The undersigned submits this petition under Code of Federal Regulations Title 21, Volume 1 Se. 10.23 (2), to request the Commissioner of Food and Drugs issue an indication for the drug modafinil (Provigil) be used in the management of multiple sclerosis related fatigue.

A. Action Requested

(1) Current wording:

Full prescribing information

1 INDICATIONS AND USAGE

PROVIGIL is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), or shift work disorder (SWD).

2. DOSAGE AND ADMINISTRATION

2.1 Dosage in Narcolepsy and Obstructive Sleep Apnea (OSA)

The recommended dosage of PROVIGIL for patients with narcolepsy or OSA is 200 mg taken orally once a day as a single dose in the morning.

Doses up to 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg/day dose [see Clinical Pharmacology (12.3) and Clinical Studies (14.1, 14.2)].

2.2 Dosage in Shift Work Disorder (SWD)

The recommended dosage of PROVIGIL for patients with SWD is 200 mg taken orally once a day as a single dose approximately 1 hour prior to the start of their work shift.

2.3 Dosage Modifications in Patients with Severe Hepatic Impairment

In patients with severe hepatic impairment, the dosage of PROVIGIL should be reduced to one-half of that recommended for patients with normal hepatic function [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

2.4 Use in Geriatric Patients

Consideration should be given to the use of lower doses and close monitoring in geriatric patients [see Use in Specific Populations

(2) Proposed addition to current wording:

1 INDICATIONS AND USAGE

PROVIGIL is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), or shift work disorder (SWD), or multiple sclerosis related fatigue.

2. DOSAGE AND ADMINISTRATION

2.1 Dosage in Narcolepsy and Obstructive Sleep Apnea (OSA)

The recommended dosage of PROVIGIL for patients with narcolepsy or OSA is 200 mg taken orally once a day as a single dose in the morning.

Doses up to 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers
additional benefit beyond that of the 200 mg/day dose [see Clinical Pharmacology (12.3) and Clinical Studies (14.1, 14.2)].
2.2 Dosage in Shift Work Disorder (SWD)
The recommended dosage of PROVIGIL for patients with SWD is 200 mg taken orally once a day as a single dose approximately 1
hour prior to the start of their work shift.
2.3 Dosage Modifications in Patients with Severe Hepatic Impairment
In patients with severe hepatic impairment, the dosage of PROVIGIL should be reduced to one-half of that recommended for patients
with normal hepatic function [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].
2.4 Use in Geriatric Patients
Consideration should be given to the use of lower doses and close monitoring in geriatric patients [see Use in Specific Populations
2.5 Dosage for multiple sclerosis related fatigue
The recommended dosage of PROVIGIL is 200 mg per day.

B. Statement of Grounds

This petition to issue an updated indication of PROVIGIL for multiple sclerosis related fatigue is based on the results of multiple research trials and the expert opinion paper issued by the National Clinical Advisory Board of the National Multiple Sclerosis Society. In summary, the issuance of an updated indication for modafinil (Provigil) would allow not only for improved management options for prescribers, but also encourage insurance companies to add modafinil (Provigil) to their formularies to improve access to this medication. There are currently other medications that have shown a more positive response than modafinil (Provigil), but also do not have a FDA issued indication for multiple sclerosis related fatigue.

Rammohan KW1, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollak CP, Nagaraja HN."Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study."J Neurol Neurosurg Psychiatry. 2002 Feb;72(2):179-83. Conclusion:These data suggest that 200 mg/day modafinil significantly improves fatigue and is well tolerated in patients with MS.

Zifko UA1, Rupp M, Schwarz S, Zipko HT, Maida EM."Modafinil in treatment of fatigue in multiple sclerosis. Results of an open-label study."J Neurol. 2002 Aug;249(8):983-7. Conclusion : Treatment with modafinil significantly improves fatigue and sleepiness and is well tolerated by patients with MS. Unlike the higher dose regimen required in narcolepsy, a low-dose regimen of modafinil is effective in MS.

Brown JN1, Howard CA, Kemp DW.
Pharmacy Service, Durham Veterans Affairs Medical Center, Durham, NC 27705, USA. "Modafinil for the treatment of multiple sclerosis-related fatigue."Ann Pharmacother. 2010 Jun;44(6):1098-103. doi: 10.1345/aph.1M705. Epub 2010 May 4. Conclusion:Based on the available data, use of modafinil for the treatment of MS-related fatigue has demonstrated benefit in all uncontrolled studies but has conflicting results from 2 controlled studies. Modafinil is a

reasonable therapeutic option in this patient population, although larger, long-term, randomized controlled studies are necessary to further elucidate the appropriate dose of modafinil, its effects on MS-related fatigue, and adverse effects associated with its use.

Department of Neurology, Johns Hopkins University, Baltimore, MD, USA.
Department of Neurology, University of California San Francisco, San Francisco, CA, USA. "Treatment of fatigue with methylphenidate, modafinil and amantadine in multiple sclerosis (TRIUMPHANT-MS): Study design for a pragmatic, randomized, double-blind, crossover clinical trial." Contemp Clin Trials. 2018 Jan;64:67-76. doi: 10.1016/j.cct.2017.11.005. Epub 2017 Nov 4. Conclusions: Results of the proposed study will provide evidence-based and personalized treatment options for patients affected by MS-related fatigue.

Department of Neurology, University Medical Center, Ljubljana, Slovenia. "Evaluating the effects of amantadine, modafinil and acetyl-L-carnitine on fatigue in multiple sclerosis--result of a pilot randomized, blind study."Clin Neurol Neurosurg. 2013 Dec;115 Suppl 1:S86-9. doi: 10.1016/j.clineuro.2013.09.029. Conclusion:One month treatment with amantadine improved fatigue in patients with relapsing-remitting MS as evaluated by MFIS. No or only a trend of improvement was seen in patients treated with modafinil or ALCAR, respectively.

The National Multiple Sclerosis Society NAtional Clinical Advisory Board 733 Third Avenue New York, NY 10017-3288 "Expert Opinion Paper: Management of MS Fatigue" Conclusion; Modafinil (Provigil) has been shown to reduce self-reported fatigue in people with MS. The recommended dosage is 200 mg per day.

C. Environmental Impact

(A) We claim categorical exclusion under 25.30, 25.31, 25.32, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter.

D. Economic Impact

(A) Economic impact information will be submitted upon request of the commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petitioner relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Signature Diane Kramer

Name of Petitioner- Diane Kramer

(b) (6)

[redacted]