Summary of scientific discussion

TABLE OF CONTENTS

ABBREVIATIONS

EMA	European Medicinal Agency (Det europeiske legemiddelkontoret).
INCB	International Narcotics Control Board
MAH	Marketing Authorization Holder
RMP	Risk Management Plan
PSUR	Periodic Safety Update Report

1. INTRODUCTION

Modafinil is a central stimulant with wake-promoting actions similar to sympathomimetic agents like amphetamine and methylphenidate. However, the pharmacological profile is not identical to that of sympathomimetic amines.

The approved indication in the EU and Norway is "*Treatment of adults with excessive sleepiness associated with narcolepsy with or without cataplexy. Excessive sleepiness is defined as difficulty maintaining wakefulness and an increased likelihood of falling asleep in inappropriate situations".*

As approved posology an initial dose of 200 mg/day is given. For patients with insufficient response, the dose can be increased to 400 mg/day.

In EU and Norway modafinil is subject to restricted medical prescription reserved for use in certain specialized area" of the Article 71 of the Directive 2001/83:

"Treatment should be initiated by or under the supervision of a physician with appropriate knowledge of the indicated disorders."

According to section 4.4 of the SmPC (Special Warnings and precautions for use), modafinil should be prescribed with precaution as the risk of dependence with long-term use cannot be excluded. Furthermore, caution during prescribing is required in patients with a history of alcohol, drug or illicit substance abuse:

"*Whilst studies with modafinil have demonstrated a potential for dependence, the possibility of dependence with long-term use cannot be entirely excluded. Caution should be exercised in administering modafinil to patients with a history of alcohol, drug or illicit substance abuse."*

However, modafinil is neither on the International Narcotics Control Board's (INCB) list of narcotic substances nor on the list of psychotropic substances. In the national regulation on narcotics ("Forskrift om narkotika m.v., Narkotikalisten") modafinil is not listed as a narcotic substance.

The product was first authorised in the EU in France in 1994. In Norway it was first approved in 2003 and since then placed into prescription group A. Now the MAH applies for a change in prescription group from A to B in order to facilitate the access of the drug.

2. REGULATION

2.1.Prescription groups in Europe

EU Countries within Mutual Recognition Procedure (DE/H/3259/001-002)

Country	Product Name	Launch date	Prescription Status – Sub-category
Austria	Modasomil	Nov 1998	Product subject to prescription which may not be renewed
Belgium	Provigil	Jun 2000	Restricted prescription to specialized physicians
Cyprus	Modiodal	Mar 2000	Prescription
Czech Republic	Vigil	May 1999	Restricted prescription to specialized physicians Stimulants (prohibited only during competition) - antidoping
Denmark	Modiodal	May 1999	Prescription may be renewed
France	Modiodal	Oct 1994	Restricted medical prescription for the use in certain specialized areas
Germany	Vigil	Nov 1998 Mar 2011	Prescription
Greece	Modiodal	Sep 1999	Restricted prescription to specialized physicians;, Schedule D (narcotics)
Iceland	Modiodal	Mar 2002	Restricted medical prescription for the use in certain specialized areas.
Ireland	Provigil	Jan 1999 Nov 2003	Product subject to prescription which may not be renewed
Italy	Provigil	Jun 2000	Prescription
Luxembourg	Provigil	Jun 2000	Prescription
Netherlands	Modiodal	Aug 2000	Prescription
Norway	Modiodal	Jun 2003	Prescription, class A (narcotics)
Portugal	Modiodal	1997	Prescription
Spain	Modiodal	Feb 1998	Restricted prescription by to specialized physicians) which may not be renewed
Sweden	Modiodal	Jan 2002	Prescription, class 4 and 5 (narcotics)
United Kingdom	Provigil	Mar 1998 Dec 2002	Prescription

EU National

Country	Product Name	Launch date	Prescription Status – Sub-category
Switzerland	Modiodal	2006	Product subject to prescription which may not be renewed (A)

From the table above it can be noted that modafinil is classified as a narcotic agent under national laws in both Greece (schedule D) and Sweden (class IV). In Sweden however, benzodiazepines are also classified as narcotics (class IV), while these are classified in prescription group B in Norway (see section 2.2.Criteria for classification into prescription groups in Norway). In other EU countries modafinil is classified in prescription groups corresponding to prescription group B or C in Norway.

Non-EU Countries

Country*	Product Name	Registration date	Prescription Status
Australia	Modavigil	2002	Prescription, schedule IV drugs/substances, lower risk of abuse and low risk of dependence
Canada	Alertec Teva Modafinil	2013 2014	Prescription Prescription
Israel	Provigil	2001	Prescription
Mexico	Modiodal	2001	Prescription Fraction IV
New Zealand	Modavigil	2001	Prescription
Taiwan	Provigil	2005	Prescription, Schedule C IV, controlled drugs
Turkey	Modiodal	2015	Prescription
South Korea	Provigil	2002	Prescription
United States	Provigil	1998	Prescription Schedule C IV, controlled substances, lower risk of abuse and low risk of dependence

Outside of Europe, modafinil is authorized in 9 countries: Australia, Canada, Israel, Mexico, New Zealand, South Korea, Turkey, Taiwan, and United States. In Australia, Taiwan and the US, modafinil is classified as a controlled substance (schedule IV, lower risk of abuse and low risk of dependence). Indications approved in the USA and other markets include obstructive sleep apnoea and shift work disorder.

2.2.Criteria for classification into prescription groups in Norway

The criteria for classification of a medicinal product into prescription groups in Norway is described in the *Regulation on medicinal products* §7-3 (In Norwegian: *Forskrift om legemidler):*

"Criteria for classification into prescription groups:

Prescription only medicinal products are classified into prescription group A, B or C.

Upon assessment of which prescription group the medicinal product should be classified into, particular regard is taken to whether the medicinal product:

a) contains a non-exempt quantity of a substance classified as a narcotic or psychotropic according to international conventions

b) if not used as recommended, it may be associated with serious risk of drug abuse, addiction or that it is used for illegal purposes

c) contains a substance that, because it is novel or has certain characteristics, as a precautionary measure, may be considered within this group.

The medicinal product may be classified into prescription group A if one or more of the criteria or considerations in the section above are fulfilled or particularly weighed."

As no criteria for prescription group B are defined, addictive or narcotic medicinal products that are not classified into prescription group A, are usually classified into prescription group B.

When modafinil was approved in Norway in 2003, little data on modafinil's potential to induce abuse and dependence of amphetamine type was available. Therefore, as a precautionary measure, modafinil was classified into prescription group A due to the lack of knowledge.

In Norway, group A mainly consists of strong opioids (as morphine and fentanyl), amphethamines and methylphenidate. Benzodiazepines and weak opioids (as codeine and tramadol) are included in group B. Rules that apply for health care professionals as regards prescribing and dispensing, are stated in the regulation "*Forskrift om rekvirering og utlevering av legemidler fra apotek"*.

In general, rules are more restrictive as regards prescription and dispensing of drugs in group A than drugs in group B.

Rules that apply for drugs in prescription group A and B:

Prescriptions of drugs in group A and B cannot be refilled, nor renewed unless the prescription is reimbursed. These drugs can only be ordered orally by phone (§§ 3.5 and 3.6). For prescriptions ordered by phone, the pharmacy should control the identity of the physician if they do not know him or her (§ 6.3).

In general, special care should be taken when drugs in prescription group A and B are prescribed and dispensed (§§ 6.5 and 8.3). If the prescriber do not know the patient, the patient should legitimize himself (§5.7). Likewise, the pharmacist can require credentials when the patient are not known for the pharmacy (§ 8.3). The pharmacy should take special care to control the authenticity of the prescriptions for drugs in group A and B (§ 6.5).

Differences between prescription group A and B:

When products are ordered via phone, a higher number of doses can be ordered for drugs in group B than for drugs in group A (seven and three daily doses, respectively). Telefax can not be used when ordering drugs in prescription group A, and electronic communication of prescriptions of drugs in group A must be done through "Reseptformidleren" (e-prescription portal) (§§ 3.5 and 3.6).

If not ordered electronically, drugs in group A must be prescribed on a special form (§ 4.5). Accordingly, these prescriptions are less prone to counterfeiting than prescriptions for drugs in group B. Additionally, when prescribing a drug in group A, the dose should be written in numbers and in letters (§ 5.9).

In the pharmacy prescriptions for drugs in group A and B should be withheld and stored for five and one year, respectively (§9.2).

3. PRESCRIPTION OF MODAFINIL IN NORWAY

According to the Norwegian Prescription Database ("Reseptregisteret"), the number of patients treated with modafinil in Norway is low. A small increase occurred during the years 2008 to 2016.

Year	2008	2009	2010	2011	2012	2013	2014	2015	2016
# Patients	288	291	329	349	366	436	486	548	582

4. CHEMICAL ASPECTS

The chemical qualities of modafinil make addictive capacity seem unlikely. Modafinil has low water solubility. A maximum of 5-10 mg can be administered in one dose by i.v. injection, which is an ineffective dosage. Neither is it possible to smoke modafinil, because it breaks down at high temperatures. Modafinil is not a precursor molecule for substances that have potential for misuse or metabolised as such. Modafinil does not show any structural relationship to substances known to induce addiction, e.g. cocaine, amphetamines, methylphenidate or pemoline.

5. NON CLINICAL ASPECTS

The pharmacological profile of modafinil is different from that for amphetamines and methylphenidate. These have shown diffuse activation of several target areas, including areas related to addiction and reward. They increase dopamine release in nucleus accumbens. In contrast, the mode of action of modafinil seems to result from a selective activation of the areas of the brain that play an important role in the normal circadian wake-sleep cycle. It activates different circuits and brain areas as compared to amphetamines and only have an indirect and weak stimulating effect on the dopaminergic system.

Animal models for dependence potential:

Modafinil has a low potential for abuse relative to CNS stimulants with a documented high abuse potential. However, modafinil may induce relapse or increase the vulnerability of addicts to the reinforcing effects of environmental triggers.

6. CLINICAL ASPECTS

Studies confirm animal studies. The abuse liability seems to be low compared with amphetamines and methylphenidate. Modafinil has even been suggested as a potential medication for psychostimulant abuse (amphetamines, cocaine). However, it has been shown that modafinil can function as a reinforcer and have abuse potential under certain circumstances. This is also reflected in the SmPC section 4.4 Special Warnings and

Precautions for Use: "*Whilst studies with modafinil have demonstrated a potential for dependence, the possibility of dependence with long-term use cannot be entirely excluded. Caution should be exercised in administering modafinil to patients with a history of alcohol, drug or illicit substance abuse.*"

7. POST-MARKETING DATA

7.1. Risk management plan (RMP)

Misuse, abuse and diversion, together with off-label use (including pediatric use) are listed as important potential risks in the RMP. These effects are routinely monitored and reported in periodic safety update reports (PSURs).

Important identified risk	Serious skin reactions
Important identified risk	Cardiovascular disorders
Important identified risk	Psychiatric disorders (including suicide/suicidal behavior)
Important identified risk	Nervous system disorders
Important identified risk	Hypersensitivity
Important potential risk	Misuse, abuse and diversion
Important potential risk	Off label use (including pediatric use)
Missing information	Exposure during pregnancy
Missing information	Use in the elderly

Safety specifications from RMP version 5.0

In Norway, only 4 spontaneous reports have been reported for modafinil since marketing. None of these concern misuse, abuse or diversion. However, as per today, few patients are treated annually with modafinil in Norway.

7.2. Abuse, dependence and withdrawal effects

Worldwide 166 case reports of abuse and dependence have been reported for the product Modiodal (modafinil) "Teva Pharma B.V." in the period 2009-2016. The marketing authorization holder (MAH) considers that 30 of these are relevant in this context. In addition, there are 19 reports were abuse/dependence was reported for modafinil in combination with other substances (cocaine, cannabis, alcohol).

In addition, seven cases of drug withdrawal and 65 cases of drug diversion were reported. Most of the latter originated from the US, and the majority were classified as non-serious.

In two reported cases, the patient took modafinil nasally. Otherwise, events like drug seeking behavior, tolerance and using higher than recommended doses have been reported.

Causality with modafinil is unclear in many of the reported cases.

Some literature reports have been published on several related adverse events:

- Drug dependence and hypersexuality in a patient with bipolar disorder in remission. The patient increased the dose from 400 to 1000 mg/day (Swapnajeet S, et al. 2016).
- Drug dependence syndrome on supratherapeutic doses of modafinil (1500 -2000 mg/day) (Kate N et al. 2012)
- Dependence syndrome on supratherapeutic doses, craving, tolerance, drug withdrawal (Raman K et al. 2015)
- Enhanced desire to smoke tetrahydrocannabinol during modafinil use in a cannabis user (Ozturk, et al., 2014).
- Onset of compulsive gambling associated with modafinil (George WT, et al. 2015).

The MAH considers that there is no trend towards an increased abuse when analyzing the number of cases reported yearly between 2009 and 2016.

These reports are monitored and reviewed in PSUR-procedures. In the last PSUR procedure (period 09.12 – 08.13) the competent authority assessing the data, concluded that no new safety information as regards abuse/dependence, was identified to alter the known safety profile of modafinil.

7.3. Misuse

Modafinil has been misused as a so-called "life style drug" to promote alertness and wakefulness in otherwise healthy subjects. One published case report describes modafinil-induced schizophrenic symptoms in a patient using at an average dose 1200 mg for exam preparation (Vidyendaran R. et al, 2012).

Recreational Use in UK students:

1,817 students participated in the study through a self-completion questionnaire exploring use and availability of stimulants. 1 % of respondents reported use (and consideration of use) of modafinil. 62.6 % of the respondents reported having been offered methylphenidate, dexamphetamine, modafinil or cocaine for purchase, and 61.3 % considered them "*easy to get hold of".*

Possible risk groups:

1) people engaged in challenging mental activities, such as students preparing for exams, professors, researchers and writers;

2) people in high power jobs that often work long hours;

3) people who, for different reasons, need or wish to be awake and alert for extended amounts of times, such as soldiers, truck drivers, medical staff and clubbers.

There have been some media attention in Norway concerning students using stimulant drugs, like amphetamines and methylphenidate, as a performance enhancer (sometimes referred to as “academic doping”/”smart drugs”). Modafinil has been mentioned in this context. We have no reliable information on the extent of this usage in Norway, but it may be an increasing trend. This is of concern.

Modafinil can be bought via internet, and it is anticipated that modafinil for this use is mainly provided illegally. Accordingly, we do not expect that this misuse of modafinil will increase as a consequence of changing the prescription group from A to B in Norway.

7.4. Off-label use

In several non-EU countries obstructive sleep apnoea and shift work disorder are approved indications. Modafinil is also prescribed to patients with chronic fatigue syndrome/excessive sleepiness caused by different systemic or degenerative diseases, psychiatric disorders (depression, ADHD, schizophrenia) or structural brain disorders (injury, neoplasm).

8. CONCLUSION:

Reclassification of the drug from prescription group A to B will increase the availability of the drug. This might possibly increase the level of off-label use. As special care should be taken when drugs in both prescription group A and B are prescribed and dispensed, we do not consider that this reclassification will seriously increase the risk of abuse or misuse of the drug. We consider that rules that apply for prescription group B are sufficient to ensure the safe use of the product. Further, in the majority of EU countries, modafinil is classified in prescription categories corresponding to prescription group B or C in Norway. In addition, the product will still be subject to restricted medical prescription.

It can be concluded that modafinil does not seem to fulfil any of the criteria or considerations which have to be fulfilled for prescription group A, and a change of prescription group from A to B can be recommended.

9. REFERENCES:

George WT, et al. New onset of compulsive gambling associated with modafinil: A case report. Primary Care Companion to the Journal of Clinical Psychiatry 17: No. 1, 2015. Available from: URL: http://doi.org/10.4088/PCC.14l01707 - USA

Kate N, et al. Dependence on supratherapeutic doses of modafinil: A case report. Primary Care Companion to CNS Disorders 14: No. 5, 2012. Available from: URL: http://dx.doi.org/10.4088/PCC.11l01333 - India

Ozturk A, et al. Drug abuse of modafinil by a cannabis user. Klinik Psikofarmakoloji Bulteni 24: 405-407, No. 4, 2014. Available from: URL: http://www.scopemed.org/fulltextpdf.php?mno=37828 – Turkey

Raman K, Krishnan VC. A rare case of modafinil dependence. J Pharmacol Pharmacother. 2015; 49-50

Swapnajeet S, et al. Modafinil dependence and hypersexuality: A case report and review of the evidence. Clinical Psychopharmacology and Neuroscience 14: 402-404, No. 4, Nov 2016.

Vidyendaran R, et al. Psychosis due to high dose self-administered modafinil – A case report. Indian Journal of Psychiatry 54: S83, Apr 2012 – India