DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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 materials[1] 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 advertisements[2] prominently present the following misleading claims under the header "Consider PROVIGIL to improve wakefulness:"

"When patients complain of FATIGUE or TIREDNESS"
"When patients present with SLEEPINESS"
"When patients complain of SLEEPINESS"

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[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

"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 aids[3] 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 website[4] 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 materials[5] 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. The PI states, "[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.

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[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

Misleading Mechanism of Action Claims

Claims contained in your promotional materials[6] 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 aids[7] and Provigil website[8] 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 aids[9] 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-

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[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
[9] PRO164, and PRO212

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}

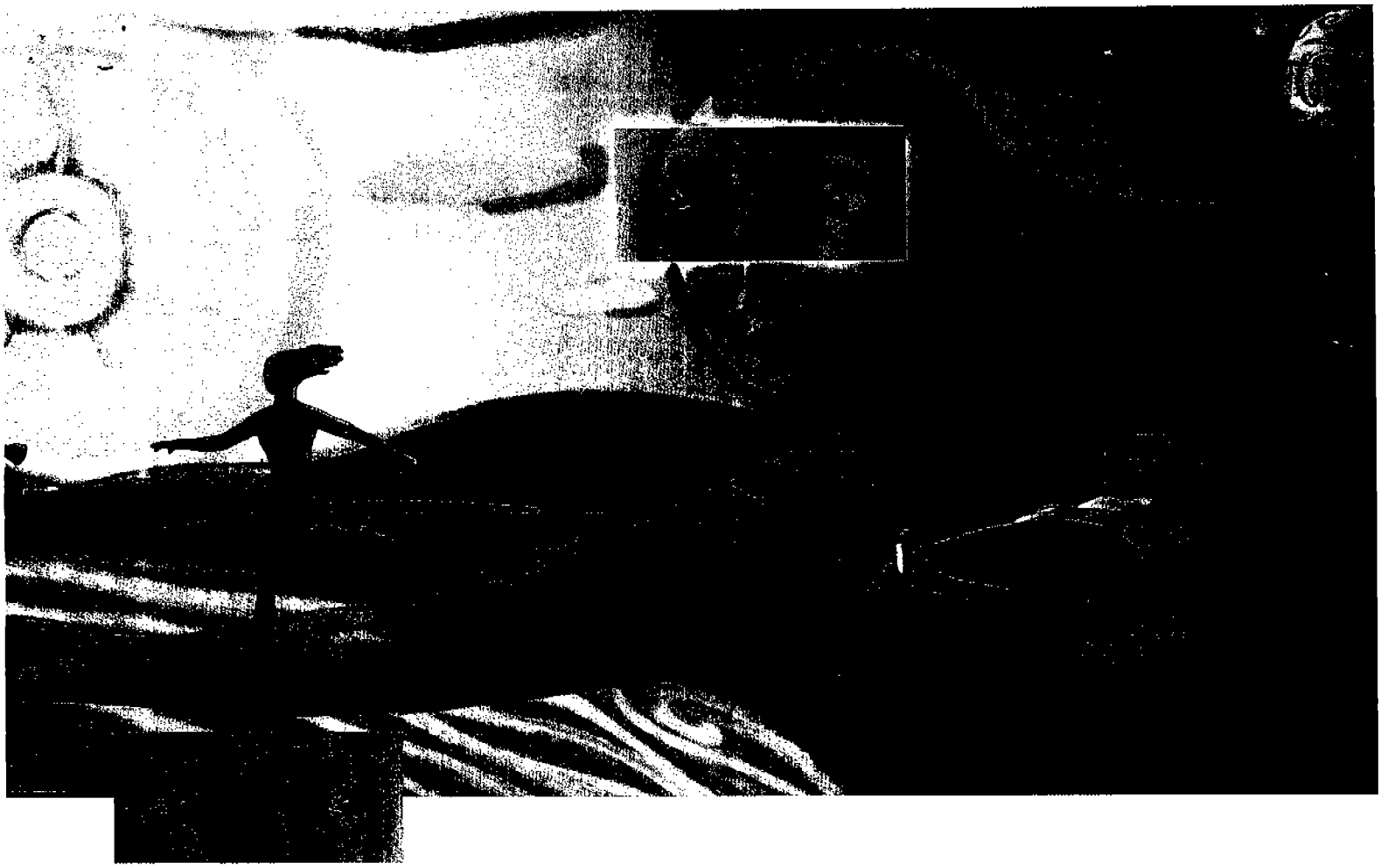
James R. Rogers, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

[10] PRO164

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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



Which patients are candidates for PROVIGIL?

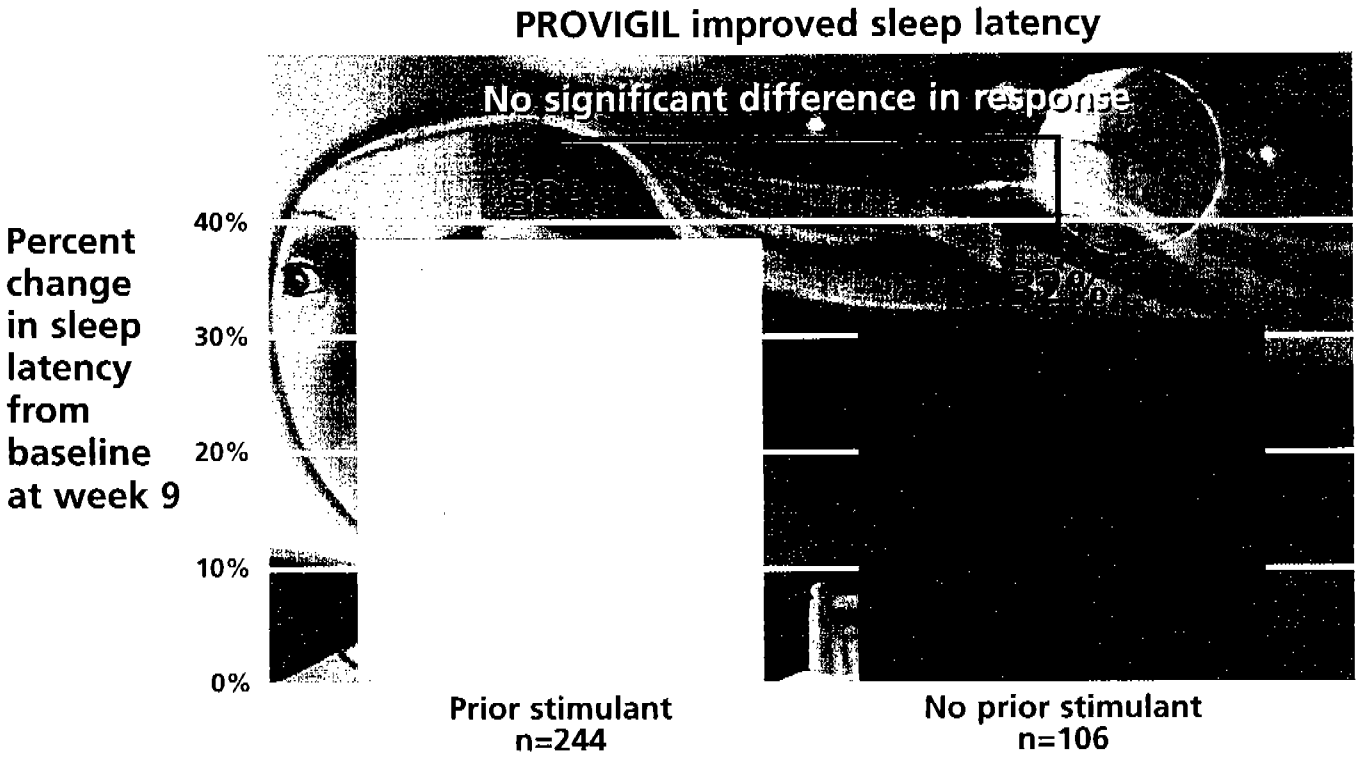
PROVIGIL®
(MODAFINIL)C-IV
Tablets

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 placebo[1]



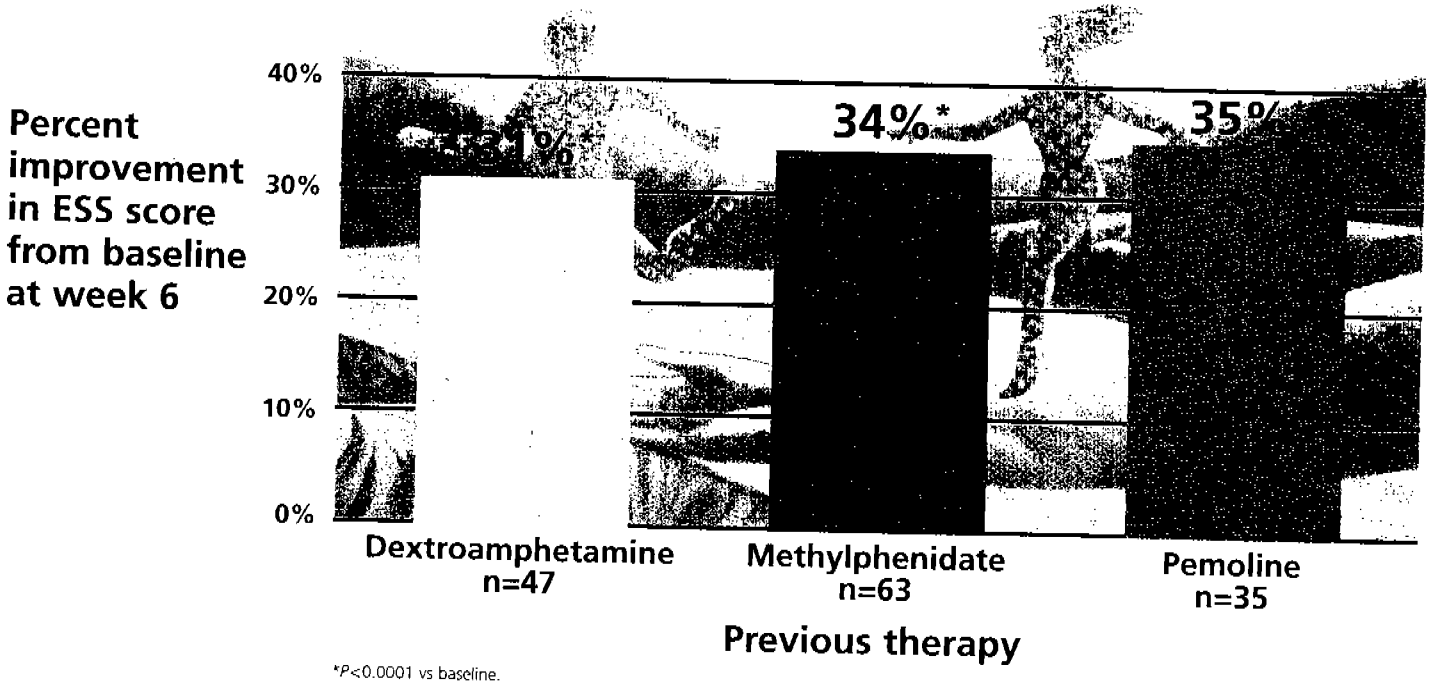
Results of two 9-week double-blind, placebo-contolled clinical trials in 530 patients with EDS due to narcolepsy.

There were no statistical differences in response to PROVIGIL between newly diagnosed patients and patients previously treated with stimulants.[1]

sleepiness associated with narcolepsy

stimulants.

PROVIGIL significantly improved daytime wakefulness in patients unsatisfactorily treated with traditional stimulants[1]



*$P<0.0001$ 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.

Please see full prescribing information on last pages.

PROVIGIL®
(MODAFINIL)C-IV
Tablets

A prescription for daytime wakefulness™

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 extensions[1]

The acute effects of PROVIGIL on mood were not significantly different from placebo as measured by Profile of Mood States[2]:

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

Vigor/activity increased with PROVIGIL

Convenient for you and your patients

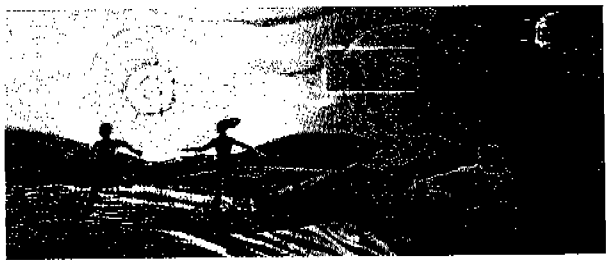
- Fewer prescribing restrictions than methylphenidate or dextroamphetamine
  - Phone-in prescriptions permitted
  - Phone-in refills permitted
  - No triplicate Rxs required

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 study[3]
- May interact with drugs that inhibit, induce, or are metabolized by cytochrome P450 isoenzymes

epiness associated with narcolepsy

lerated agent.

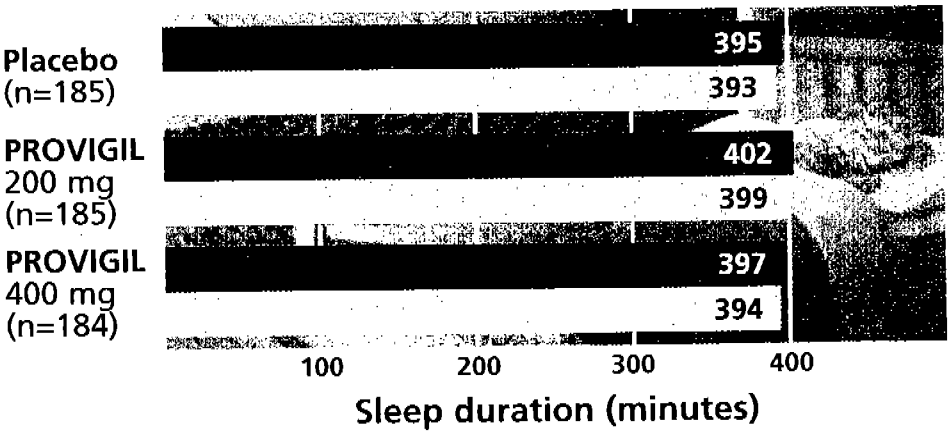


PROVIGIL did not interfere with nighttime sleep architecture after 9 weeks of treatment[1]*

Placebo (n=185)

PROVIGIL 200 mg and 400 mg (n=369)

PROVIGIL did not affect sleep duration[1]*



*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.

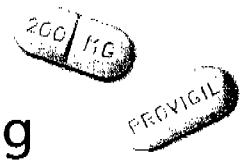
PROVIGIL® (MODAFINIL) C-IV Tablets

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.

PROVIGIL® (MODAFINIL)© Tablets

A prescription for daytime wakefulness™

Cephalon®

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.

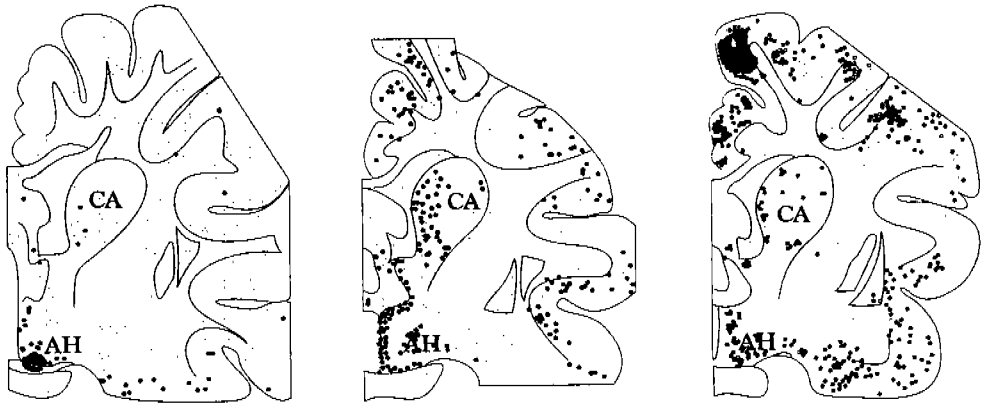
PROVIGIL®
(MODAFINIL) C-IV
Tablets

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*

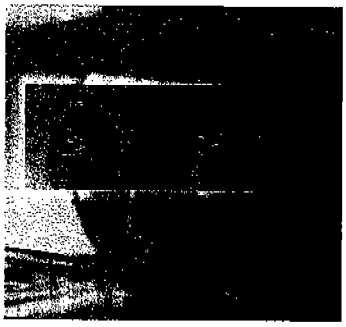


PROVIGIL amphetamine methylphenidate

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

- ***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***

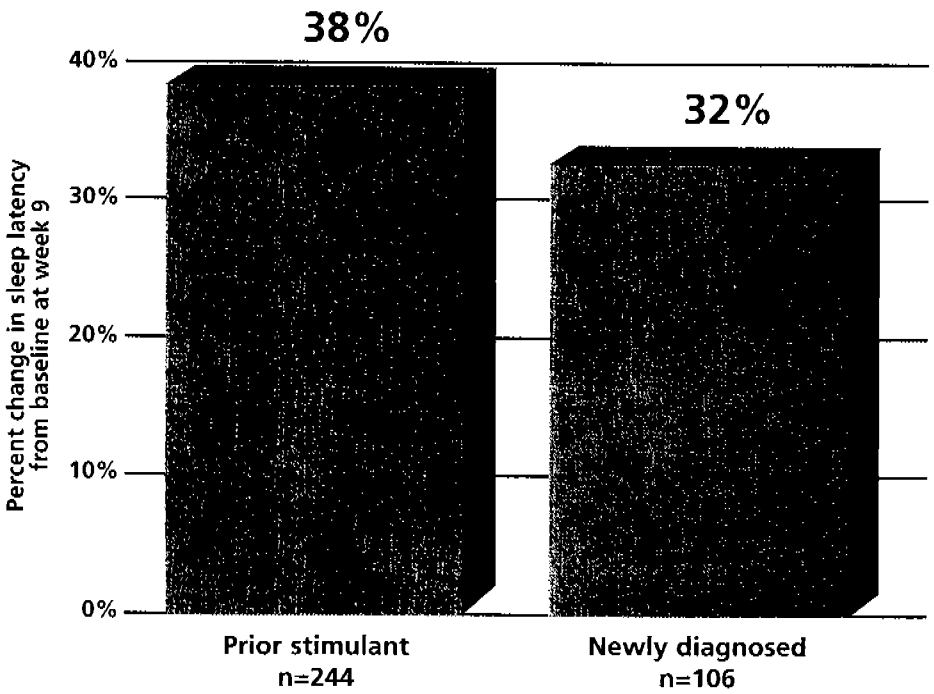
*The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.



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]

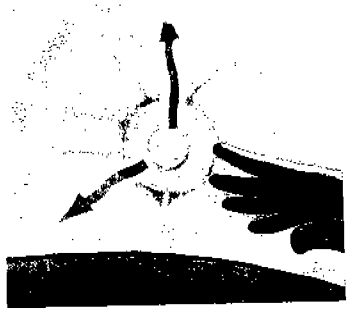
PROVIGIL®
(MODAFINIL) C-IV
Tablets

A prescription for daytime wakefulness™

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

Please see full prescribing information on last pages.

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 trials[4,5]
- 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 States[7]:

- 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

- ***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***

PROVIGIL®
(MODAFINIL)C-IV
Tablets
A prescription for daytime wakefulness™

* 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.

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 hypersomnolence 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.

PROVIGIL®
(MODAFINIL)C
Tablets

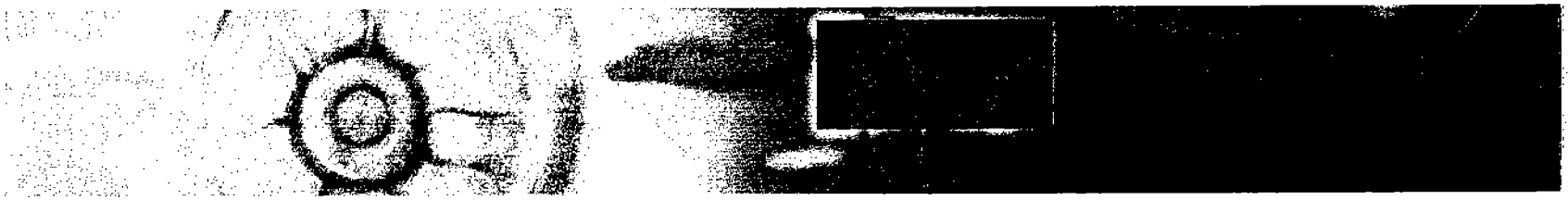
Promotes wakefulness all day long – and still lets them sleep at night

Cephalon®

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

PROVIGIL®
(MODAFINIL) C-IV
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 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.

PROVIGIL®
(MODAFINIL)©
Tablets

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]	**IV**	**NO**	**YES***	**YES**
Methylphenidate[6,7]	II	Yes	No	No
Dextroamphetamine[6,8]	II	Yes	No	No

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]	**QD**	**200 mg QD**	**NO**
Methylphenidate[7]	BID-TID	10-60 mg BID to TID Dose must be individually adjusted	Yes (TID)
Dextroamphetamine[8]	BID-TID	5-60 mg BID to TID Dose must be individually adjusted	Yes (TID)

PROVIGIL®
(MODAFINIL)©
Tablets

A prescription for
daytime wakefulness™

*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.

	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

- ***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.***

PROVIGIL® (MODAFINIL)© Tablets

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 yourself.

Simply complete and return the sample request card enclosed.

References: **1.** 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. **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, 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. **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; 2000:345. **7.** Ritalin® (methylphenidate HCl) prescribing information. East Hanover, NJ: Novartis Pharmaceuticals; 2000. **8.** Dexedrine® (dextroamphetamine sulfate) prescribing information. Philadelphia, Pa: SmithKline Beecham Pharmaceuticals; 2000.

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.

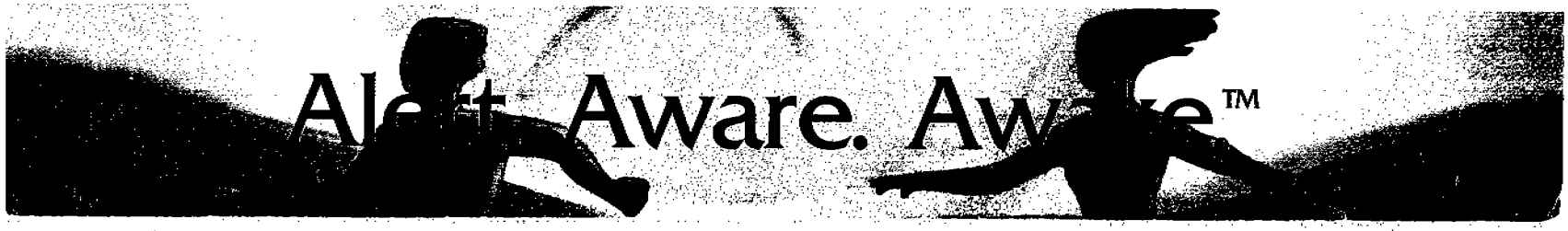
PROVIGIL®
(MODAFINIL)C IV
Tablets

For excessive daytime sleepiness associated with narcolepsy™

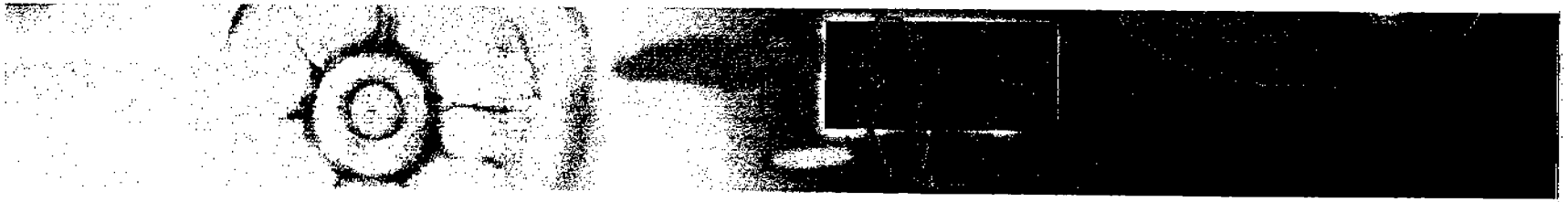
Cephalon®

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

PROVIGIL®
(MODAFINIL) C-IV
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.

*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.

PROVIGIL®
(MODAFINIL)C
Tablets

For excessive daytime sleepiness associated with narcolepsy

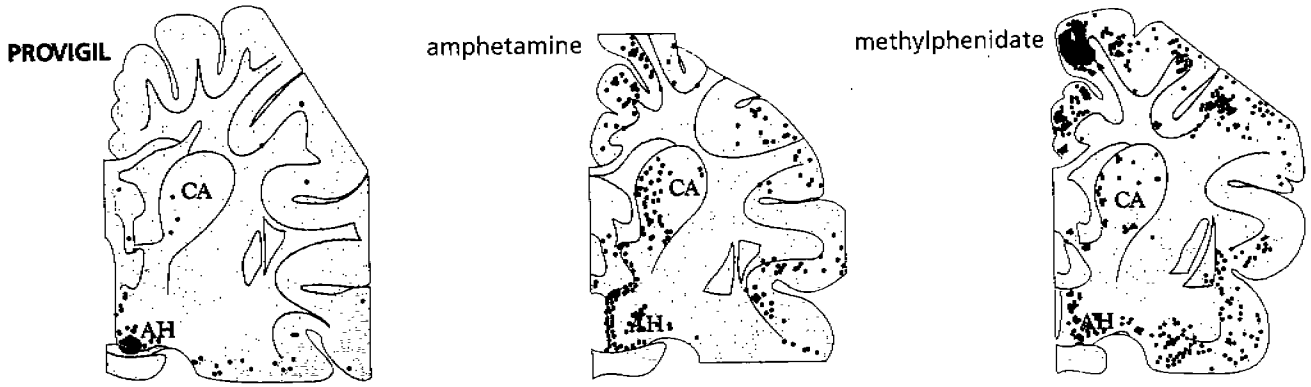
PROVIGIL has a proven safety profile.

- *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.*[5,6]
- *PROVIGIL did not interfere with nighttime sleep architecture.*[1,2]*
- *Adverse events with PROVIGIL were generally mild to moderate in severity.*

PROVIGIL®
(MODAFINIL)©
Tablets

A prescription for daytime wakefulness™

The highly selective CNS activity of PROVIGIL is distinct from amphetamine and methylphenidate in pre-clinical models.[7,8†]



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

*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.

†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.

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 methylphenidate at 4 PM	Next AM start **PROVIGIL** 200 mg/day	Continue **PROVIGIL** 200 mg/day	Continue **PROVIGIL** 200 mg/day
With washout	Stop methylphenidate at 4 PM	No drug	No drug	Start **PROVIGIL** 200 mg/day
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- ***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.***

*Randomized study of 35 patients.

PROVIGIL®
(MODAFINIL)©
Tablets

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. 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. 2. US Modafinil in Narcolepsy Multicenter Study Group. Modafinil administration and withdrawal in narcolepsy patients with excessive daytime somnolence. *Neurology.* 2000;54:1166-1175. 3. Key to controlled substances categories. In: *Physicians' Desk Reference.* 54th ed. Montvale, NJ: Medical Economics Co; 2000:345. 4. 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. 5. Data on file. Cephalon, Inc. 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. Lin J-S, 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. 8. Edgar DM, Seidel WF. Modafinil induces wakefulness without intensifying motor activity or subsequent rebound hypersomnolence in the rat. *J Pharmacol Exp Ther.* 1997;283:757-769.

PROVIGIL®
(MODAFINIL)C-IV
Tablets

For excessive daytime sleepiness associated with narcolepsy

Please see full prescribing information in pocket.

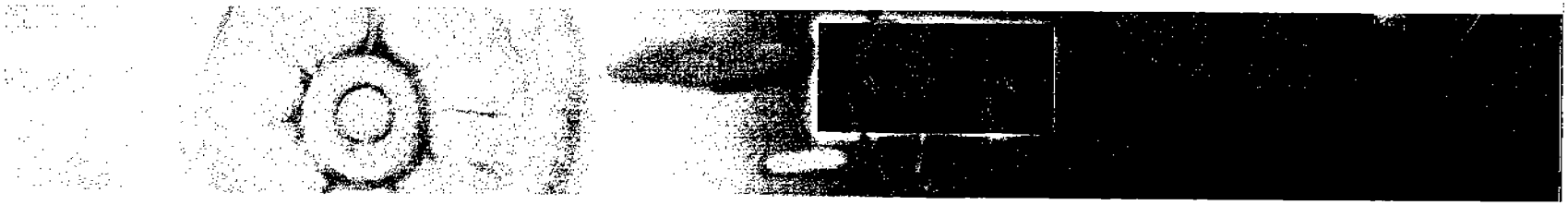
For more information about PROVIGIL, please visit our Website at **www.PROVIGIL.com** or call Cephalon Professional Services at 1-800-896-5855.

Cephalon®

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

PROVIGIL®
(MODAFINIL) C-IV
Tablets

PROVIGIL: A prescription for daytime wakefulness™



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- 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.

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- May interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.

PROVIGIL®
(MODAFINIL)C
Tablets

For excessive daytime sleepiness associated with narcolepsy

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(MODAFINIL)C
Tablets

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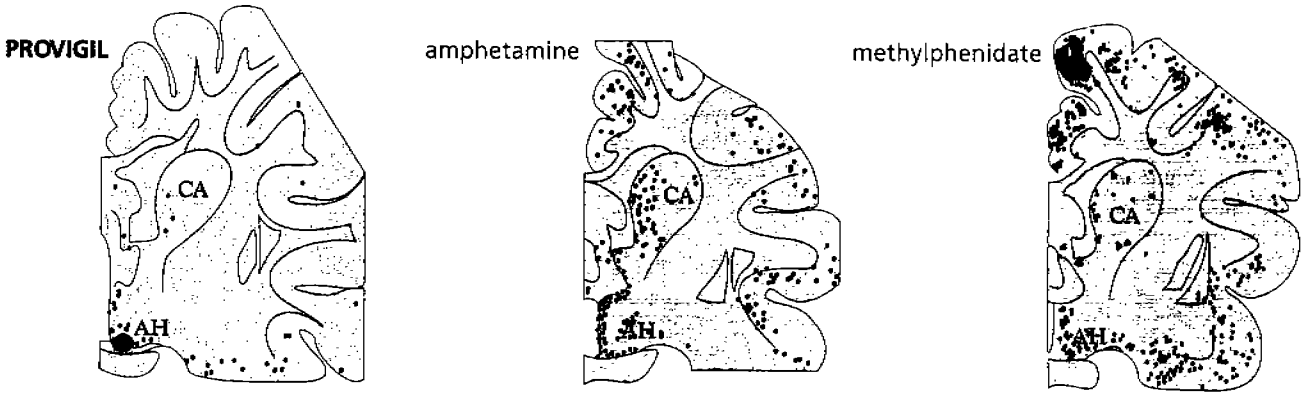

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Please see full prescribing information in pocket.

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Select the approach that works best for your patients.

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(MODAFINIL)©
Tablets

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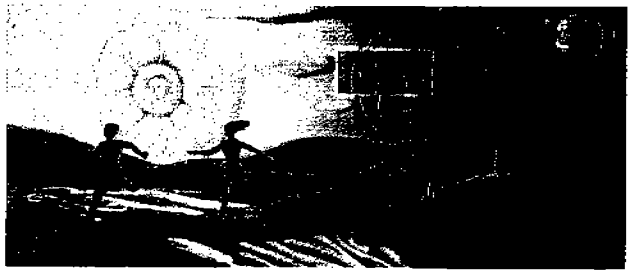

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- No black box warning
- Phone-in Rxs and refills permitted, no triplicate Rxs required

Send for more information about PROVIGIL.

Simply complete and return the reply card enclosed.

References: 1. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in 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.* 2000;54:1166-1175. 3. Key to controlled substances categories. In: *Physicians' Desk Reference.* 54th ed. Montvale, NJ: Medical Economics Co; 2000:345. 4. 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. 5. Data on file. Cephalon, Inc. 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. Lin J-S, 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. 8. Edgar DM, Seidel WF. Modafinil induces wakefulness without intensifying motor activity or subsequent rebound hypersomnolence 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.

PROVIGIL®
(MODAFINIL)C
Tablets

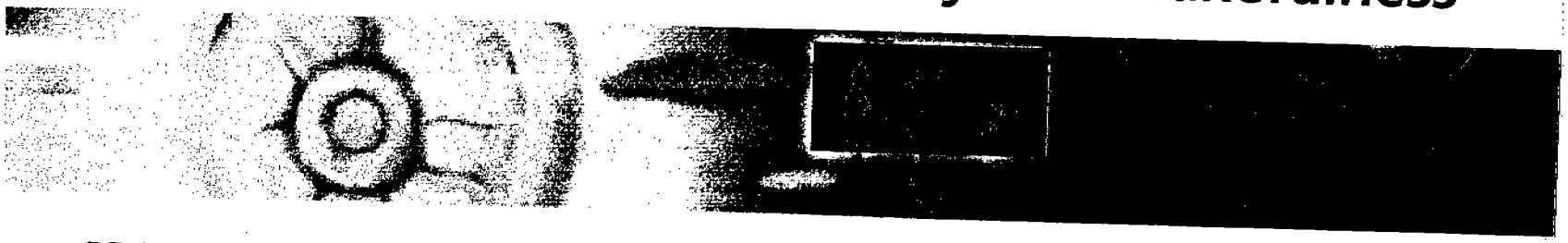
For excessive daytime sleepiness associated with narcolepsy

Cephalon

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

Alert. Aware. Awake.™

PROVIGIL: A prescription for daytime wakefulness™



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- 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]
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PROVIGIL®
(MODAFINIL)
Tablets

For excessive daytime sleepiness associated with narcolepsy

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]	**IV**	**NO**	**YES***	**YES**
Methylphenidate[6,7]	II	Yes	No	No
Dextroamphetamine[6,8]	II	Yes	No	No

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]	**QD**	**200 mg QD**	**NO**
Methylphenidate[7]	BID-TID	10-60 mg BID to TID Dose must be individually adjusted	Yes (TID)
Dextroamphetamine[8]	BID-TID	5-60 mg BID to TID Dose must be individually adjusted	Yes (TID)

PROVIGIL®
(MODAFINIL)©
Tablets

A prescription for
daytime wakefulness™

*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.

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

- ***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.***
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PROVIGIL®
(MODAFINIL) C
Tablets

A prescription for daytime wakefulness™

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- 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 Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in 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, 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. 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; 2000:3455. 7. Ritalin® (methylphenidate HCl) prrescribing information. East Hanover, NJ: Novartis Pharmaceuticals; 2000. 8. Dexedrine® (dextroamphetamine sulfate) prescribing information. Philadelphia, Pa: SmithKline Beecham Pharmaceuticals; 2000.

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.

PROVIGIL®
(MODAFINIL)C
Tablets

For excessive daytime sleepiness associated with narcolepsy™

Cephalon®

Prescribing PROVIGIL is easy.

For you...

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	Schedule	Triplicate Forms	Refills	Phone-In Rxs
PROVIGIL[5,6]	**IV**	**NO**	**YES***	**YES**
Methylphenidate[6,7]	II	Yes	No	No
Dextroamphetamine[6,8]	II	Yes	No	No

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]	**QD**	**200 mg QD**	**NO**
Methylphenidate[7]	BID-TID	10-60 mg BID to TID Dose must be individually adjusted	Yes (TID)
Dextroamphetamine[8]	BID-TID	5-60 mg BID to TID Dose must be individually adjusted	Yes (TID)

PROVIGIL®
(MODAFINIL)©
Tablets

A prescription for
daytime wakefulness™

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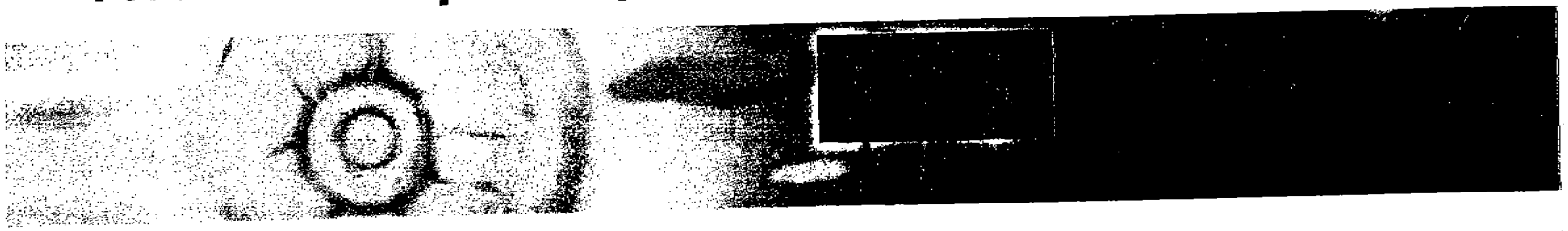
Please see full prescribing information in pocket.

PROVIGIL: A prescription for daytime wakefulness™



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PROVIGIL®
(MODAFINIL)©
Tablets

For excessive daytime sleepiness associated with narcolepsy

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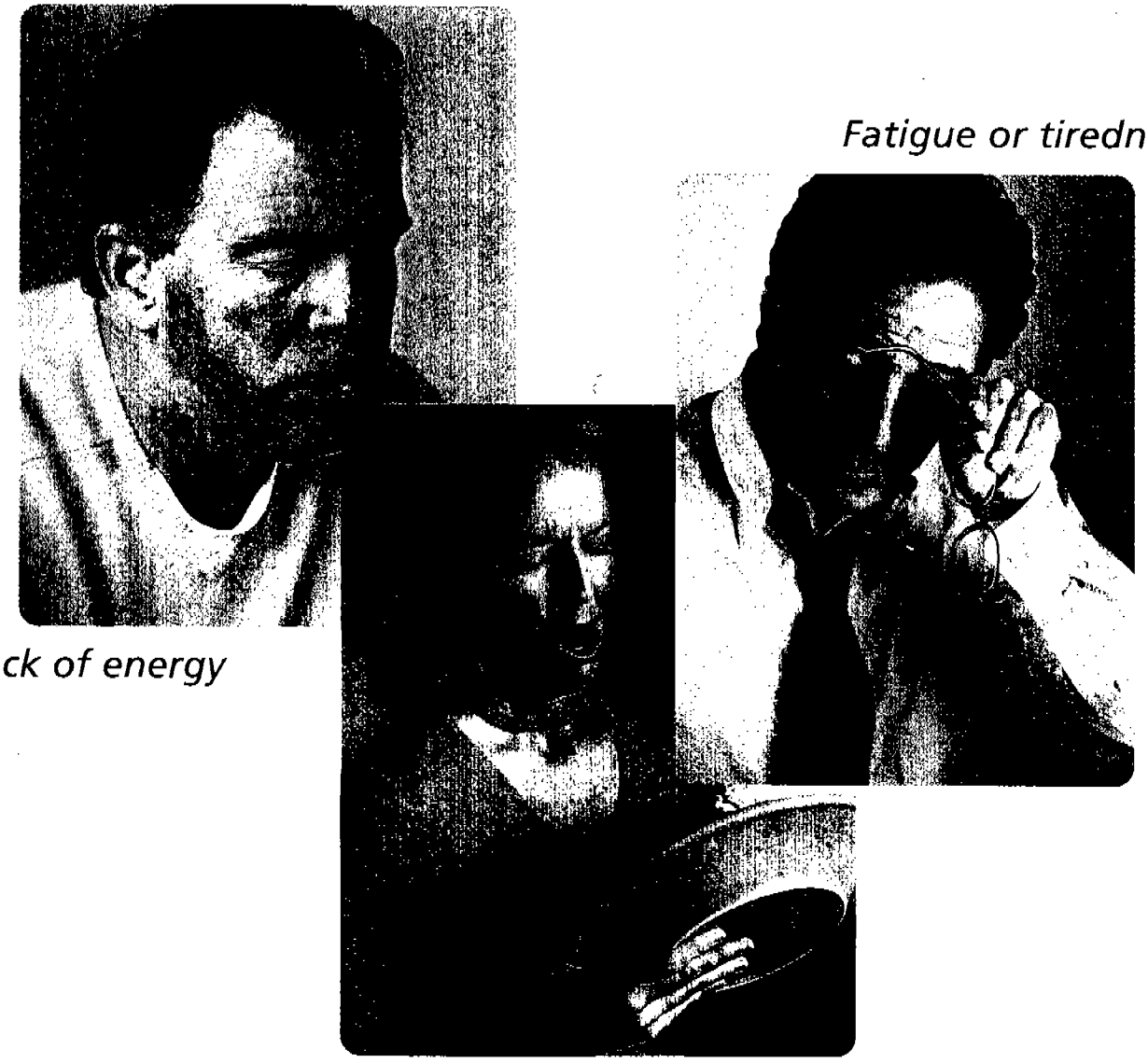
‡CGI-C: Clinical Global Impression-Change over time, a validated independent physician rating assessment.

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



Lack of energy

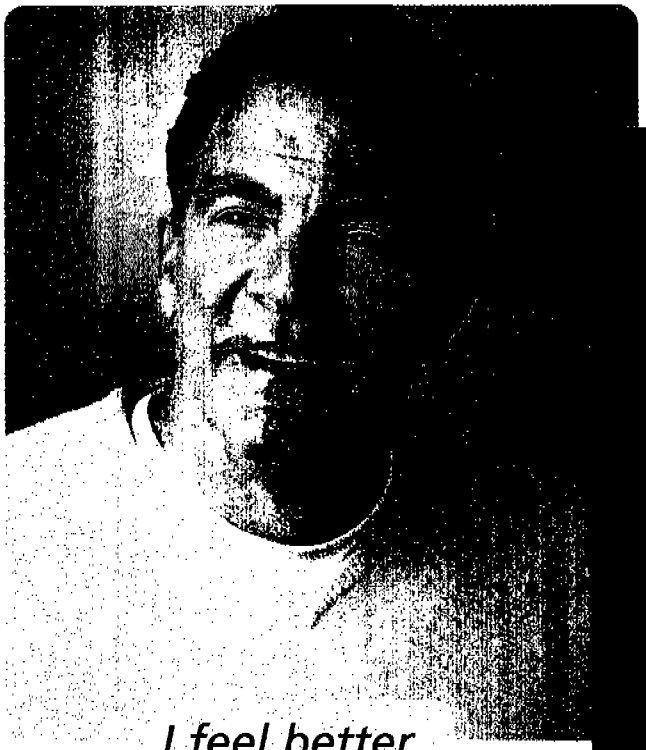
Fatigue or tiredness

Sleepiness

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

PROVIGIL®
(MODAFINIL)C IV
Tablets

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**.[1,2†]

* 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 measurement of sleepiness.

‡ 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.

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.

Now I can sit and read without dozing off.

PROVIGIL improved narcolepsy patients' ability to remain awake during the day by 33%–39% in **MWT**.[1,2‡]

PROVIGIL keeps patients Alert, Aware, Awake all day.

And still lets them sleep at night.

PROVIGIL works differently from stimulants in preclinical models.[3-4§]

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

Pharmacologic activities in preclinical models.[4§]

	PROVIGIL	*Amphetamine*	*Methylphenidate*
Wakefulness	++	++	++
Locomotor activity	−/+	++	++
Stereotypy	−	++	++
Anxiety	−	++	++
Intense NREM rebound	−	++	++
Blood pressure	−	+	+
Heart rate	−	+	+

− = no activity −/+ = minimal activity ++ 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.[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.
- 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.[6]
  - 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.

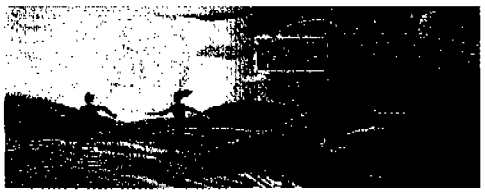
For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at www.PROVIGIL.com

PROVIGIL®
(MODAFINIL)Ⓒ
Tablets

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

PROVIGIL®
(MODAFINIL)C-IV
Tablets

PROVIGIL® (modafinil) 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.
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, 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 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 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. ***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* 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 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:



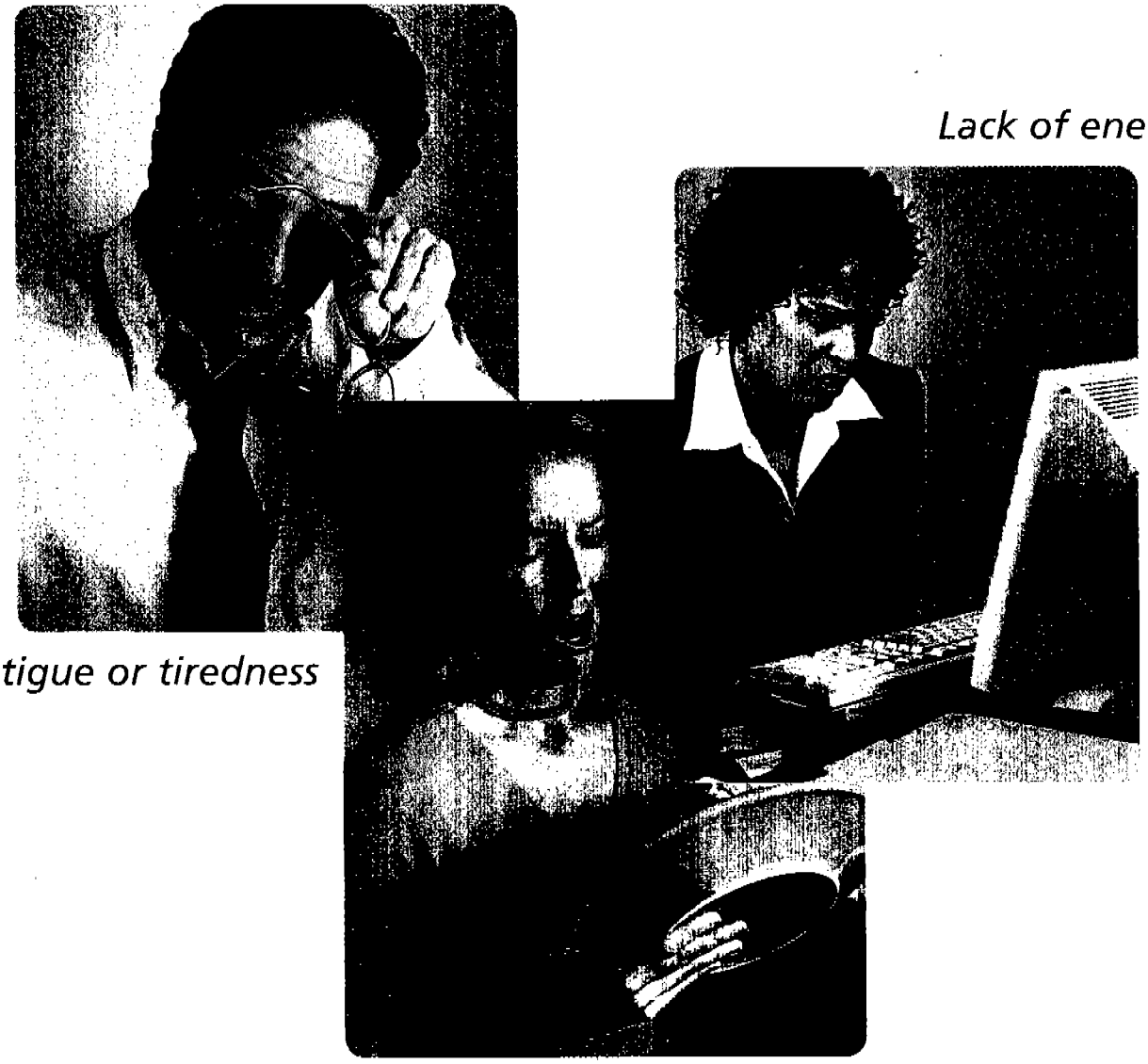
A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed.
A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4 substrates (eg, cyclosporine, steroidal contraceptives, theophylline).
An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels of CYP2C9 substrates (eg, warfarin, 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, desipramine).
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 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 assess effects on fertility.
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/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.
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 (≥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.
Body as a whole: Headache,[1] chest pain, neck pain, chills, rigid neck, fever/chills
Digestive: Nausea,[1] diarrhea,[1] dry mouth,[1] anorexia,[1] abnormal liver function,[2] vomiting, mouth ulcer, gingivitis, thirst
Respiratory system: Rhinitis,[1] pharyngitis,[1] lung disorder, dyspnea, asthma, epistaxis
Nervous system: Nervousness,[1] dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,[3] 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[4]
[1]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 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-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 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 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

Cephalon®

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

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



Lack of energy

Fatigue or tiredness

Sleepiness

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

PROVIGIL®
(MODAFINIL)C
Tablets

Consider PROVIGIL, a unique wake-promoting agent.

I'm feeling like myself again.

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**.[1,2†]

* CGI-C: Clinical Global Impression-Change over time, a validated independent physician rating assessment.
† 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.
§ 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]. *Sleep.* 2000;23(suppl 2):A306. **4.** Data on file, Cephalon, Inc. **5.** Lin JS, Hou Y, Jouvet M. *Proc Natl Acad Sci USA.* 1996;93:14128-14133. **6.** Edgar DM, Seidal WF. *J Pharmacol Exp Ther.* 1997;283:757-769. **7.** *Physician's Desk Reference,* current edition.

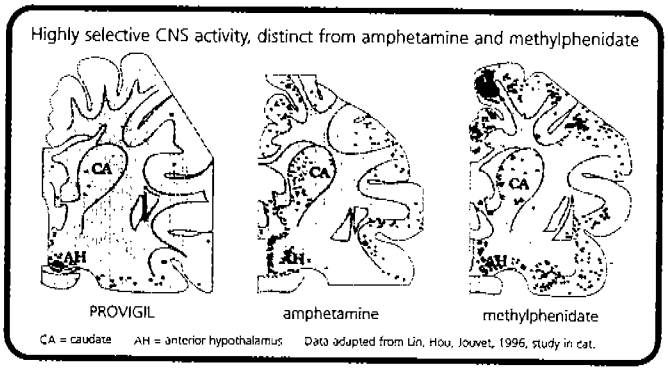
Please see brief summary of prescribing information at the end of this advertisement.

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‡]

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

PROVIGIL works differently from stimulants in preclinical models.[5,6§]



- 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 Ⓒ agent, has fewer prescribing restrictions than Ⓒ 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.

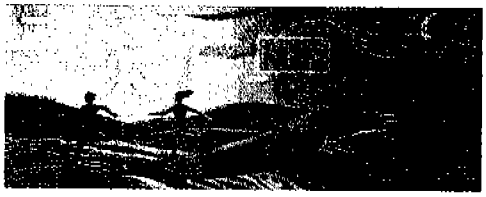
For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at www.PROVIGIL.com

PROVIGIL®
(MODAFINIL) Ⓒ
Tablets

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

PROVIGIL®
(MODAFINIL)C-IV
Tablets

PROVIGIL® (modafinil) 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.
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, 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 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 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. ***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* 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 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, 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, desipramine).
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 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 assess effects on fertility.
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/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.
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 (≥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.
Body as a whole: Headache,[1] chest pain, neck pain, chills, rigid neck, fever/chills
Digestive: Nausea,[1] diarrhea,[1] dry mouth,[1] anorexia,[1] abnormal liver function,[2] vomiting, mouth ulcer, gingivitis, thirst
Respiratory system: Rhinitis,[1] pharyngitis,[1] lung disorder, dyspnea, asthma, epistaxis
Nervous system: Nervousness,[1] dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,[3] 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[4]
[1]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 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-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 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 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) C-IV
Tablets

PROVIGIL® (modafinil) 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.
CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL
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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.
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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 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. ***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* 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 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, 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, desipramine).
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 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 assess effects on fertility.
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/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.
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 (≥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.
Body as a whole: Headache,[1] chest pain, neck pain, chills, rigid neck, fever/chills
Digestive: Nausea,[1] diarrhea,[1] dry mouth,[1] anorexia,[1] abnormal liver function,[2] vomiting, mouth ulcer, gingivitis, thirst
Respiratory system: Rhinitis,[1] pharyngitis,[1] lung disorder, dyspnea, asthma, epistaxis
Nervous system: Nervousness,[1] dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,[3] 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[4]
[1]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 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-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 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 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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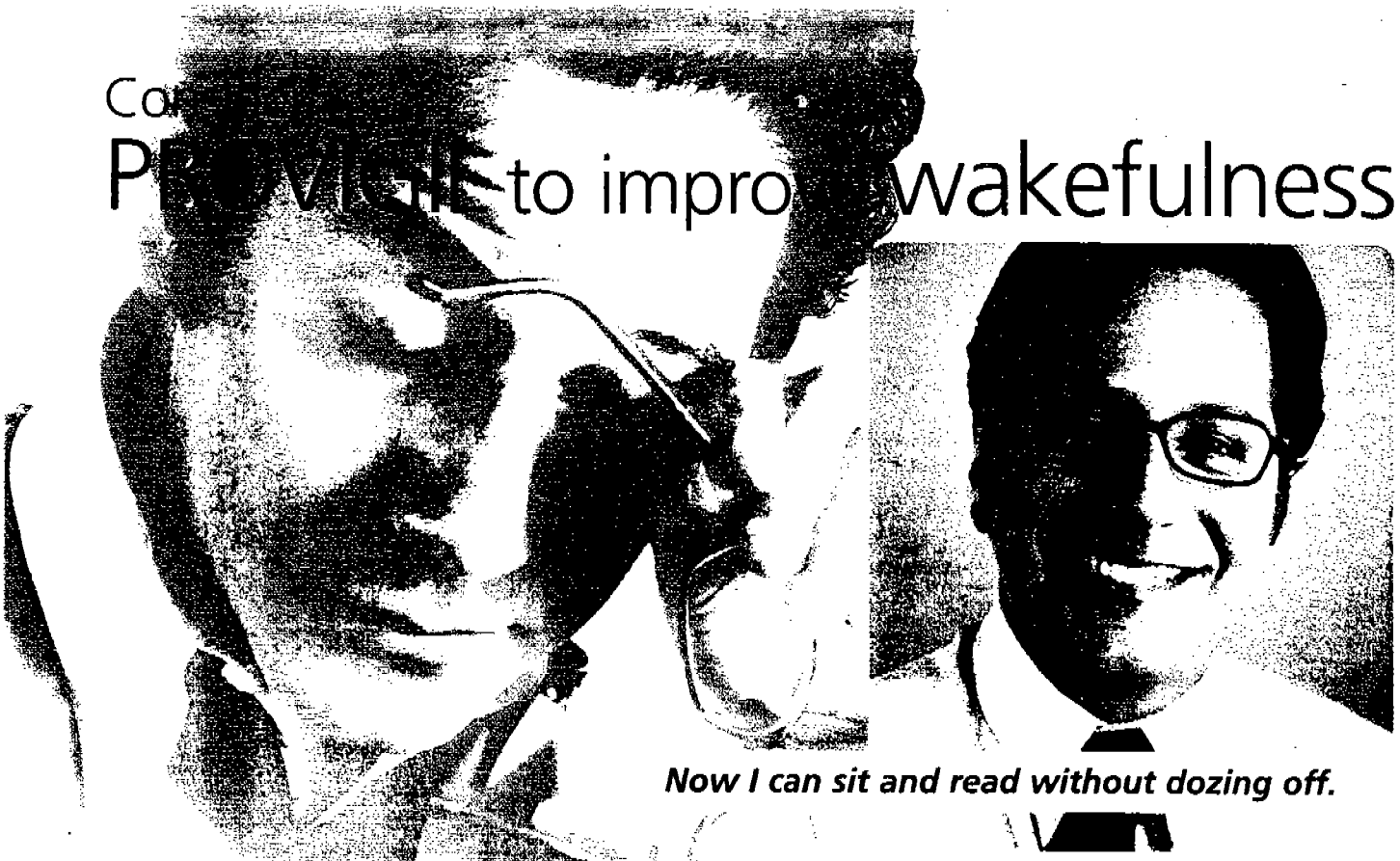
For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at **www.PROVIGIL.com**

Co

P[illegible] to impro[illegible] wakefulness



Now I can sit and read without dozing off.

When patients present with FATIGUE or TIREDNESS

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.[1,2]

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**.[1,2*]
- Prior stimulant users and newly diagnosed patients both stayed awake longer.[3]

Works differently.[4,5†]

- 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 Ⓒ 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

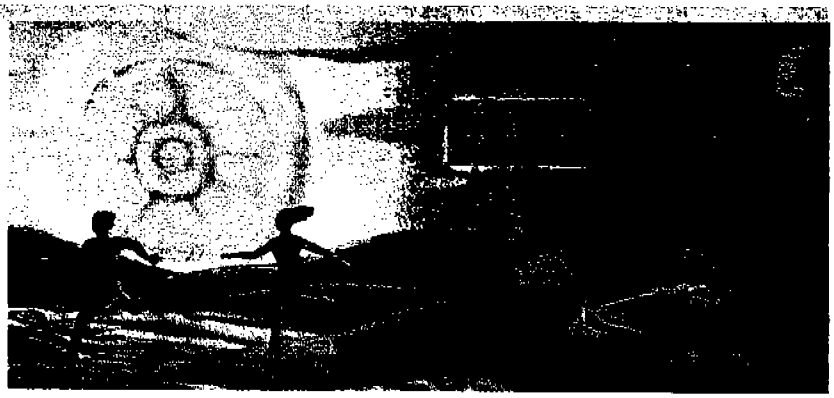
* MWT: Maintenance of Wakefulness Test; an objective assessment of sleepiness that measures patients' ability to remain awake.
† The precise mechanism of action is unknown.
‡ The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.

References: 1. US 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.** 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.

PROVIGIL®
(MODAFINIL) Ⓒ
Tablets

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



PROVIGIL®
(MODAFINIL) C-IV
Tablets

PROVIGIL® (modafinil) 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.
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, 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 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 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. ***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* 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 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, 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, desipramine).
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 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 assess effects on fertility.
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/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.
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 (≥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.
Body as a whole: Headache,[1] chest pain, neck pain, chills, rigid neck, fever/chills
Digestive: Nausea,[1] diarrhea,[1] dry mouth,[1] anorexia,[1] abnormal liver function,[2] vomiting, mouth ulcer, gingivitis, thirst
Respiratory system: Rhinitis,[1] pharyngitis,[1] lung disorder, dyspnea, asthma, epistaxis
Nervous system: Nervousness,[1] dizziness, depression, anxiety, cataplexy,[3] insomnia, paresthesia, dyskinesia,[3] 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[4]
[1]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 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-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 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 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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gIL to improve wakefulness

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.[1,2]

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%.[1,2*]
- Prior stimulant users and newly diagnosed patients both stayed awake longer.[3]

Works differently.[4,5†]

- PROVIGIL promotes wakefulness without widespread CNS stimulation in preclinical models.[4]
- Unlike stimulants, PROVIGIL does not appear to be mediated by a dopaminergic mechanism.[4‡]

Proven safety profile.

- PROVIGIL is generally well tolerated. Most frequently reported adverse events: headache, nausea, nervousness, anxiety, dizziness and insomnia. Adverse events were mild to moderate.
- Does not interact with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.[6]

Easy to prescribe.

- PROVIGIL, a Ⓒ 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

* ESS: [illegible] that provides a subjective measurement of sleepiness.
† The precise mechanism of action [illegible]
‡ The significance of these findings [illegible] 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. 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.

PROVIGIL®
(MODAFINIL) Ⓒ
Tablets

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

PROVIGIL®
(MODAFINIL)C-IV
Tablets

PROVIGIL® (modafinil) 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.
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, 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 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 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. ***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* 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 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, 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, desipramine).
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 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 assess effects on fertility.
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/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.
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 (≥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.
Body as a whole: Headache,[1] chest pain, neck pain, chills, rigid neck, fever/chills
Digestive: Nausea,[1] diarrhea,[1] dry mouth,[1] anorexia,[1] abnormal liver function,[2] vomiting, mouth ulcer, gingivitis, thirst
Respiratory system: Rhinitis,[1] pharyngitis,[1] lung disorder, dyspnea, asthma, epistaxis
Nervous system: Nervousness,[1] dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,[3] 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[4]
[1]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 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-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 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 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

Cephalon®

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

When patients complain of 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.[1,2]

Efficacy confirmed by objective and subjective measures of wakefulness in narcolepsy patients.[1,2]

- PROVIGIL improved patients' ability to remain awake during the day as measured by MWT.*
- Does not interfere with [illegible] archi[illegible] dura[illegible]

Works differently.[3,4†]

- PROVIGIL promotes wakefulness without widespread CNS stimulation in preclinical models.[illegible]
- PROVIGIL acts [illegible] in areas of [illegible] believed [illegible] norm[illegible]
- [illegible]

Proven safety profile.

- PROVIGIL is generally well tolerated. Most frequently reported adverse events [illegible] headache, nausea, [illegible] anxiety, [illegible] insomnia. [illegible] events [illegible] to moderate.
- [illegible] interact with drugs [illegible] inhibit, induce or [illegible] metabolized by cytochrome P450 isoenzymes.

Low abuse potential.[5]

- PROVIGIL, a (C)IV agent, has fewer prescribing restrictions than (C)II 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.

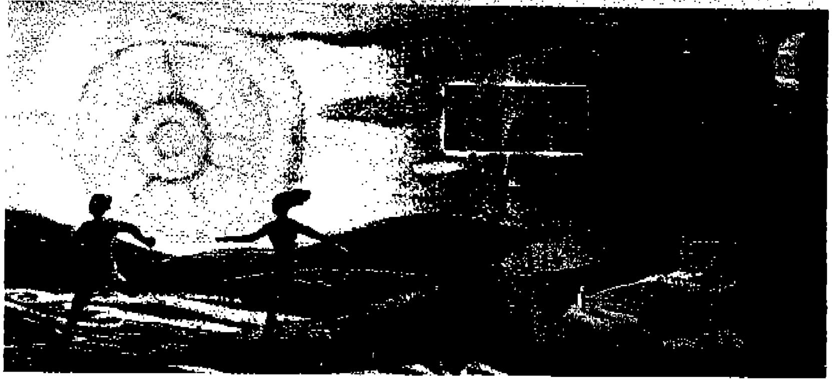
* MWT [illegible] sleepiness that measures patients' ability to remain awake.
† The [illegible]
‡ The [illegible] PROVIGIL in humans has not been established.

References: 1. US Modafinil in [illegible] Group. *Ann Neurol.* 199[illegible]:[illegible]-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.* [illegible] 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 [illegible] adjacent page.

PROVIGIL®
(MODAFINIL) (C)IV
Tablets

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



PROVIGIL®
(MODAFINIL)C-IV
Tablets

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

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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. ***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 assess effects on fertility.
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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 (≥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.
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[1]Incidence ≥5%, [2]Elevated liver enzymes, [3]Oro-facial dyskinesias, [4]Incidence adjusted for gender.
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Vital Sign 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.
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ECG Changes: No treatment-emergent pattern of ECG abnormalities was found in US studies following administration of PROVIGIL.
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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 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 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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For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at **www.PROVIGIL.com**

Consider PROVIGIL to improve waket

I can now be more active during the

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 sl

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.[1,2]

Works differently.[5,6†]

- PROVIGIL promotes 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.

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.

Low abuse potential.[7]

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

Conven once-a-d may ent compliar

- Recomm 200 mg daily in th
- 200 mg a doses are generally v

For more infor PROVIGIL, plea 1-800-896-5855 Website at ww

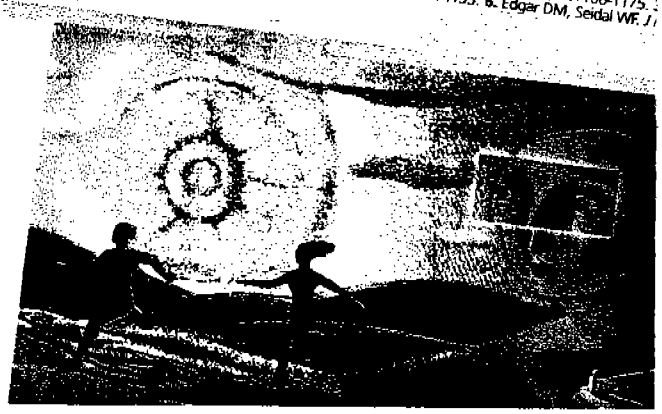
* ESS: Epworth Sleepiness Scale; a validated patient self-questionnaire that provides a subjective measurement of sleepiness.
† The precise mechanism of action is unknown.
‡ The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.

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. et al. [Abstract 1189.K2]. *Sleep.* 2000;23(suppl 2):A306. **4.** Data on file, Cephalon, Inc. **5.** Lin JS, Hou Y, Jouvet M. *Proc Natl Acad Sci USA.* 1996;93:14128-14133. **6.** Edgar DM, Seidal WF. *J Ther.* 1997;283:757-769. **7.** *Physician's Desk Reference*, current edition.

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

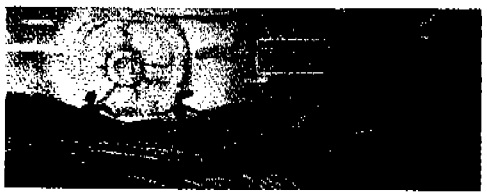
PROVIGIL®
(MODAFINIL) C
Tablets

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



PROVIGIL® (MODAFINIL)C-IV Tablets

PROVIGIL® (modafinil) 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.
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, 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 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 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. ***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* 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 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:



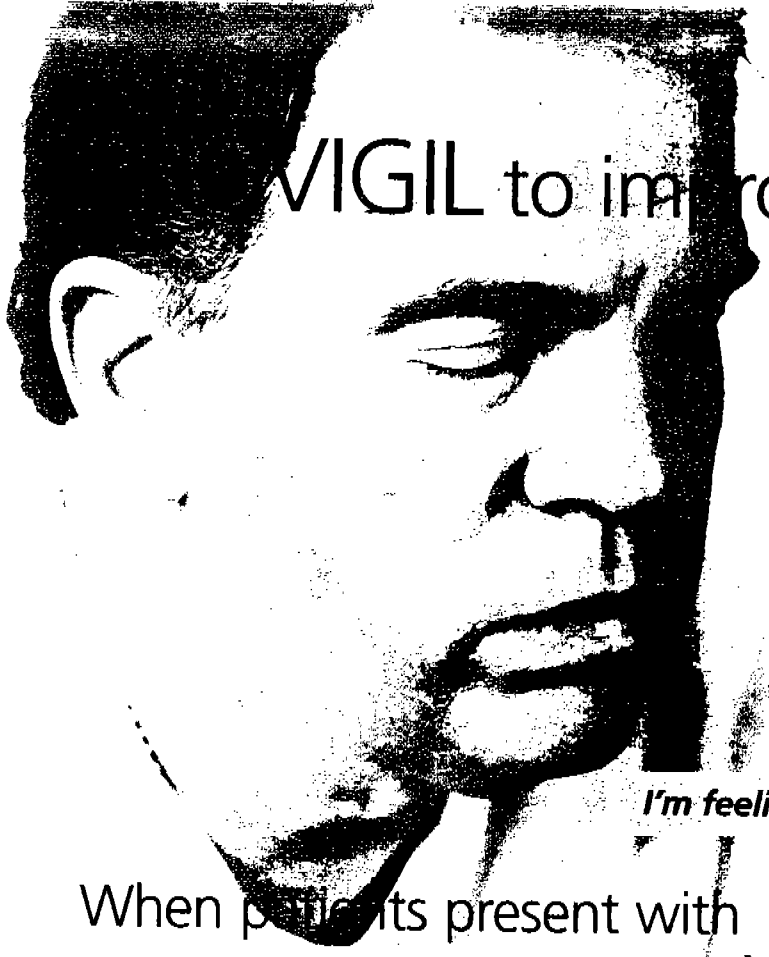
A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed.
A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4 substrates (eg, cyclosporine, steroidal contraceptives, theophylline).
An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels of CYP2C9 substrates (eg, warfarin, 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, desipramine).
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 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 assess effects on fertility.
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/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.
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 (≥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.
Body as a whole: Headache,[1] chest pain, neck pain, chills, rigid neck, fever/chills
Digestive: Nausea,[1] diarrhea,[1] dry mouth,[1] anorexia,[1] abnormal liver function,[2] vomiting, mouth ulcer, gingivitis, thirst
Respiratory system: Rhinitis,[1] pharyngitis,[1] lung disorder, dyspnea, asthma, epistaxis
Nervous system: Nervousness,[1] dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,[3] 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[4]
[1]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 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-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 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 urinary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

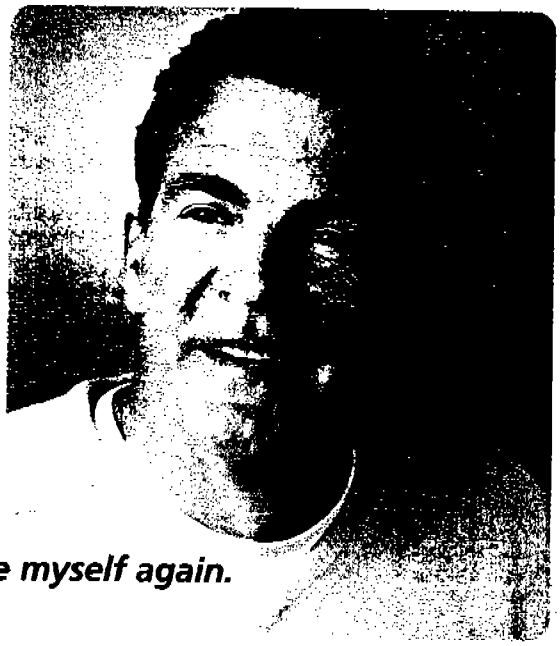
Manufactured for: **Cephalon, Inc.**, West Chester, PA 19380

Cephalon®

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

VIGIL to improve wakefulness





I'm feeling like myself again.

When patients present with

Lack of ENERGY

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.[1,2]

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

- 58%–72% of patients showed improvement in **CGI-C** with PROVIGIL.[1,2*]
- Prior stimulant users and newly diagnosed patients both stayed awake longer.[3]

Works differently.[4,5†]

- 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 Ⓝ 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

* 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 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.** 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.

PROVIGIL®
(MODAFINIL)Ⓒ
Tablets

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

PROVIGIL®
(MODAFINIL) C-IV
Tablets

PROVIGIL® (modafinil) 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.

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, 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 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 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. ***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* 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 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, 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, desipramine).

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 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 assess effects on fertility.

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/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.

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 (≥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.

Body as a whole: Headache,[1] chest pain, neck pain, chills, rigid neck, fever/chills

Digestive: Nausea,[1] diarrhea,[1] dry mouth,[1] anorexia,[1] abnormal liver function,[2] vomiting, mouth ulcer, gingivitis, thirst

Respiratory system: Rhinitis,[1] pharyngitis,[1] lung disorder, dyspnea, asthma, epistaxis

Nervous system: Nervousness,[1] dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,[3] 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[4]

[1]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 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-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 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 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

Cephalon®

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 PRO231 Jan 2001 Printed in USA.

PROVIGIL to improve wakefulness

I can participate in more activities during the day.

When patients [illegible] sleepiness and [illegible] decreased ACTIVITY

Patients with [illegible] various symptoms. PROVIGIL, a unique wake-promoting agent [illegible] ware, Awake all day. And lets them sleep at night.[1,2]

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

- ESS* [illegible] significant [illegible]
- [illegible] Week Wakefulness Test (MWT) [illegible]

- Does not interfere with nighttime sleep architecture or sleep duration.[1,2,6]

- [illegible] medicine wakefulness by a dopaminergic mechanism.

safety profile.

[illegible]IGIL is generally well [illegible]ted. Most frequently [illegible]ted adverse events [illegible]headache, nausea, [illegible]usness, anxiety, [illegible]ion and insomnia. [illegible]adverse events [illegible]ild to moderate.

[illegible]eract with drugs [illegible]hibit, induce or [illegible]abolized by cytochrome P450 isoenzymes.

Low abuse potential.[7]

- 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.

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.

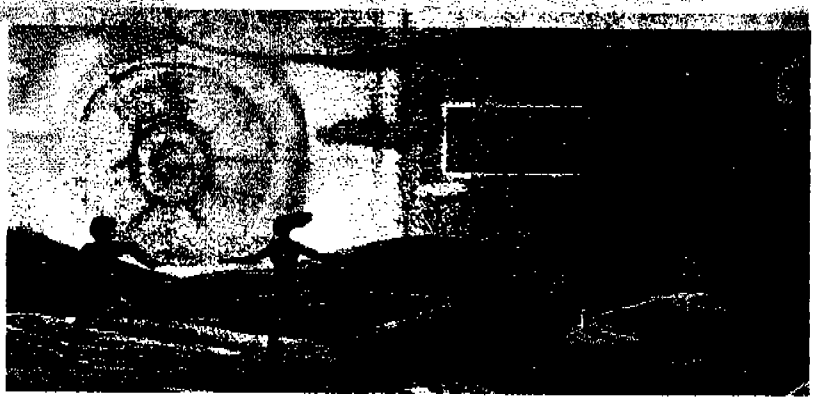
* ESS: Epworth Sleepiness Scale, a validated patient self-questionnaire that provides a subjective measurement of sleepiness.
† The precise mechanism of action is unknown.
‡ The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.

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]. *Sleep.* 2000;23(suppl 2):A306. **4.** Data on file, Cephalon, Inc. **5.** Lin JS, Hou Y, Jouvet M. *Proc Natl Acad Sci USA.* 1996;93:14128-14133. **6.** Edgar DM, Seidal WF. *J Pharmacol Exp Ther.* 1997;283:757-769. **7.** *Physician's Desk Reference,* current edition.

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

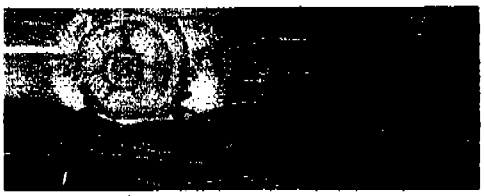
PROVIGIL®
(MODAFINIL)Ⓒ
Tablets

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



PROVIGIL®
(MODAFINIL)C
Tablets

PROVIGIL® (modafinil) 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.
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, 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 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 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. ***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* 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 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, 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, desipramine).
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 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 assess effects on fertility.
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/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.
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 (≥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.
Body as a whole: Headache,[1] chest pain, neck pain, chills, rigid neck, fever/chills
Digestive: Nausea,[1] diarrhea,[1] dry mouth,[1] anorexia,[1] abnormal liver function,[2] vomiting, mouth ulcer, gingivitis, thirst
Respiratory system: Rhinitis,[1] pharyngitis,[1] lung disorder, dyspnea, asthma, epistaxis
Nervous system: Nervousness,[1] dizziness, depression, anxiety, cataplexy,[3] insomnia, paresthesia, dyskinesia,[3] 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[4]
[1]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 Sign 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 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-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 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 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

Cephalon

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

rove wakefulness

I am able to be more active during the day.

n sleepiness and

ecreased ACTIVITY

various symptoms. PROVIGIL, a unique wake-ware, Awake all day. And lets them sleep at night.[1,2]

Efficacy confirmed by objective and subjective measures of wakefulness.

- ESS*
- Patients with PROVIGIL (P<0.001)†
- Prior stimulant users and newly diagnosed patients both stayed awake longer.‡

safety profile.

IGIL is generally well ted. Most frequently ted adverse events headache, nausea, usness, anxiety, ion and insomnia. adverse events ild to moderate.

- teract with drugs that inhibit, induce or are metabolized by cytochrome P450 isoenzymes.

Easy to prescribe.

- PROVIGIL, a Ⓥ agent, has few prescribing restrictions and low abuse potential compared to Ⓘ 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

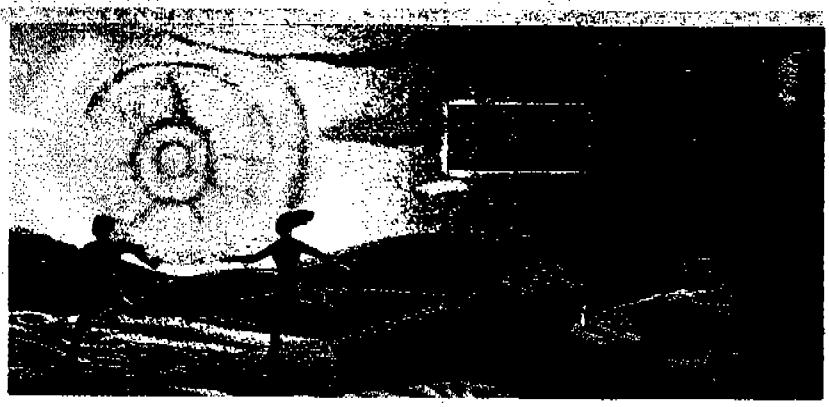
* ESS: Epworth Sleepiness Scale, a validated patient self-questionnaire that provides a subjective measurement of sleepiness.
† The precise mechanism of action is unknown.
‡ The relationship of these findings in animals to the effects of PROVIGIL in humans has not been established.

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]. *Sleep.* 2000;23(suppl 2):A306. **4.** Data on file, Cephalon, Inc. **5.** Lin JS, Hou Y, Jouvet M. *Proc Natl Acad Sci USA.* 1996;93:14128-14133. **6.** Edgar DM, Seidel WF. *J Pharmacol Exp Ther.* 1997;283:757-769. **7.** *Physician's Desk Reference,* current edition.

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

PROVIGIL®
(MODAFINIL)Ⓒ
Tablets

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



PROVIGIL® (MODAFINIL) C-IV Tablets

PROVIGIL® (modafinil) 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.

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

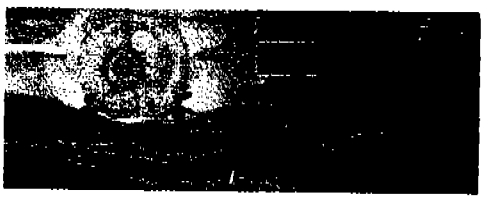
Patients with Severe Hepatic Impairment: PROVIGIL should be administered at a reduced dose because its clearance is decreased.

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 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. ***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* 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 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, 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, desipramine).

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 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 assess effects on fertility.

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/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.

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 (≥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.

Body as a whole: Headache,[1] chest pain, neck pain, chills, rigid neck, fever/chills

Digestive: Nausea,[1] diarrhea,[1] dry mouth,[1] anorexia,[1] abnormal liver function,[2] vomiting, mouth ulcer, gingivitis, thirst

Respiratory system: Rhinitis,[1] pharyngitis,[1] lung disorder, dyspnea, asthma, epistaxis

Nervous system: Nervousness,[1] dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,[3] 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[4]

[1]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 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-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 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 urinary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

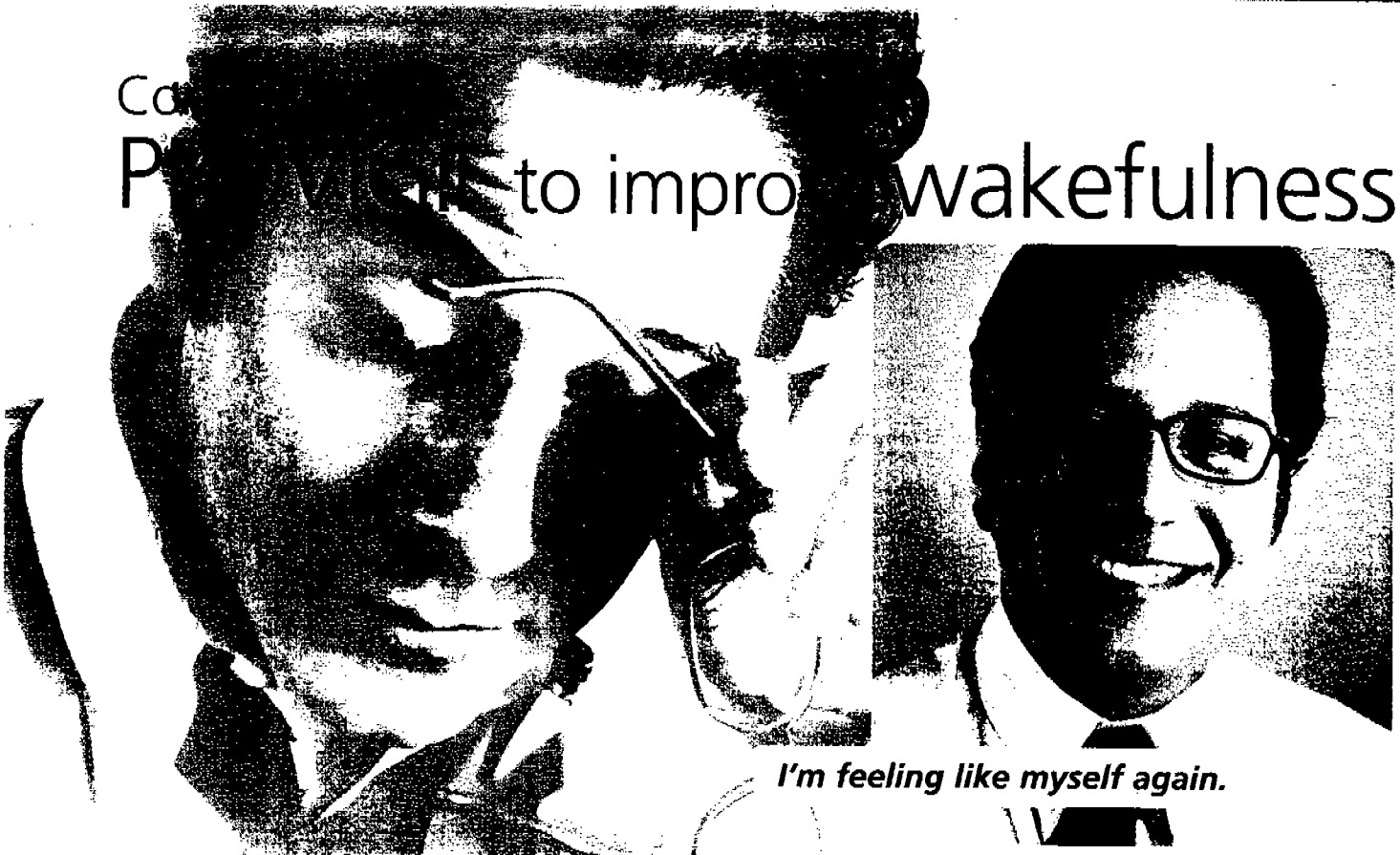
Manufactured for: **Cephalon, Inc.**, West Chester, PA 19380

Cephalon®

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

Co

P to impro wakefulness



I'm feeling like myself again.

When patients complain of feeling FATIGUED or TIRED

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.[1,2]

Efficacy confirmed by objective and subjective measures of wakefulness in narcolepsy patients.[1,2]

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

Works differently.[3,4†]

- PROVIGIL promotes 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.

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.

Low abuse potential.[5]

- 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.

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 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.** *Physician's Desk Reference,* current edition.

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

PROVIGIL®
(MODAFINIL)C-IV
Tablets

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

Alert Aware Awake™

PROVIGIL® (MODAFINIL)© Tablets

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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:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance of 0	1
Sitting and reading	◉	○
Watching television	◉	○
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)	◉	○
In a car, while stopped in traffic	◉	○
Your Score		

Printable Version

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.

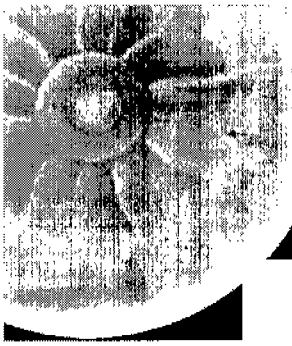
This scale is not intended to be a medical diagnosis. Only your physician can accura whether you may suffer from a sleep disorder.

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.

Sleep Info Hotline 1-888-41-AWAKE Medical Information 1-800-8

Prescribing Information



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(MODAFINIL) C-IV
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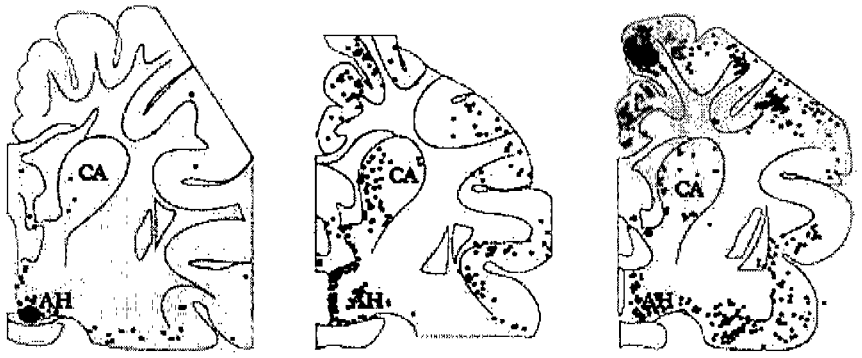
PROVIGIL Information

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

- 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 preclinical models [2]

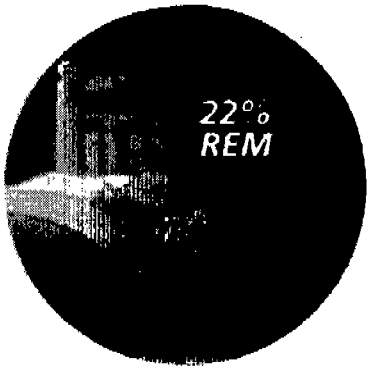
	PROVIGIL	Amphetamine	Methylphenidate
Wakefulness	++	++	++
Locomotor activity	−/+	++	++
Stereotypy	−	++	++
Anxiety	−	++	++
Intense NREM rebound	−	++	++
Blood pressure	−	+	+
Heart rate	−	+	+

− = no activity −/+ = minimal activity ++ marked activity

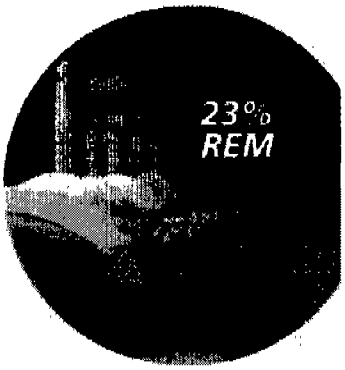
* The relationship of these findings in animals to the effects of PROVIGIL in humans has not been

PROVIGIL promotes wakefulness without affecting nighttime sl

- 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]



Placebo (n=185)



PROVIGIL 200 mg and 400 mg (

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):	C-II (AMPHETAMINE & METHYLPHEN
LOW POTENTIAL FOR ABUSE. Use may lead to limited physical or psychological dependence. Prescriptions may be oral or written up. Up to 5 renewals are permitted within 6 months.	**HIGH POTENTIAL FOR ABUSE.** Use ma severe physical or psychological depende 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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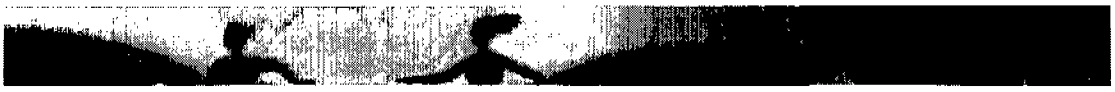
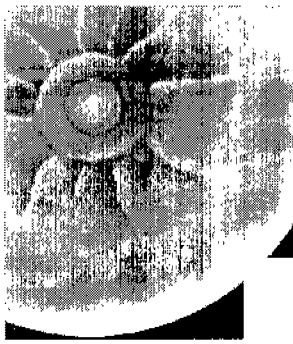
References:

1. 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

Sleep Info Hotline 1-888-41-AWAKE Medical Information 1-800-8
Prescribing Information





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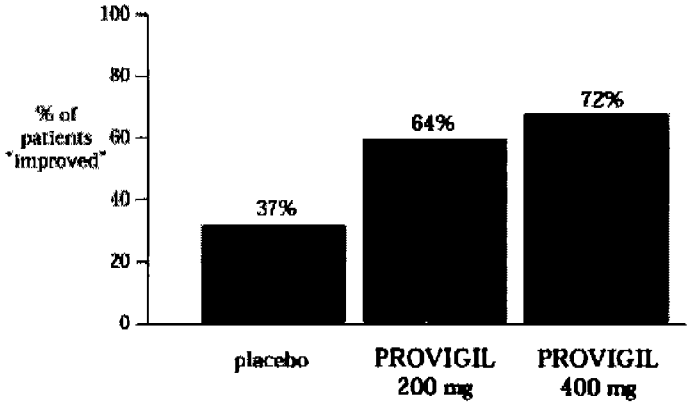
Promotes daytime wakefulness . . . without affecting ni sleep

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

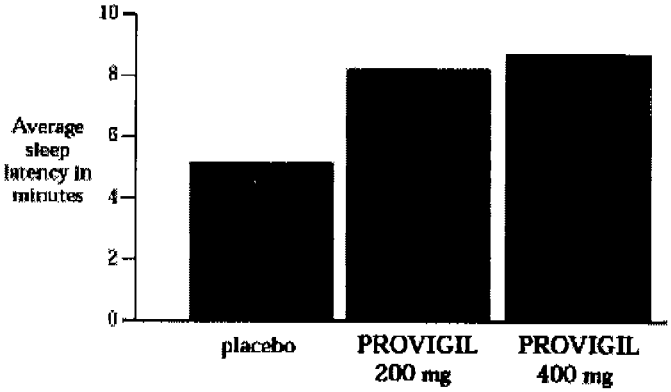


P<0.001 vs placebo. 18-center study: **CGI-C** at endpoint

* 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



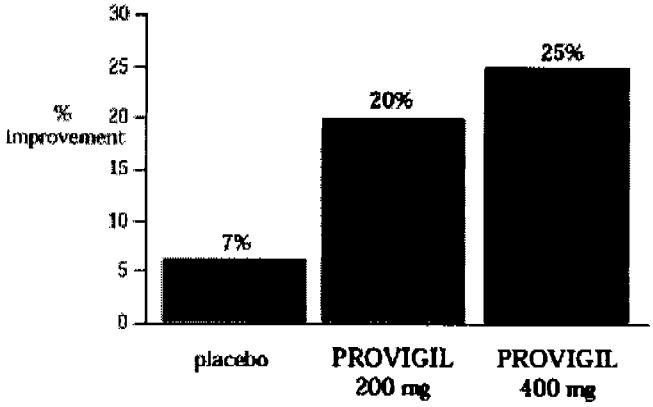
P<0.001 vs placebo. 18-center study: **MWT** at endpoint

* there was no statistical difference between the 200 mg and the 400 mg dose groups

- In the 18- and 21-center studies, PROVIGIL 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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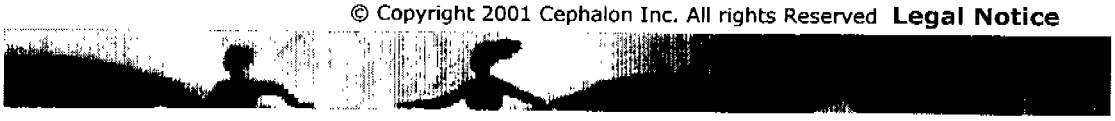
Definitions:

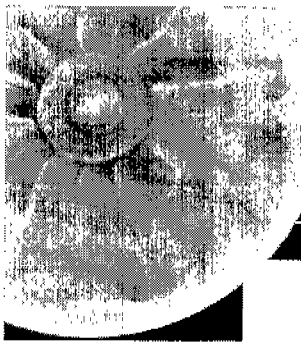
Maintenance of Wakefulness Test (MWT)
The Maintenance of Wakefulness Test (MWT), a 20-minute assessment of sleep late administered 4 to 5 times a day at 2-hour intervals, beginning 2 hours after noctur polysomnography, measured time to sleep onset after a patient is instructed to re seated in a dark 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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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:
  - 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]
  - No statistical difference vs placebo in nighttime sleep duration.

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

	Schedule	Triplicate Forms	Refills
PROVIGIL[1,2]	**C-IV**	**NO**	**YES***
Methylphenidate[2,3]	C-II	Yes	No
Dextroamphetamine[2,4]	C-II	Yes	No

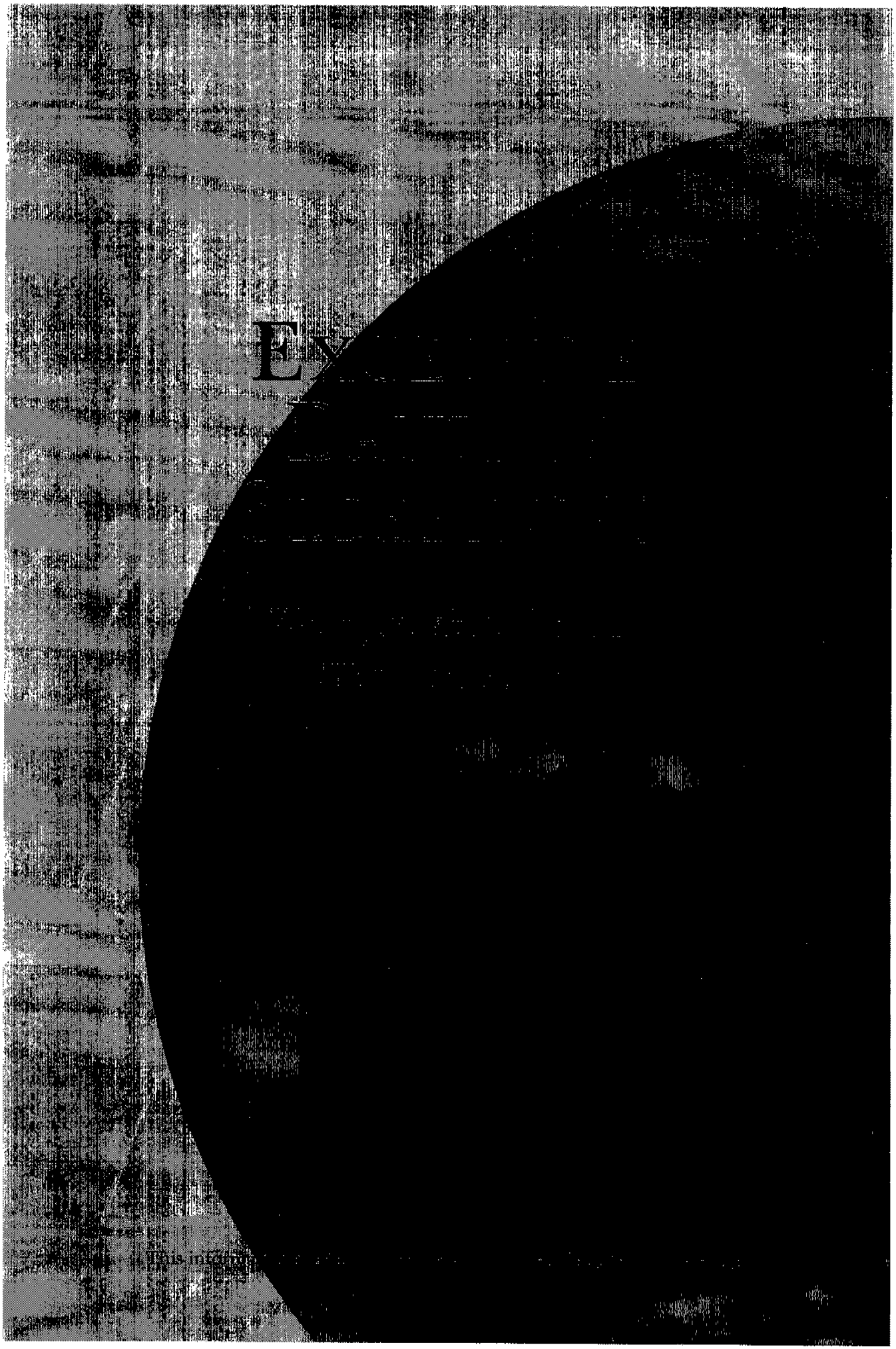
*Up to 5 refills permitted within 6 months.

- 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%;



WHAT IS EXCESSIVE DAYTIME SLEEPINESS?

Excessive Daytime Sleepiness (EDS) means feeling drowsy and tired and having a need to sleep during the day. It means being unable to stay awake in the daytime, even after getting enough [redacted] and it means falling asleep at times [redacted] sleep. People with EDS frequently [redacted] where they need to be [redacted]

Excessive day[redacted] concentrate [redacted] often report [redacted] being [redacted] in life [redacted]

in the second decade of life and, once it appears, is a life-long condition.

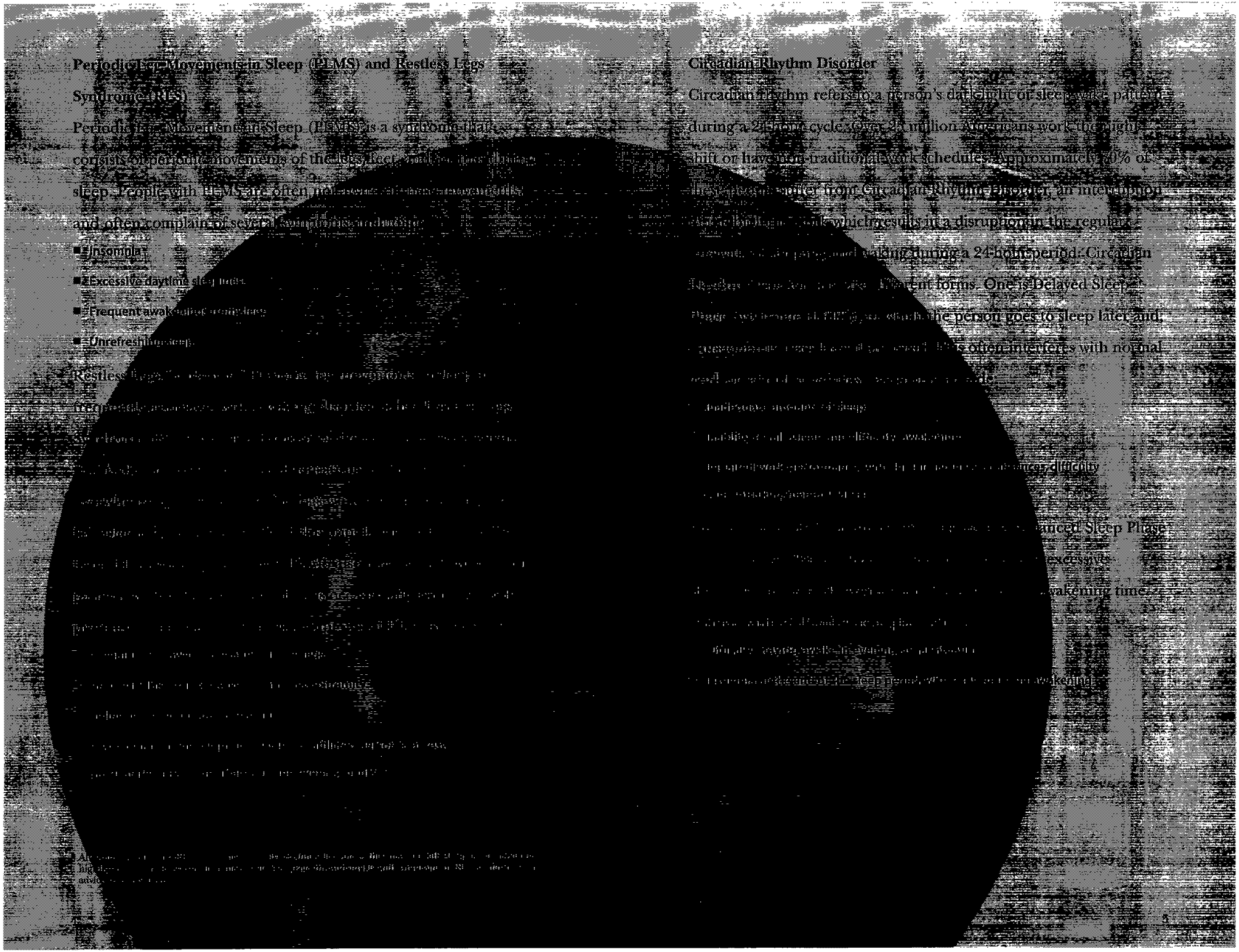
Symptoms of narcolepsy include:

- Frequent drowsiness throughout the day, even after getting enough sleep at night
- Sudden episodes of loss of muscle control ranging from slight weakness to [redacted] which are often precipitated by intense emotions
- [redacted] or move when falling asleep or waking up
- [redacted] very vivid and often frightening, and which [redacted]
- [redacted] awakenings
- [redacted] falling asleep or dozing [redacted]
- [redacted] talking, driving, [redacted]

[redacted] symptoms

[redacted] stops breathing [redacted] aware of the [redacted] common cause [redacted] have sleep apnea. [redacted] symptoms may include:

- [redacted] choking [redacted]
- [redacted] while driving, [redacted]
- [redacted]



Periodic Leg Movements in Sleep (PLMS) and Restless Legs Syndrome (RLS)

Periodic Leg Movements in Sleep (PLMS) is a syndrome that consists of repetitive movements of the legs during sleep. People with PLMS are often not

and often complain of several symptoms including:

- Insomnia
- Excessive daytime sleepiness
- Frequent awakenings
- Unrefreshing sleep

Restless

Circadian Rhythm Disorder

Circadian rhythm refers to a person's daily pattern of sleep/wake during a 24-hour cycle. Over 25 million Americans work through shift or have non-traditional work schedules. Approximately 10% of suffer from Circadian Rhythm Disorder, an interruption in the which results in a disruption in the regular sleeping during a 24-hour period. Circadian

forms. One is Delayed Sleep

the person goes to sleep later and

interferes with normal

difficulty

Sleep Phase

excessive

awakening time

awakening

DO YOU SUFFER FROM EXCESSIVE DAYTIME SLEEPINESS?

The following questionnaire will help you measure your general level of daytime sleepiness, based on your chance of dozing or falling asleep during different routine daytime situations.

Answers to the questions are rated on a reliable scale called the Epworth Sleepiness Scale (ESS). Each item is rated from 0 to 3, with 0 meaning you would never doze or fall asleep in a given situation, and 3 meaning that there is a very high likelihood that you would doze or fall asleep in that situation.

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

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

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

It is important that you put a number (0 to 3) in each of the 8 boxes.

Situation	Chance of dozing (0–3)
Sitting and reading	
Watching television	
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)	
In a car, while stopped in traffic	

SCORING YOUR RESULTS

Now that you have completed the questionnaire, it is time to score your results and evaluate your own level of daytime sleepiness. It is simple. Just add up the numbers you placed in each box to get your total score.

THE EPWORTH SLEEPINESS SCALE KEY

A total score of less than 10 suggests that you are not suffering from excessive daytime sleepiness.

A total score of 10 or more suggests that you may need further evaluation by a physician to determine the cause of your excessive daytime sleepiness and whether you have an underlying sleep disorder.

YOUR NEXT STEPS

This scale should not be used to make a diagnosis. It is intended as a tool to help you track your own level of daytime sleepiness, which is a symptom of many sleep disorders.

If you think you may suffer from excessive daytime sleepiness and/or one of the sleep disorders discussed in this brochure, make an appointment to see your doctor. Be sure to describe all your symptoms, as clearly as possible, to aid in your diagnosis and treatment.

It is important to remember that RLS is almost always caused by an underlying medical condition that can be easily diagnosed and effectively treated. For additional information, please refer to the sources provided on the back page of this brochure.

*Although people with RLS may have excessive daytime sleepiness, they may not fall asleep in the situations highlighted on the Epworth Sleepiness Scale. Individuals with symptoms of RLS should seek the advice of a physician.

American Sleep Disorders Association (ASDA)
1610 14th Street NW, Suite 300, Rochester, MN 55901
Web site: http://www.asda.org E-mail: asda@asda.org
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/narnet
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 nonprofit 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.

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