14128-14133. 6. Edgar DM, Seidal WF. J Pharmacol Exp. This: 1997;283:757-769. 7. Physician's Desk Reference, current edition.

Please see brief summary of prescribing information on the adjacent page.



To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy







PROVIGIL® (modafinii) TABLETS

BRIEF SUMMARY: Cons alt Package lusert for Complete Prescribing information

INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated

CONTRAINDICATIONS; Known hypersensitivity to PROVIGIL

PRECAUTIONS: General: Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy with not adversely affect their ability to

Cardiovascular System: In clinical studies of PROVIGIL, signs and symptoms including chest pain, Cartinuagectar opstants, in canical studies of PHOVISIL, styris and symptoms including chest pain, palpitations, dyspinea, and transient ischemic T-wave changes on ECG were observed in 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PPOVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve protapse in association with CNS stimulant use. Patients with a recent history of Mil or unstable angina should be treated with caution. Periodic

softlinging use, if auctions with a recent meaning or who is introduce original shows use weather which abused in recent monitoring of hypertensive patients taking PROVIGIL may be appropriate.

Combat Network System: Caution should be exercised when PROVIGIL is given to patients with a history of psychosis. Patients with Severe Reads Impairment: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modafinil acid, but not PROVIGIL itself.

Patients with Severe Hepatic Impair ent: PROVIGIL should be administered at a reduced dose because

Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Alternative or concomitant methods of contraception are recommended during and for 1 month after treatment.

Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL: Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing fetus w not conducted so as to ensure a comprehensive evaluation of the potential of PROVIGIL to above affectivity, or cause embryolethality or teratogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased pregnant or intensity to become pregnant usually userably. They should be caused to one possible and risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation. *Neursing*: Patients should notify their physician if they are breast feeding. Concomitant Medication: Patients should inform their physician if they are taking or plan to take any prescription or over-the-courter drugs, because of the potential for drug interactions. Alcohol: It is prudent to avoid alcohol while taking PROVIGIL. Allergic Reactions: Patients should notify their physician if

they develop a rash, hives, or a related allergic phenomenon.

Drug Interactions: CNS Active Orage: in a single-dose study, coadministration of PROVIGIL 200 mg with methylphenidate 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single dose of clomipramine 50 ng with PROVIGIL 200 mg/day did not affect the pharmacokinetics of either drug. One incident of increased levels of clomipramine and its

active metabolite desmethylclomipramine has been reported. In a single-dose study with PROVIGIL (50, 100 or 200 mg) and triazolam 0.25 mg, no clinically important alterations in the safety profile of either drug were noted. In the absence of interaction studies with monoamine oxidase (MAO) inhibitors, caution should be exercised. Potential Interactions with Drugs That Inhibit, Induce, or Ars Metabolized by Cytochrome P-468 isoenzymes and Other Hepatic Enzymes: Chronic dosing of PROVIGIL 400 mg/day resulted in -20% mean decrease in PROVIGIL plasma trough concentration suggesting that PROVIGIL may have caused induction of its metabolism. Coadministration of potent inducers of

CYP3A4 (eg. carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg. ketoconazole, itraconazole) could alter the levels of PROVIGIL. Caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on hepatic enzymes for their clearance, some dosage adjustment may be required. Potentially relevant in vivo effects of PROVIGIL based on in vitro data are:

A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed.

A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4 substrates (eg, cyclosporine, steroidal contraceptives, theophylline).

An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels

of CYP2C9 substrates (eg, warfarin, phemytoin).

A reversible inhibition of CYP2C19 may result in higher levels of CYP2C19 substrates (eg. diazepam, propranolol,

phenytoin, S-membersytoin).
In some patients deficient in CYP2D6, the amount of metabolism via CYP2C19 may be substantially larger. Co-therapy with PROVIGIL may increase levels of some tricyclic antidepressants (eg. clomipramine,

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Carcinogenesis, Nutagenesis, impairment of Ferumay

Carcinogenesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or

3 times (rat) the maximum recommended human daily dose of 200 mg on a mg/m² basis. There was
no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because
the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the
carcinogenic potential in that species has not been fully evaluated. Matagenesis: There was no evidence of
mutagenic or clastogenic potential of PROVIGIL. Impairment of Fertility: When PROVIGIL was administered acably to make and famale rate princ to and throughout making and nectation at up to 100/providence. tered orally to male and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/m² basis) no effects on fertility were seen. This study did not use sufficiently high doses or large enough sample size to adequately assess effects

ncy Calegory C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVIGIL throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these affects was 100 mg/kg/day resorption, hydronephrosis, and sizema variations, the not-effect dose for these effects was for myrkgroup (5 times the maximum recommended daily human dose on a mg/m² basis). When rabbits received on a PROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended daily human dose on a mg/m² basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweighs the potential risk.

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received PROVIGIL during pregnancy.

Nersing Mothers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution should be exercised when PROVIGIL is administered to nursing woman.

PEDIATRIC USE: Safety and effectiveness in individuals below 16 years of age have not been established. GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established. ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersomnia were given at least 1 dose of PROVIGIL. In controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (25%) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, neuerousness, aroiety, and insomnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (21%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narrolepsy patients at a rate of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are fisted below. Consult full prescribing information on adverse events.

Body as a whole: Headache, 'chest pain, neck pain, chills, rigid neck, fever/chills provided the patients of the provided trials are streamed to the provided trials are streamed to the patients of the provided trials are streamed to the provided trials are streamed to the patients of the provided trials are streamed to the provided trials are the provided trials are the provided trials are streamed to the provided trials are the patients and the provided trials are the

Respiratory system: Rhimits, pharyngits, lung disorder, dyspnea, asthma, epistaxis
Nervous system: Nervousness, dizziness, depression, anxiety, cataplexy, insormia, paresthesia, dyskinesia, hypertonia, confusion, amnesia, emotional lability, ataxia, tremor

Cardiovascular: Hypotension, hypertension, vasodilation, arrhythmia, syncope

c/Lymphatie: Eosinophilia

Special senses: Ambiyopia, abnormal vision Metabolic/Nutritional: Hyperglycemia, albuminuria

sculo-skeletat: Joint disorde adages: Heroes simplex dry skin

Urogenital: Abnormal urine, urinary retention, abnormal ejaculation

Incidence ≥5%, Elevated liver enzymes, Pro-facial dyskinesias; Incidence adjusted for gender.

Dose Dependency: In US trials, the only adverse experience more frequent (≥5% difference) with PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.

Vital Signs Changes: There were no consistent effects or patterns of change in vital signs for patients treated with PROVIGIL in the US triefs.

Weight Changes: There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo.

Laboratory Changes: Mean plasma levels of gamma-glutamyl transferase (GGT) were higher follow

administration of PROVIGIL but not placebo. Few subjects (1%) had GGT elevations cutside the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the ces were not clinically significant.

ECG Changes: No treatment-emergent pattern of ECG abnormalities was found in US studies following administration of PROVIGIL.

DRUG ABUSE and DEPENDENCE: Abuse Potential and Dependence: In addition to wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euph alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. In vitro, PROVIGIL binds to the dopamine reputative site and causes an increase in extracellular dopamine but no increase in dopamine release. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies PROVIGIL was also partially discriminated as stimulant-His Physicians should follow patients closely, especially those with a history of drug and/or stimulant (e.g., methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (eg., incrementation of doses or drug-seeking behavior). In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feekings consistent with other scheduled CNS stimulants (methylphenidate). Patients should be observed for signs of misuse or abuse. Witadrawat: Following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawal were observed from a continuous of observed them.

Withdrawait: Following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in nanoteleptic patients.

DYERDOSASE: Human Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or agritation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day, including assessment with the 21 measurement of fiday. including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sieep disturbances, nausea, diarrhea, and decreased prothrombin time. Overhance Management: No specific antidote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive detects of Province overloads are over numeroused. Overloaded surpout or managed what premaring supporting care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or uninary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

Manufactured for: Cophalon, Inc., West Chester, PA 19380



For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at www.PROVIGIL.

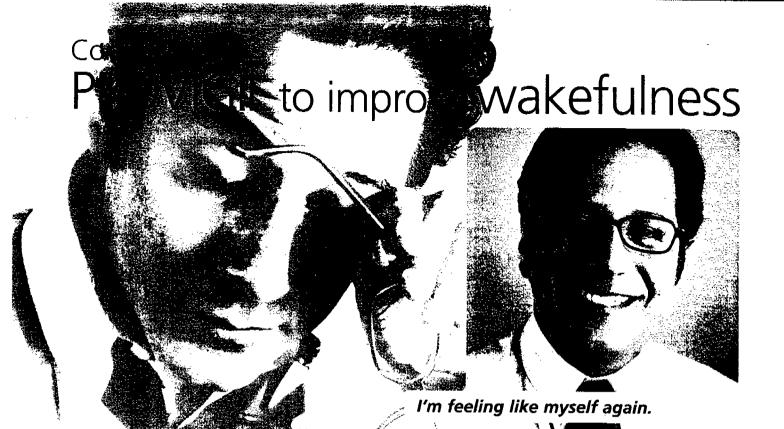
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PRO228

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When patients complain of feeling

FATIGUED or TIRED

Patients with sleep disorders present with various symptoms. PROVIGIL, a unique wakepromoting agent, keeps patients Alert, Aware, Awake all day. And lets them sleep at night.12

Efficacy confirmed by objective and subjective measures of wakefulness in: narcolepsy patients.12

- 58%-72% of patients showed improvement in CGI-C with PROVIGIL *
- · Does not interfere with nighttime sleep architecture or sleepduration.

Works differently.3At

- PROVIGIL promotes wakefulness without widespread CNS stimulation in preclinical models.*
- PROVIGIL acts selectively in areas of the brain believed to regulate normal wakefulness.
- Unlike sumulants, PROVIGIL does not mediate wakefulness by a dopaminergic mechanism.

- PROVIGIL is generally well tolerated. Most frequently reported adverse events were headache, nausea, nervousness, anxiety, infection and insomnia. Most adverse events were mild to moderate.
- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.

Proven safety profile. Low abuse potential. Convenient

- PROVIGIL, a (V agent, has fewer prescribing restrictions than @agents such as methylphenidate or dextroamphetamine.
 - Phone-in prescriptions and refills permitted.
- No triplicate/multiple prescriptions required.

once-a-day dosing may enhance compliance.

- Recommended dose: 200 mg taken once daily in the morning.
- 200 mg and 400 mg doses are effective and generally well tolerated.

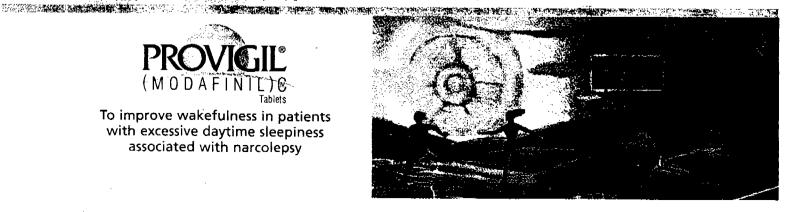
For more information about PROVIGIL, please call 1-800-896-5855 or visit our Website at www.PROVIGIL.com

* CGI-C: Clinical Global Impression-Change dues tisse, a validated independent physician rating assessment.
† The precise medianism of action is unknown.
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† The relationship of these findings in animals to file effects of PROVIGIL in humans has not been established.

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* References: 1; US Modafinii in Narcolepsy Multicenter Study Group. Neurology. 2000;54:1166-1175. 3. Lin JS, Hou Y, Jouvet M. Proc Natl Acad Sci USA. 1996;93:14128-14133. 4. Edgar DM, Seidal WF. J Pharmacol Exp Ther. 1997;283:757-769. 5. Physician's Desk Reference, current edition. Please see brief summary of prescribing information on the adjacent page.

To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy





Sleep Test

Sleep Facts ©

Sleep Stages 9

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Resources

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Sleep Centers

Reimbursement

Materials

Alert Aware Awake™



Interactive Sleep Test

Do you suffer from excessive daytime sleepiness?

The following questionnaire will help you measure your general level of daytime sle you to rate the chances that you would doze off or fall asleep during different, routi situations. Answers to the questions are rated on a reliable scale called the Epwort Scale (ESS). Each item is rated from 0 to 3, with 0 meaning you would never doze given situation, and 3 meaning that there is a very high likelihood that you would d in that situation.

How likely are you to doze off or fall asleep in the following situations, in contrast t tired? Even if you haven't done some of these things recently, think about how the affected you.

Use the following scale to choose the most appropriate number for each situation:

) = would never doze	2 = moderate chance of dozing
L = slight chance of dozing	3 = high chance of dozing

Situation	Chanc	e of
Situation	Ç	3 .
Sitting and reading	(\subset
Watching television	(\subset
Sitting inactive in a public place, for example, a theater or meeting	©	\subset
As a passenger in a car for an hour without a break	(\subset
Lying down to rest in the afternoon	©	Γ
Sitting and talking to someone	(\subset
Sitting quietly after lunch (when you've had no alcohol)	©	$\overline{}$
In a car, while stopped in traffic	©	\subset
Your Score	<u> </u>	

rant Printage Massiciate

The Epworth Sleepiness Scale key

Total score of less than 10 suggests that you are not suffering from excessive dayti

A total score of 10 or more suggests that you may need further evaluation by a ph

determine the cause of your excessive daytime sleepiness and whether you have a sleep disorder.

This scale is not intended to be a medical diagnosis. Only your physician can accura whether you may suffer from a sleep disorder.

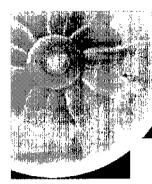
The Epworth Sleep Scale is an informational tool to help you identify your own leve sleepiness, which is a symptom of many sleep disorders. If your score is 10 or mor this information with your physician. Be sure to describe all your symptoms, as cle to aid in your diagnosis and treatment.

It is important to remember that true excessive daytime sleepiness is almost alway underlying medical condition that can be easily diagnosed and effectively treated.

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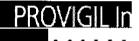
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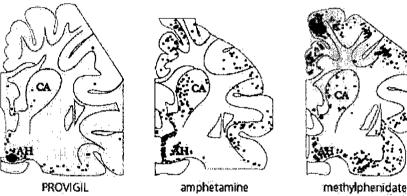
PROVIGIL Information

PROVIGIL Summary

PROVIGIL is a unique wake-promoting agent indicated to improve wakefulness in p excessive daytime sleepiness associated with narcolepsy. PROVIGIL keeps patients Awake™ all day and won't interfere with the architecture of nighttime sleep or with ability to fall asleep when needed.

PROVIGIL works differently from stimulants in preclinical mode

Highly selective CNS activity, distinct from amphetamine and methylphenidate



CA = caudate AH = arcerior hypothalamus Data adapted from Lin, Hou, Jouvet, 1996, study in calc

- PROVIGIL promotes wakefulness without widespread CNS stimulation.
- PROVIGIL acts selectively in areas of the brain believed to regulate normal w
- Unlike stimulants, PROVIGIL does not mediate wakefulness by a dopaminerg

Pharmacologic activities in	n preciinical m	odels ²	
	PROVIGIL	Amphetamine	Methylphenidate
Wakefulness	++	++	++
Locomotor activity	-/+	++	++
Stereotypy	-	++	++
Anxiety	-	++	++
Intense NREM rebound	-	++	++
Blood pressure	-	+	+
Heart rate	-	+ .	+
	- = no activity	-/+ = minimal activit	y ++ marked activity

^{*} The relationship of these findings in animals to the effects of PROVIGIL in humans has not been

PROVIGIL promotes wakefulness without affecting nighttime sl

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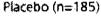
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A CONTRACTOR OF THE CONTRACTOR

- PROVIGIL efficacy established, objectively and subjectively, in the largest Ph conducted in patients with narcolepsy.
- PROVIGIL did not interfere with the architecture of nighttime sleep after 9 w treatment, as shown below, compared to plecebo.4







PROVIGIL 200 mg and 400 mg (r

PROVIGIL has a proven safety profile

- PROVIGIL is generally well tolerated.
- Long-term safety has been established for up to 136 weeks in open-label stu
- Most frequently reported adverse events were headache, nausea, nervousne infection and insomnia. Most adverse events were mild to moderate. PROVIG with drugs that inhibit, induce or are metabolized by cytochrome P450 isoen

PROVIGIL has low potential for abuse

PROVIGIL (Modafinil) is listed in Schedule IV of the Controlled Substances Act.

Adapted from the Key to Controlled Substances Categories

C-IV (MODAFINIL):

LOW POTENTIAL FOR ABUSE. Use may lead to limited physical or may be oral or written up. Up to 5 renewals are permitted within 6 months.

C-II (AMPHETAMINE & METHYLPHEN

HIGH POTENTIAL FOR ABUSE. Use ma severe physical or psychological depende psychological dependence. Prescriptions Prescriptions must be written in ink, or ty signed by the practitioner. Verbal prescri confirmed in writing within 72 hours, and only in a genuine emergency. No renewal permitted.

Convenient once-a-day dosing

- PROVIGIL provides the convenience of once-daily dosing.
- The recommended dose for PROVIGIL is 200 mg taken orally once daily in th

• PROVIGIL doses 200 mg and 400 mg QD, were shown to be effective compa

PROVIGIL is easy to prescribe

	Schedule	Multiple Forms	Refills
PROVIGIL ^{1,2}	C-IV	NO	YES*
Methylphenidate ^{7,8}	C-II	Yes	No
Dextroamphetamine ^{7,9}	C-II	Yes	No
*Up to 5 refills permitted within 6	months.		

- Written and phone-in prescriptions are permitted.
- Refills are permitted.
- No triplicate or multiple prescriptions are required.

The following links contain more detailed information about PROVIGIL:

Efficacy
Safety
Dosage and Patient Selection
Drug Interactions

For more information about PROVIGIL, contact Cephalon Professional Services at 1

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References:

- Lin JS, Hou Y, Jouvet M. Potential brain neuronal targets for amphetamine-, methylphenida induced wakefulness, evidenced by c-fos immunocytochemistry in the cat. Proc Natl Acad S 1996;93:14128-14133.
- 2. Edgar DM, Seidal WF. Modafinil induces wakefulness without intensifying motor activity or hypersomnolence in the rat. J Pharmacol Exp Ther. 1997;283:757-769.
- 3. IMS NPA Audit.
- 4. Data on file, Cephalon, Inc.
- 5. Physicians' Desk Reference, current edition.
- 6. PROVIGIL full prescribing information.
- 7. Physician's Desk Reference, current edition.
- 8. Ritalin® (methylphenidate HCl) prescribing information. Novartis Pharmaceuticals.
- 9. Dexedrine® (dextroamphetamine sulphate) prescribing information. GlaxoSmithKline Phar

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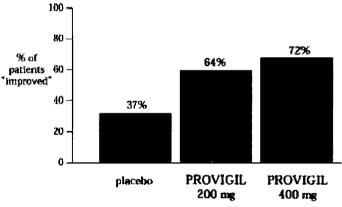
PROVIGIL Ir

Promotes daytime wakefulness . . . without affecting ni sleep

PROVIGIL efficacy established, objectively and subjectively, in Phase 3 trials ever conducted in patients with narcolepsy

- Two double-blind, placebo-controlled, 9-week U.S. studies; patients (N=558 ICD-9 and American Sleep Disorders Association criteria for narcolepsy were centers (one 18-center study and one 21-center study)
- Patients in both studies were randomized to a daily dose of 200 mg PROVIGI PROVIGIL, or placebo
- Significant improvements were observed in both studies -- by sleep lab mea MSLT), by physicians in clinical practice (CGI-C), and by their patients with daytime sleepiness (EDS) associated with narcolepsy (ESS)

PROVIGIL efficacy confirmed by physicians in a clinical setting



P<0.001 vs placebo.

18-center study: CGI-C at endpoint

- * there was no statistical difference between the 200 mg and the 400 mg dose groups
 - In the 18- and 21-center studies, 58% to 72% of patients receiving PROVIGI improvement, compared to 37% to 38% with placebo

PROVIGIL efficacy established in the sleep laboratory

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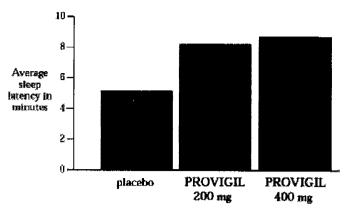
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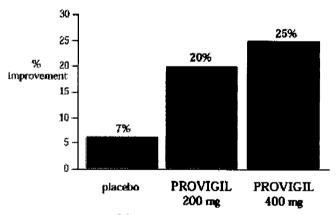


P<0.001 vs placebo.

18-center study: MWT at endpoint

- st there was no statistical difference between the 200 mg and the 400 mg dose groups
 - In the 18- and 21-center studies, PROVIGIL increased daytime wakefulness sleep latency 47% to 76% vs placebo (P<0.001)
 - PROVIGIL also increased time to sleep onset on the MSLT
 - Nighttime sleep measured with nocturnal polysomnography was not affected

Improves patients' ability to stay awake and participate in daily PROVIGIL efficacy documented by patients



P<0.001 (based on **ESS** change scores vs placebo).

18-center study: ESS at endpoint

- * there was no statistical difference between the 200 mg and the 400 mg dose groups
 - In the 18- and 21- center studies, PROVIGIL improved patients' ability to pa activities by 20% to 32%
 - Patients reported improved ability to participate in daily activities-such as sit watching television, or sitting and talking to someone

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Definitions:

Maintenance of Wakefulness Test (MWT)

The Maintenance of Wakefulness Test (MWT), a 20-minute assessment of sleep late administered 4 to 5 times a day at 2-hour intervals, beginning 2 hours after noctur polysomnography, measured time to sleep onset after a patient is instructed to re seated in a dark room without stimulus.

Multiple Sleep Latency Test (MSLT)

The Multiple Sleep Latency Test (MSLT) is similar to the MWT. However, the MSLT MWT in that it measures the time to sleep onset after a patient is instructed to fall lying down in a dark room without stimulus.

Clinical Global Impression of Change (CGI-C)

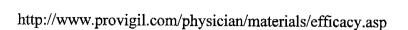
In the Clinical Global Impression of Change (CGI-C), an independent physician clini patients at baseline and post-baseline visits. To prevent potential bias, evaluators treatment groups as well as to results from other efficacy measures. Patients who i included those who were minimally, much, or very much improved.

Epworth Sleepiness Scale (ESS)

In the Epworth Sleepiness Scale (ESS), patients rated the likelihood of falling aslee performing 8 non-stimulating daily activities.

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<u>PROVIGIL In</u>

Safety

PROVIGIL is generally well tolerated.1

- Most frequently reported adverse events were headache, nausea, nervousne infection and insomnia. Most adverse events were mild to moderate.
- In double-blind 9-week studies:
 - o No significant difference vs placebo in the incidence of elevated liver f
 - No clinically significant change in hemodynamic parameters such as h blood pressure.

PROVIGIL has a proven safety profile

- 136-week study demonstrates long-term safety profile of PROVIGIL.²
- No significant difference in the incidence of elevated liver function enzymes i treated patients vs placebo, 3% and 2% respectively.¹
- No clinically significant change in hemodynamic parameters such as heart ra pressure.¹

PROVIGIL does not disrupt nighttime sleep patterns.^{3,4}

- Won't interfere with patients' ability to fall asleep when needed.
- PROVIGIL did not interfere with the architecture of nighttime sleep after 9 w treatment, as shown below, compared to placebo.²
 - o No statistical difference vs placebo in nighttime sleep duration.



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- Safety ©
- Dosage ©
- Interactions ©



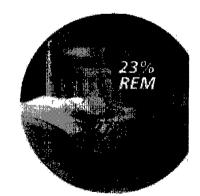
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Placebo (n=185)



PROVIGIL 200 mg and 400 mg ()



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Dosage and Administration

PROVIGIL provides the convenience of once-daily dosing

- The recommended dose for PROVIGIL is 200 mg taken orally once daily in th
- The 200mg and 400mg doses are effective and generally well tolerated
- Steady state is reached within 2-4 days; physician may choose to evaluate p after one week.
- The 15-hour half-life of PROVIGIL supports once-daily dosing in the morning
- PROVIGIL can be taken with or without food, although food delays the absor hour.
- In elderly patients, a lower dose should be considered.
- In patients with severe hepatic impairment, PROVIGIL should be administere recommended dose (i.e. 100mg).

PROVIGIL offers convenience for both patients and physicians

	Scheaule	Triplicate Forms	Refills
PROVIGIL ^{1,2}	C-IV	NO	YES*
Methylphenidate ^{2,3}	C-II	Yes	No
Dextroamphetamine ^{2,4}	C-II	Yes	No
*Up to 5 refills permitted within 6	months.		

- Written and phone-in refills are permitted.
- Triplicate RX forms are not required.

Switching to PROVIGIL is easy

Select the approach that works best for your patients.*

	Day 1	Day 2	Day 3
No washout	Stop methylphenidate at 4 PM	Next AM start PROVIGIL 200 mg/day	Continue PROVIGIL 200 mg/day
With washout	Stop methylphenidate at 4 PM	No drug	No drug
Step down	Reduce methylphenidate	Maintain methylphenidate dose;	Reduce methylphenidate dose by an additional 20%-40%;

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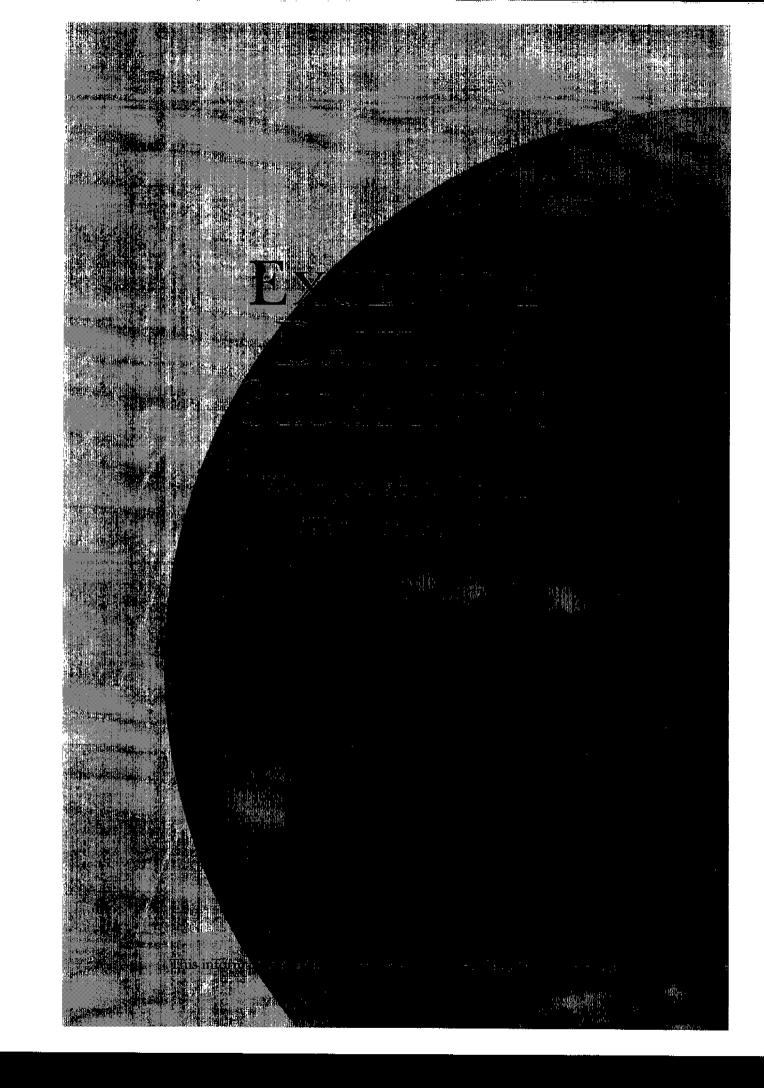
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Sitting inactive in a public place, for example, a theater or meeting
As a passenger in a car for an hour without a break
Lying down to rest in the afternoon
Sitting and talking to someone
Sitting quietly after lunch (when you've had no alcohol)

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American Sleep Disorders Association (ASDA)

1610 14th Street NW, Suite 300, Rochester, MN 55901

To receive a list of sleep centers with physicians who specialize in the management of sleep disorders, contact the ASDA through their Web site, by e-mail, or by sending a self-addressed stamped envelope to the above address.

American Sleep Apnea Association (ASAA)

2025 Pennsylvania Avenue NW, Suite 905, Washington, DC 20006

Tel: (202) 293-3650 Fax: (202) 293-3656

Web site: http://asaa.nicom.com

The ASAA is a nonprofit organization that promotes awareness of sleep apnea in order to reduce injury, disability, and death from this common but treatable disorder. The ASAA serves as an advocate for people affected by sleep apnea, sponsors the ASAA A.W.A.K.E. Network of support groups, and publishes an educational newsletter.

Narcolepsy Network

PO Box 42460, Cincinnati, OH 45242

Tel: (513) 891-3522 Fax: (513) 891-9936

Web site: http://www.websciences.org/namet

The Narcolepsy Network is a national, nonprofit, patient-based organization whose members are people who have narcolepsy (or related sleep disorders), their families and friends, and professionals involved in treatment, research. and public education.

National Sleep Foundation (NSF)

729 Fifteenth Street NW, Fourth Floor, Washington, DC 20005

E-mail: natsleep@erols.com Web site: http://www.sleepfoundation.org The NSF is a national nouprofit organization dedicated to improving the lives of the millions of Americans who suffer from sleep disorders, and to the prevention of catastrophic accidents caused by sleep deprivation, sleep disorders, and disturbed sleep. Please send a self-addressed stamped envelope for further information.

Restless Legs Syndrome Foundation, Inc.

PO Box 7050, Department CP, Rochester, MN 55903-7050

Web site: http://www.rls.org

The RLS foundation is a nonprofit organization dedicated to achieving universal awareness, developing effective treatments, and finding a definite cure for Restless Legs Syndrome. Please send a self-addressed stamped envelope for information.