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Patient Health Protection

Assessment report for modafinil containing medicinal products

International non-proprietary name: modafinil

Procedure number: EMEA/H/A-31/1186

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 14 May 2009, the United Kingdom triggered a referral under Article 31 of Directive 2001/83/EC, as amended (see enclosure 1). The CHMP was requested to give its opinion on whether the marketing authorisations for medicinal products containing modafinil should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

2. Scientific discussion

2.1. Introduction

Modafinil is a wakefulness promoting agent, currently licensed in 21 countries in Europe. The approved indications vary throughout Europe. Sleepiness associated with narcolepsy is the only indication approved in all Member States where the product is approved. The other indications for modafinil are excessive sleepiness associated with:

- Idiopathic hypersomnia (IH), approved in 4 member states;

- Obstructive Sleep Apnoea (OSA), approved in 11 member states;

- Moderate to severe chronic shift work sleep disorder (SWSD), approved in 10 member states.

Modafinil was first authorized in the EU in France, in June 1992. The mechanism of action is not entirely understood, but the most consistent findings of the various studies performed are the inhibitory effects on the dopamine and norepinephrine transporters.

In 2007, concerns relating to serious psychiatric disorders (suicidal thoughts/behaviour, symptoms of psychosis and mania) and serious skin and subcutaneous tissue disorders (including erythema multiforme and Stevens-Johnson syndrome) prompted a review of the available data from clinical trials and spontaneous adverse reaction reports by the Pharmacovigilance Working Party (PhVWP). The data from clinical trials in particular raised concerns about the risk of serious skin disorders requiring hospitalization in association with the use of modafinil in children. As a result, the product information for modafinil was updated across Europe to include strengthened warnings.

A later review performed by the MHRA revealed additional concerns regarding the benefit-risk balance of some of the indications for which very limited efficacy data exists. Because of the newly identified risks of psychiatric and skin reactions in conjunction with cardiovascular risks, but also evidence of significant off label use and concerns about potential abuse, misuse or diversion, a formal review of the full benefit-risk balance of modafinil was initiated by the CHMP through an article 31 referral procedure.

In this assessment of the benefit-risk profile of modafinil in its different indications, the CHMP reviewed available data from pre-clinical and clinical studies, spontaneous reports, published literature and other data submitted by the MAHs as relevant. The CHMP Scientific Advisory Group (SAG) was also consulted.

2.2. Clinical efficacy

2.2.1. Results

<u>Narcolepsy</u>

The efficacy of modafinil in narcolepsy was assessed mainly in 2 phase 3, multicenter, double blind, placebo controlled, randomized clinical trials (301 and 302). The two trials were similar in size and

design, employing the same methods to assess efficacy. Objective methods were the Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT). Severity of illness was measured with the subjective Clinical Global Impression of Change (CGI-C). Patient self assessment of sleepiness was determined by the subjective Epworth Sleepiness Scale (ESS) which has been validated for use in measuring excessive sleepiness in narcolepsy.

Table 1 - Main narcolepsy studies included in efficacy review

Narcolepsy studies / short-term and long-term data						
Study number	Dose		Study duration		Total no. of evaluable patients	
	Short-term	Long-term	Short-term	Long-term	Short-term	Long-term
Principal placebo-controlled						
C1538a/301/NA/US	200 mg QD 400 mg QD	400 mg QD 300 mg QD 200 mg QD	9 weeks/DB	Total 232 OL weeks (40 week OL + 48 week OL extension + three 48 week OL continuous phases)	181 modafinil (95 at 200 mg and 86 at 400 mg) 92 placebo	238 total
C1538a/302/NA/US	200 mg QD 400 mg QD	400 mg QD 300 mg QD 200 mg QD	9 weeks DB	Total 232 OL weeks (40 week OL + 48 week OL extension + three 48 week OL continuous phases)	169 modafinil (83 at 200 mg and 86 at 400 mg) 88 placebo	240 total

A total of 554 patients were enrolled in the two studies, receiving fixed daily doses of modafinil 200 or 400 mg or placebo over nine weeks. The first study was followed by an open-label treatment period, whereas the second included a 2-week discontinuation phase to evaluate modafinil withdrawal effects. Inclusion criteria were diagnosis of narcolepsy based on the International Classification of Sleep Disorders (ICSD-1) criteria and a MSLT score of < 8 minutes.

Results for MSLT, MWT and CGI-C are summarized in table 2.

Table 2 – Results at final visit in narcolepsy studies (week 9)

	Placebo		**Modafinil 200mg**		**Modafinil 400mg**	
MSLT(min)						
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
Baseline	2.8	2.2	2.9	3	3.3	2.8
Week 9	3.3	3.5	4.7	5	5.1	5.1
Change	**0.5**	**1.3**	**1.8**	**2.0**	**1.8**	**2.3**
MWT (min)						
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
Baseline	5.8	6.0	5.8	6.1	6.6	5.9
Week 9	5.1	5.3	8.2	8.3	8.9	7.9
Change	**-0.7**	**-0.7**	**2.4**	**2.2**	**2.3**	**2.0**

	Placebo		**Modafinil 200mg**		**Modafinil 400mg**	
CGI-C rating (%)						
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
Very much improved	4	0	7	8	9	6
Much improved	9	14	26	25	41	28
Minimally improved	24	24	31	24	22	27
Total % improved	**37**	**38**	**64**	**57**	**72**	**61**
No change	47	48	28	33	20	30
Minimally worse	12	10	5	8	3	6
Much worse	3	5	2	1	1	3
Very much worse	1	0	0	0	0	0
Total % worsened	**16**	**15**	**7**	**9**	**4**	**9**

In study 301, statistically significant increases in the MSLT and MWT values were observed in both modafinil groups (200 and 400 mg) when compared with baseline values or with the placebo group. However, the size of the increases did not differ between the two modafinil groups. Statistically significant improvement on the CGI-C scale was also noted for both modafinil groups when compared to placebo.

Significant increases were also observed at the end of the trial in the number of patients who were able to remain awake throughout three of the four daily 20 minute MWTs. At baseline, 4% of patients receiving 200 mg of modafinil and 3% of those receiving 400 mg modafinil or placebo were able to remain awake for at least three tests. On week 9, those figures were increased to 14% and 20% in the groups receiving 200 mg and 400 mg modafinil respectively, with no changes observed in the placebo group.

In study 302, MSLT was statistically significantly increased at week 9 in all 3 groups when compared to baseline values. Improvements in MWT and CGI-C were also statistically significant for both modafinil groups. However, for MSLT, MWT and CGI-C no statistically significant difference could be observed between the two modafinil groups.

Self reported sleepiness, measured by the ESS (a secondary outcome) was also found to be statistically significantly reduced in the modafinil groups compared to placebo at all time point measured. For trial 301, ESS scores improved by 1.4, 3.6 and 4.3 points for patients receiving placebo, 200mg and 400mg modafinil, respectively. The difference between the two modafinil groups was not statistically significant. For trial 302, ESS scores improved by 1.7, 4.3 and 5.7 points for patients receiving placebo, 200mg and 400mg modafinil, respectively. As in the first study, the difference between the two modafinil groups was not statistically significant.

The two studies 301 and 302 were continued as open label studies. The improvements in subjective ESS scores and subjective assessment of disease severity were maintained.

Obstructive Sleep Apnoea (OSA)

The efficacy of modafinil as an adjunct therapy in obstructive sleep apnoea for residual daytime sleepiness despite regular use of nasal continuous positive airway pressure therapy (CPAP) has been evaluated mainly in two phase 3 randomised, double blind, placebo controlled trials (303 and 402). The participants had been previously diagnosed with OSA and were required to meet CPAP effectiveness criteria which were defined as $\geq$ 4 hours of CPAP usage per night on at least 70% of the nights. Patients were diagnosed with excessive sleepiness based on the self-assessment ESS, with a score of $\geq$ 10 at screening.

Table 3 - Main OSA studies included in the efficacy review

Obstructive sleep apnoea/hyponea syndrome (OSAHS) studies / short-term and long-term data						
Study number	Dose		Study duration		Total no. of evaluable patients	
	Short-term	Long-term	Short-term	Long-term	Short-term	Long-term
Principal placebo-controlled						
C1538a/303/AP/US-UK	200 mg, 400 mg; once daily in AM	200, 300, or 400 mg/day	12 weeks	12 months	291 (99 at 200 mg, 92 at 400 mg, 100 pbo)	266 (229 pts received $\geq$ 6 mo; 136 pts $\geq$ 12 mo
C1538a/402/AP/US	200 mg once in AM for 1 week, then 400 mg in AM for 3 weeks	200, 300, or 400 mg/day[a]	4 weeks	12 weeks	155 (75 modafinil[b], 80 pbo)	125 (89 pts received at least 12 weeks)

The studies had important differences with regard to the duration and the dosages of modafinil. Both used the same subjective measurements of efficacy (ESS, CGI-C) but different objective measurements (MWT in 303 and MSTL for 402). Results are summarized in table 4.

Table 4 - Results at final visit in OSA studies

	Placebo		Modafinil 200mg		Modafinil 400mg	
MWT(min)						
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
Baseline	13.7	-	13.1	-	13.6	-
Week 12	12.6	-	14.7	-	15.0	-
Change	**-1.1**	-	**1.6**	-	**1.4**	-
MSLT (min)						
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
Baseline	-	7.4	-	-	-	7.6
Week 4	-	7.2	-	-	-	8.6
Change	-	**-0.2**	-	-	-	**1.0**
ESS						
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
Baseline	14.7	14.4	15.7	-	14.9	14.2
Week 4	-	12.4	-	-	10.4	9.6
Week 12	12.9	-	11.2	-	-	-
Change	**-1.8**	**-2.0**	**-4.5**	-	**-4.5**	**-4.6**
CGI-C (% of improved patients)						
	Study 1	**Study 2**	**Study 1**	**Study 2**	**Study 1**	**Study 2**
Responders	37	34	60	-	68	68

It should be noted that none of the studies included an objective measurement of sleepiness in the inclusion criteria, which raises questions regarding the appropriateness of the population recruited.

In study 303, mean MWT values increased by 1.6 and 1.4 minutes for patients treated with 200 and 400 mg of modafinil, respectively. Patients treated with placebo had a mean reduction of MWT of 1.1 minutes. At the end of the study, patients in both modafinil groups had a 4.5 point decrease in the EES score, compared to a 1.8 decrease for the placebo arm. No statistically significant differences were observed between the two modafinil dosages in any of the parameters. Treatment with modafinil significantly improved the overall clinical condition as assessed by CGI-C, with 37%, 60% and 68% of patients reporting improvement with placebo, modafinil 200 mg and 400 mg, respectively.

Significant differences ($p<0.001$) were found in study 303 for the total score of the Functional Outcomes of Sleep Questionnaire (FOSQ). Significant improvement ($p<0.02$) was reported specifically for the aspects vigilance, general productivity and activity. Neither modafinil nor placebo had a negative effect on sleep quality or CPAP use.

The discontinuation rate due to adverse events was 2.8% for placebo, 9.6% for modafinil 200 mg and 10.9% for modafinil 400 mg. LOCF was used as the primary analysis method and this may have influenced the results in favour of modafinil.

In study 402, MSLT values remained unchanged for patients in the placebo group but were statistically significantly increased in the modafinil 400 mg group, from 7.6 minutes at baseline to 8.6 minutes at the end of week 4. There was no statistically significant difference in the percentage of subjects who normalised their MSLT scores (i.e. to above 10 minutes) between the placebo and the modafinil groups (25% and 29%, respectively).

The percentage of patients that experienced improvement in the CGI-C values was significantly higher for modafinil (68%) when compared to placebo (34%). ESS changes at the end of the trial were also statistically significant between placebo (-2.0) and modafinil (-4.6). Nocturnal polysomnography parameters and CPAP were also monitored, and while no differences were seen in time spend in the various sleep stages or in total CPAP use, a small but significant difference occurred in the arousal index (number of arousals per hour of sleep) between the modafinil (14.3) and placebo (11.8) groups.

The two studies 303 and 402 were continued as open label. During the 12-months open label extensions of the studies, subjective parameters such as ESS, psychomotor vigilance test (PVT), FOSQ and the short form-36 health survey (SF-36) continued to be monitored and results indicate that a beneficial effect of modafinil was maintained. However, no objective measures were assessed in the long term.

Shift Work Sleep Disorder (SWSD)

The effectiveness of modafinil in the treatment of excessive daytime sleepiness associated to shift work sleep disorder was investigated in one phase 3 randomised, double-blind, placebo-controlled study (305). The Marketing Authorisation Holder did submit data on a second phase 3 randomised, double-blind, placebo-controlled study (306) but this was a safety study with no efficacy endpoints and therefore not relevant for the assessment of efficacy.

Table 5 - SWSD studies included in the efficacy review

Shift Work Sleep Disorder (SWSD) / Short-term and Long-term Data						
Study number	**Dose[a]**		**Study duration**		**Total no. of evaluable Patients**	
	Short-term	**Long-term**	**Short-term**	**Long-term**	**Short-term**	**Long-term**
Principal placebo-controlled						
Study 305	200 mg QD	200 mg QD	12 weeks	12 months	193 (89 modafinil, 104 pbo)	113
Study 306	200 mg QD 300 mg QD	200 mg QD[b] 300 mg QD[b]	12 weeks	12 months	262 (86 at 200 mg and 90 at 300 mg modafinil, 86 pbo)	161

QD = once daily dosing; pbo = placebo
[a] Only taken on nights the patient worked.
[b] Dose was decided upon by the investigator.

In study 305, 209 subjects with SWSD were randomly assigned to a three-month trial receiving modafinil at 200 mg daily or placebo before each night shift; 153 patients completed the study. Participants had worked at least five night shifts per month (of which at least 3 had to be consecutive) and had a diagnosis of SWSD according to criteria stipulated in ICSD (i.e. excessive sleepiness on the shift and insomnia during daytime). Subjects also had to have reported chronic excessive sleepiness of at least 3 months, a CGI-C rating of at least 'moderately ill' for sleepiness during shifts, a MSLT score of 6 minutes or less and sleep efficiency of 87.5% or less. The primary efficacy variables were MSLT (objective) and CGI-C (subjective). As the MSLT is not validated for use as an objective measure of sleepiness during the night, the Psychomotor Vigilance Test (PVT) was used by the investigators as a secondary measure of efficacy. Other secondary measures included the subjective Karolinska Sleepiness Scale (KSS). Patients also completed an electronic diary with questions on caffeine use, sleep and sleepiness during the night shift and the commute home. Results for the main parameters can be found in table 6.

Table 6 - Results of study 305

	Placebo	Modafinil 200mg
MSLT (min)		
Baseline	2	2.1
Week 4	2.4	3.8
Change	**0.4**	**1.7**
CGI-C (% of improved patients)		
Improved		
Very much	8	24
Much	13	31
Minimal	15	19
Total improved	**36**	**74**
No change	59	23
KSS		
Baseline	7.1	7.3
Week 4	6.7	5.8
Change	**-0.4**	**-1.5**

The study was conducted over 3 months, during which 51 participants withdrew at various time points. Only 81 placebo-treated and 72 modafinil treated subjects completed the study.

After 12 weeks of treatment, modafinil 200 mg significantly increased the mean MSLT score from 2.1 to 3.8 minutes and this difference was statistically significantly different from placebo. CGI-C values were significantly increased in modafinil subjects, as were the KSS values. Results from individual variables are described below in table 7. It should be noted that baseline values were not provided for some of the variables.

Table 7 - Variables for subjects in study 305 as derived from diaries

Variable	Placebo (N=108)			Modafinil (N=96)			P Value
	Baseline	After Baseline	Change	Baseline	After Baseline	Change	
During night shift							
Maximum level of sleepiness — score†	7.4±1.0	6.6±1.3	−0.9±1.0	7.3±0.9	5.4±1.5	−1.9±1.4	<0.001‡
No. of unintentional sleep episodes†	1.2±1.3	0.6±0.7	−0.6±1.0	1.0±1.1	0.2±0.4	−0.8±0.9	0.20
No. of intentional sleep episodes†	0.5±0.8	0.4±0.5	−0.1±0.5	0.4±0.5	0.2±0.4	−0.2±0.4	0.13
No. of caffeinated drinks consumed†	1.3±1.1	1.1±0.9		1.3±1.2	1.0±1.0		0.10
Patients reporting mistakes, accidents, or near accidents — no. (%)§		59 (55)			46 (48)		0.34
During the commute home							
Level of sleepiness — score†	5.9±1.8	5.4±1.7	−0.6±1.2	5.5±1.8	4.4±1.6	−1.1±1.5	0.012‡
Patients reporting unintentional sleep episodes — no. (%)§		47 (44)			34 (35)		0.24
Patients reporting accidents or near accidents — no. (%)§		58 (54)			28 (29)		<0.001¶

Importantly, modafinil had no significant effect on unintentional or intentional sleep episodes, caffeine consumption or reported mistakes, accidents or near accidents during the night shift. In contrast, the median lapses of attention, measured for the PVT, decreased significantly with modafinil when compared to placebo (p=0.0065).

Study 305 was continued as open label. During the 12-month open label extension, 125 patients continued to receive 200 mg modafinil and only the subjective FOSQ was measured. No clinically or statistically significant improvement was observed in this study in terms of quality of life.

Idiopathic Hypersomnia (IH)

In order to support efficacy in this condition, the MAH submitted 7 legacy studies conducted in the combined narcolepsy/idiopathic hypersomnia population. Only one of these studies was controlled, the remaining did not provide any evidence of efficacy. Three of these 7 studies were open label with only qualitative details of efficacy, one was an open label safety study, one was a named patient programme with no formal evaluation of efficacy, and the last one was a retrospective, non-GCP compliant analysis of patients treated with modafinil.

Table 8 - IH studies submitted in support of efficacy

Idiopathic hypersomnia (IH) / short-term and long-term data						
Study number	Dose		Study Duration		Total no. of evaluable patients	
	Short-term	Long-term	Short-term	Long-term	Short-term	Long-term
MOD-024[a]	100 mg BID	NA	6 weeks/DB crossover	NA	6	NA
NPP[b]	NA	50 mg/day to 1000 mg/day	NA	up to 108 weeks	NA	15
MOD-026	NA	100 mg/day – 500 mg/day	NA	3 months – 3 years	NA	30
MOD-027	NA	100 mg/day – 300 mg/day	NA	120 days	NA	7
MOD-028	NA	50 mg/day – 600 mg/day	NA	1 month – 10 years	NA	59
E1027	NA	100 mg/day – 400 mg/day	NA	24 months	NA	101
Retrospective study	NA	Not specified	NA	Not specified/OL	NA	67

[a]Minimum duration of 6 weeks: a 15-day reference period w/no treatment; a 4-week DB crossover, modafinil 200 mg/day (100 mg AM and 100 mg PM) or placebo; and an optional 2-week OL modafinil 300 mg/day (200 mg am and 100 mg pm) for patients who did not respond to treatment during the DB period. Note: Only data for the DB portion are summarized in this section.
[b]Named patient program (UK/Ireland).
NOTE: These studies included both patients with narcolepsy and with idiopathic hypersomnia.

The double-blind crossover trial MOD-024 had duration of 6 weeks and included 36 patients, of which 30 were diagnosed with narcolepsy and another 2 had sleep apnoea. It can therefore be concluded that only 4 patients with a true diagnostic of idiopathic hypersomnia were included.

Following a 2 week period with no treatment, patients received either modafinil (100 mg twice a day) or placebo for another two weeks. In the last 2 weeks of the study, those previously on placebo would switch to modafinil and those on modafinil would switch to placebo. Only subjective measurements of efficacy were used. Results calculated for 6 patients (including 2 with sleep apnoea) showed significant decrease in incidence of diurnal sleep episodes ($p<0.05$), even though 2 of the participants did not report any improvement of the symptoms.

2.2.2. Discussion

Narcolepsy

In the two studies presented, results obtained with both objective efficacy measures used were consistent and demonstrated statistically significant benefits of modafinil when compared to placebo. Improvements were also noted in the subjective measurements. Overall, these studies provide proof of the short term efficacy of modafinil in treating excessive daytime sleepiness in patients with narcolepsy.

It is however noted that the dose-response profile does not seem to be linear. In fact, no statistically significant difference was noted between the two modafinil doses used (200 and 400 mg) in any of the measurements.

Maintenance of the efficacy in the long term has not been demonstrated, as the existing long term data is uncontrolled.

Obstructive Sleep Apnoea

In the two studies presented, modest improvement was seen in the objective parameters measured. In study 303, 200 mg and 400 mg of Modafinil resulted in increases of MWT of 1.6 and 1.4 minutes, respectively, when compared to baseline. In addition, the difference between modafinil and placebo was very small (6-10%) for robust differences in MWT. In study 402, MSLT increased from 7.6 minutes at baseline to 8.6 minutes. These differences, although statistically significant, are very small and

therefore its clinical significance is questioned. After 4 weeks of treatment, subjects in study 402 still presented with MSLT values below the normal (i.e. 10 minutes). In addition, there was no significant difference between placebo and modafinil in the percentage of patients who normalise their MSLT scores, which is indicative that a clinically relevant effect has not been established.

It should be noted that none of the studies included an objective measurement of sleepiness in the inclusion criteria, which raises additional questions regarding the appropriateness of the population recruited.

While small short-term improvements could be observed in objective sleep measurements, the more pronounced effects were seen in subjective measurements of sleepiness. The effects of modafinil on the subjective sleepiness should be interpreted with caution, due to possible unblinding of treatment during the trials because of the neuropsychiatric profile of modafinil.

The SAG considered that amongst OSA patients fully optimised on disease modifying treatment (such as CPAP) and in which all other causes of sleepiness have been treated, only a small subpopulation of patients could potentially benefit from modafinil treatment. However, after assessing a subgroup analysis of OSA patients based on possible prognostic factors, the CHMP concluded that it did not allow identification of any specific subgroup where modafinil would have the greatest chance of benefit. Furthermore, it was noted that differences likely to be clinically significant in objective measures of sleepiness between modafinil and placebo were limited to a very small percentage of the patient population in the modafinil clinical trials.

As in the narcolepsy studies, no dose response effect was observed. The 400 mg dose in study 303 did not lead to higher MWT differences or improved ESS score than the 200 mg dose.

The efficacy in the long term has also not been demonstrated, as the existing long term data is uncontrolled and only subjective parameters were measured.

Shift Work Sleep Disorder

In study 305, a modest but statistically significant improvement was observed in the MSLT score. However, the clinical relevance of this increase is questionable as, at the end of the study, the patients would still be characterised as severely ill (severe illness according to ICSD-1 is usually associated to MSLT scores below 5). This is further illustrated by the fact that patients at the end of the trial were sufficiently sleepy to meet the entrance criteria for the study (MSLT<6 minutes).

While a significant improvement was seen in CGI-C and PVT scores for modafinil treated subjects, these are subjective measures and their validity for use in this specific type of sleep disorder is unclear.

While improvement was reported on the number of accidents or near accidents during the commute, no account was taken for the type or duration of the commute and no baseline values were collected. Therefore this information is of limited value.

The efficacy in the long term has also not been demonstrated. Existing long term data are not controlled, are based on a subjective parameter and have failed to demonstrate a significant effect of modafinil.

Following consultation with the SAG, the CHMP concluded that the effects on both subjective and objective measures did not provide clear evidence of overall beneficial effect.

Idiopathic Hypersomnia

Data presented in support of this indication includes a total of 6 patients, of which at least 2 actually presented with excessive sleepiness due to sleep apnoea. Even though the prevalence of idiopathic hypersomnia is thought to be very low (between 1/10 000 and 1/25 000 for IH with long sleep time and between 1/11 000 and 1/100 000 for IH without long sleep time) and the difficulties in conducting large scale trials are acknowledged, no conclusions can be drawn to support the efficacy of the product with such a limited dataset.

2.3. Clinical safety

Total worldwide exposure to modafinil was estimated to be around 1 666 976 patient treatment-years (PTY). A breakdown of the exposure in Europe between 1 March 2009 and 31 August 2009 is included in table 9.

Table 9 - Estimated patient exposure to modafinil in Europe (between 31 March 2009 and 31 August 2009)

Country	Exposure (patient-treatment years)
Austria	369.9
Belgium	1203.2
Czech Republic	128.6
Denmark	712.0
France	10068.5
Germany	3872.6
Greece	1824.4
Hungary	4.8
Ireland	638.6
Italy	847.6
Luxemburg	27.7
Netherlands	940.6
Poland	2.1
Portugal	249.8
Slovakia	47.1
Spain	3815.8
Sweden	2211.0
United Kingdom	6111.9

2.3.1. Results

Skin and hypersensitivity reactions

Skin reactions
The MAH's clinical database included 5849 patients (4227 adults and 1622 children) on modafinil. A total of 481 (8%) of these patients experienced an adverse event included in the Standardised MedDRA Query (SMQ) for severe cutaneous adverse reactions (SCARs), and incidence was higher in children (12%) than in adults (7%). At least three cases were considered to be serious and associated with modafinil. All three cases occurred in children.

Table 10 - Cases identified in clinical trials with clinical features suggestive of SCARs

Study	*Age (y)*	*Adverse event*	*Days on treatment*	*Modafinil dosage (mg/day)*	*Duration of event (days)*	Intervention /outcome
C1538d/311/AD/US	7	EM/SJS	16	340	15	Discontinued/ Resolved
C1538/213/AD/US	8	EM	23	300	36	Discontinued/ Resolved
C1538a/207/AD/US	11	Morbiliform rash	3	200	13	Discontinued/ Resolved

EM = Erythema Multiforme; SJS = Stevens Johnson Syndrome

Patients exposed to modafinil on placebo-controlled studies experienced skins reactions more frequently than patients exposed to placebo (5.7% and 4.2% respectively for narcolepsy; 4.1% and 1.3% respectively for OSA).

Cumulative post-marketing data revealed the following spontaneous reports of serious skin reactions:

- Stevens Johnson Syndrome (n=11)
- Toxic Epidermal Necrolysis (n=3)
- Erythema Multiforme (n=3)
- Drug rash with eosinophilia and systemic symptoms (n=3)

- Exfoliative dermatitis (n=1)
- Other (n=31)

Three out of the 16 reported cases of SJS/TEN/EM had a fatal outcome. All reports were for adults with the exception of one case in a 17 year old treated for attention-deficit hyperactivity disorder (ADHD). In at least 6 of these 16 cases, modafinil was being used for a non approved indication. Causality could not be excluded in the majority of cases.

For the 3 reported cases of drug rash with eosinophilia and systemic symptoms (DRESS), no specific risk factors could be identified. However it is noted that in 2 of these cases the event onset coincided with the dose increase up to 400 mg daily.

Of the remaining serious skin reactions, the most commonly terms reported were hyperhidrosis (8), rash (4) and rash pruritic (4). A fatal outcome was reported in one case, but cause of death was unknown, and 2 other cases required hospitalization.

Hypersensitivity reactions
A review of the MAH's clinical studies database identified a total of 894 (15%) patients who experienced a hypersensitivity reaction. The overall incidence was higher is children (25%) than in adults (12%). In 52 patients, the adverse events of possible drug-related hypersensitivity led to the withdrawal of the study drug. Most commonly reported terms were rash (10), dyspnoea (9) and chest discomfort (9). An additional case identified in this review was a child who presented features consistent with multi-organ hypersensitivity syndrome (fever, urticaria, facial swelling and elevated liver functions tests).

In double blind studies, preferred terms with the biggest differences in incidence between the modafinil and placebo treated patients per indication are presented in the table below:

Table 11 – Incidence (%) of hypersensitivity terms in modafinil double-blind studies

Trial indication	Narcolepsy		OSA		SWSD		Other	
	Modafinil		Modafinil		Modafinil		Modafinil	
Treatment	+	-	+	-	+	-	+	-
Chest discomfort	1.0	0	1.5	0.9	1.1	0.5	0.6	0.1
Pyrexia	2.2	1.2	-	-	-	-	2.1	1.4
Cough	2.7	1.8	-	-	1.8	1.0	-	-
Asthma	0.8	0	-	-	-	-	-	-
BP diastolic increased	0.7	0	-	-	-	-	-	-
Dyspnoea	0.8	0.3	-	-	1.1	0.5		
Eosinophil count increased	0.5	0	-	-	-	-	-	-
Seasonal allergy	-	-	0.9	0	-	-	-	-
Sneezing	-	-	0.6	0	-	-	-	-
Flushing	-	-	0.9	0	1.5	0.5	-	-

A review of the MAH's pharmacovigilance database identified 698 cases of hypersensitivity reactions, 113 of which were considered to be serious. Among these, there were 16 reported cases of anaphylactic reaction, 34 cases of urticaria/angioedema and 7 cases of multi-organ hypersensitivity. Two of the cases reporting anaphylactic reaction had fatal outcome, and in at least one, causality was considered to be very likely. Close temporal association between event onset and modafinil and positive de-challenge/re-challenge suggest that anaphylaxis is related to modafinil.

Cases of multi-organ hypersensitivity were identified based on the presence of fever, rash, lymphadenopathy and evidence of other concurrent organ involvement. Modafinil was prescribed for non-approved indications in all but one of these cases. In addition, one fatal case was identified from the published literature and described as 'acute necrotizing eosinophilic myocarditis with a systemic necrotizing inflammatory process also involving skeletal muscle, the liver and the spinal cord, most consistent with severe drug-induced hypersensitivity reaction'.

Nervous system disorders

In total, 2076 (35%) of the patients in the MAH's clinical database experienced an adverse event captured by the nervous system search. The overall incidence was similar in adults (36%) and children (35%). Table 13 summarizes the terms with the biggest differences in incidence between the modafinil and placebo treated patients per indication in placebo controlled studies.

Withdrawals in clinical trials due to nervous system adverse events occurred in 4% of adults and 2% of children. The majority was due to headache. There were 16 serious adverse events in adult patients (0.4%) and 4 serious events in children (0.2%).

The most frequent spontaneously reported adverse events identified from the nervous system disorders search in the MAH's database were headache (n=639), dizziness (n=227) and somnolence (n=220). The serious reports were classified as follows:

Dizziness (n=10)
A positive re-challenge was reported in 6.8% of the non-serious reports.

Convulsions (n=43)
Causality assessment is not possible for many cases due to insufficient information included in the reports.

Cerebrovascular disorders (n=24)
While in many cases these patients had risk factors for cerebrovascular disorders, the majority of the cases that contained information on time to onset were suggestive of a temporal association with the product.

Table 12 - Incidence (%) of nervous system disorders terms in modafinil double-blind studies

Trial indication	Narcolepsy		OSA		SWSD		Other	
	Modafinil		Modafinil		Modafinil		Modafinil	
Treatment	+	-	+	-	+	-	+	-
Headache	35.8	24.8	23.1	11.6	22.0	16.0	18.6	13.3
Cataplexy	2.5	1.2	-	-	-	-	-	-
Hypo-aesthesia	1.0	0	-	-	-	-	-	-
Muscle spasms	1.0	0.3	1.8	0	1.1	0.5	1.0	0.1
Muscle Tightness	0.7	0	-	-	-	-	0.7	0
Disturbance in attention	0.7	0	1.8	0.4	-	-	-	-
Musculoskeletal stiffness	0.5	0	-	-	-	-	-	-
Balance disorder	0.5	0	-	-	-	-	-	-
Memory impairment	0.5	0	-	-	-	-	-	-
Tic	0.5	0	-	-	-	-	0.6	0
Dizziness	-	-	5.6	2.7	-	-	3.0	1.4
Somnolence	-	-	1.2	0	-	-	-	-
Dysgeusia	-	-	0.9	0	1.1	0	-	-
Paraesthesia	-	-	0.9	0	-	-	0.9	0.1
Psychomotor hyperactivity	-	-	0.6	0	1.5	0	-	-
Syncope	-	-	0.6	0	-	-	-	-
Tremor	-	-	-	-	1.8	0	2.2	0.8
Restlessness	-	-	-	-	1.5	0	-	-

Extrapyramidal symptoms (n=54)
Positive re-challenge or de-challenge were reported in cases of bruxism, dyskinesia, tremor, increased psychomotor activity, paraesthesia and muscle spasms.

Psychiatric disorders

A total of 2026 (35%) of the patients included in the MAH's clinical database experienced an adverse event captured by the psychiatric disorders search. Table 14 summarizes the terms with the biggest differences in incidence between the modafinil and placebo treated patients per indication in placebo controlled studies.

Withdrawals due to psychiatric adverse events occurred in 5.5% of the patients. The most commonly reported events leading to study discontinuation were insomnia, anxiety, irritability, depression and agitation. There were 20 serious adverse events identified in adult patients and 12 serious events in children. These cases included a case of suicide in a patient with a history of depression, a case of suicidal ideation in a narcoleptic patient, a case of aggression in an elderly patient with dementia and a psychotic episode in a healthy patient with no medical history of interest. In 28 out of the 32 serious cases, the dose of modafinil was greater than 200 mg.

The most frequent spontaneously reported adverse events identified from the psychiatric disorders search in the MAH's database were:

Hostility/aggression (n=517)
Of these, 103 were serious and 4 had a fatal outcome. While many cases lacked sufficient information to allow for causality assessment, reasonable temporal association and positive de-challenge and/or re-challenge information exists for some of the other cases.

Psychosis/psychotic disorders (n=331)
Of these, 80 were serious and one had a fatal outcome. Despite the limited information available in many of the reports, causal association was considered possible in some cases.

Table 13 - Incidence (%) of psychiatric disorders terms in modafinil double-blind studies

Trial indication	Narcolepsy		OSA		SWSD		Other	
	Modafinil		Modafinil		Modafinil		Modafinil	
Treatment	+	-	+	-	+	-	+	-
Irritability	3.0	1.8	-	-	-	-	-	-
Insomnia	2.7	0.6	4.4	0.4	6.2	1.5	12.0	4.0
Anxiety	2.4	0.6	6.4	1.3	2.9	0.5	6.3	1.3
Depression	2.2	1.5	1.2	0.4	0.7	0	1.1	0.3
Nervousness	1.8	1.2	2.9	0.4	2.6	0.5	2.5	0.4
Disturbance in attention	0.7	0	1.7	0.4	-	-	-	-
Confusional state	0.7	0	-	-	-	-	-	-
Initial insomnia	0.8	0.3	-	-	1.1	0	4.0	1.2
Memory impairment	0.5	0	-	-				
Agitation	0.5	0	0.6	0	0.7	0	3.4	1.2
Tic	0.5	0	-	-	-	-	-	-
Psychomotor hyperactivity	-	-	0.6	0	1.5	0	0.6	0
Restlessness	-	-	-	-	1.5	0	-	-
Abnormal. Dreams	-	-	-	-	0.7	0	-	-
Euphoric mood	-	-	-	-	-	-	2.1	1.1
Sleep disorder	-	-	-	-	-	-	1.2	0.7
Tension	-	-	-	-	-	-	1.1	0.1
Bruxism	-	-	-	-	-	-	0.8	0
Aggression	-	-	-	-	-	-	0.8	0.3
Personality disorder	-	-	-	-	-	-	0.5	0
Total	**16.7**	**10.9**	**19.6**	**6.2**	**17.2**	**3.6**	**34.1**	**16.1**

Depression (n=330)
Of these, 36 were considered serious. Many were considered to be likely related to the underlying medical condition.

Suicide and self-injury (n=118)
Of these, 85 were considered serious, and 15 had a fatal outcome. Many of the patients with suicidal behaviour presented alternative aetiologies such as pre-existing psychiatric history, drug-abuse history and previous suicidal behaviour.

Cardiovascular disorders

A total of 615 (11%) of the modafinil treated patients included in the MAH's clinical database experienced an adverse event captured by the cardiovascular search, comparing to only 6% in the placebo group. The majority of withdrawals were due to palpitations (n=16), dyspnoea (n=9), chest pain (n=9), hypertension (n=8) and increased blood pressure (n=6). Preferred terms with the highest difference in incidence between the modafinil and placebo treated patients per indication are presented in the table below.

Table 14 - Incidence (%) of cardiovascular terms in modafinil double-blind studies

Trial indication	Narcolepsy		OSA		SWSD		Other	
	Modafinil		Modafinil		Modafinil		Modafinil	
Treatment	+	-	+	-	+	-	+	-
Decreased diastolic BP	0.7	0	-	-	-	-	-	-
Dyspnoea	0.8	0.3	-	-	1.1	0.5	-	-
Hypertension	0.7	0	-	-	2.6	0	-	-
Increased blood pressure	-	-	2.6	0.4	1.1	0	-	-
Palpitations	-	-	2.3	0	2.2	0	3.0	0.7
Chest pain	-	-	2.0	0	1.5	0.5		
Increased heart rate	-	-	0.9	0	1.5	0.5	0.9	0.3
Increased diastolic BP	-	-	0.6	0	-	-	-	-
Syncope	-	-	0.6	0	0.7	0	-	-
Prolonged QT	-	-	-	-	1.1	0	-	-
Pitting oedema	-	-	-	-	0.7	0	-	-
Tachycardia	-	-	-	-	-	-	1.4	0.6

Serious adverse events occurred in clinical trials with modafinil include cases of moderate chest pain linked to symptomatic mitral valve prolapse (in temporal association with initiation of treatment), increased heart rate, congestive heart failure, cardiomegaly, palpitations, syncope, bradycardia. Fatal outcome was reported in 3 cases (cardiomyopathy, cardiac failure and syncope). However, in addition to the serious cases presented, a number of non-serious cases were significant enough to warrant a visit to the emergency department or required medication to treat the reported events. In the majority of these cases (including at least 2 of the fatal cases) time to onset of events is consistent with a causal association to modafinil.

A review of the MAH's pharmacovigilance database identified 873 spontaneous reports of cardiovascular disorders, of which 171 were serious and 17 had a fatal outcome. Some were reports from non-MAH sponsored studies.

Torsades de pointes/QT prolongation (n=69)
Of these, 30 were serious and in 8 a fatal outcome was reported. Positive de-challenge was reported in a limited number of cases.

Cardiac arrhythmia (n=405)
The most commonly reported terms were palpitations (n=125), tachycardia (n=59) and increased heart rate (n=80) and included some cases reporting positive de-challenge (n=23) or re-challenge (n=8). Despite not being confirmed by electrocardiographic data, a large number of reports occurred in close temporal association with modafinil and no alternative explanation was provided. One literature case of premature ventricular contractions included positive de-challenge and re-challenge information.

Cardiac failure (n=74)
Of the 74 cases of cardiac failure, 19 were considered serious and 3 had a fatal outcome, including a young patient with no significant medical history who died from lymphocytic myocarditis approximately 17 months after initiation of modafinil treatment for narcolepsy. Sixty-one out of the 74 cases identified under cardiac failure were for oedema or peripheral oedema.

Cardiomyopathy (n=462)
Ninety-two of the cardiomyopathy cases were serious and 9 had a fatal outcome.

Ischemic heart disease (n=57)

This SMQ captured 57 reports of which 35 were serious and 4 reported a fatal outcome.

Hypertension (n=211)
Of the 211 reports identified, 45 were serious and one case was fatal. There was one case of pseudo-pheocromocytoma with positive de-challenge and re-challenge. Hypertension is known to be associated to modafinil and is reflected in the Company Core Data Sheet (CCDS). The CCDS also states that blood pressure should be monitored in patients with hypertension.

Paediatric use

Modafinil is not recommended for paediatric treatment in most EU Member States, and is explicitly contraindicated only in Portugal and Poland.

The pharmacokinetic profile of modafinil in children and adolescents is characterised by a relatively rapid rate of absorption with time to maximum plasma concentration of 2 to 3 hours (2 to 4 hours in adults). Half-life is significantly lower in children (approximately 7 hours for children 6-7 years) when compared to adults (10-14 hours).

Reports of paediatric adverse reactions were identified both from clinical trials and postmarketing exposure, and confirm that the risk of severe cutaneous adverse reactions and multi-organ hypersensitivity reactions and serious psychiatric reactions is also applicable to children.

Data on the skin and hypersensitivity disorders is particularly suggestive of a higher incidence of serious adverse reactions in the paediatric population.

Pregnancy and lactation

Pre-clinical reproductive toxicity data in rats and rabbits submitted for modafinil revealed increased incidence in skeletal variations (changes in the numbers of ribs and delayed ossification), embryo-fetal lethality (peri-implantation loss and resorptions) and some evidence of an increase in stillbirths (rats only), in the absence of maternal toxicity, at clinically relevant exposures. There was no effect on fertility and no evidence of teratogenic potential at systemic exposures equivalent to the maximum recommended human dose.

Reproduction toxicity studies revealed no effect on fertility, nor any teratogenic effect, nor any effect on viability, growth or development of the offspring. Animal exposure to modafinil, based on actual plasma levels in the general toxicology, reproductive and carcinogenicity studies, was less than or similar to that expected in humans. This circumstance is the result of metabolic auto-induction noted in the pre-clinical studies. However, animal exposure on a mg/kg dose basis to modafinil in the general toxicology, reproductive and carcinogenicity studies was greater than the expected exposure, calculated on a similar basis, in humans.

In the rat peri-post-natal study, modafinil concentration in milk was about 11.5 times higher than in plasma.

Table 15 lists the clinical and spontaneous reports in the MAH's database on pregnancy outcomes.

Table 15 - Reports of pregnancy outcomes

Pregnancy outcome	Number of cases			
	Clinical studies	Spontaneous cases	Published literature	Total
Healthy birth	14	72	1	87
Congenital abnormality	2	7	0	9
Spontaneous abortion	2	16	0	18
Elective abortion	4	7	0	11
Premature labour	1	10	0	11
Abnormal labour	0	2	0	2
Stillbirth	0	1	0	1
Lost to follow up	2	64	0	66
Unknown	0	34	0	34

Many of these cases are poorly documented and have significant confounding factors. Overall, the limited data available are insufficient to establish or exclude an association between human pregnancy exposure to modafinil and congenital malformations, spontaneous abortions, or other birth complications.

Potential risk of abuse, misuse and diversion

A search of the MAH's pharmacovigilance database revealed a total of 485 reports related to abuse, misuse, dependency and tolerance associated to modafinil use. A monitoring programme to assess the abuse and misuse potential of modafinil was conducted between 1999 and 2007, and consisted of online monitoring of modafinil references and messages. Misuse and illicit use accounted for less than 3% of posted messages online. However, there have been reports of modafinil being used as a performance enhancer.

Off label use

It is noted that, if we account for the totality of the adverse event reports contained in the MAH's database, 80% (5381) provided the indication for use and, of these, 49% did not correspond to an approved indication. Table 16 contains an overview of the modafinil use by indications in the Member States where use is higher: France, Germany and UK. It should be noted that reasonable estimates of usage per indication can be derived only in Germany and the UK.

Table 16 - Modafinil use by indication in France, Germany and the UK

Country	Total number of prescriptions/country	Disease category (ICD10 classification)	Total prescriptions (%)
France	16080	Narcolepsy and cataplexy	45%
		Hypersomnias	40%
		Sleep apnoea	3%
		Disturbed-sleep wake schedule	0%
		Drug rehabilitation	18%
Germany	33944	Narcolepsy and cataplexy	46%
		Hypersomnias	4%
		Sleep apnoea	12%
		Disturbed-sleep wake schedule	2%
		Sleep disorder unspecified	3%
		Depressive episode unspecified	4%
		Multiple sclerosis	2%
		Post-viral fatigue syndrome	2%
		Unspecified	24%
UK	64569	Narcolepsy and cataplexy	6%
		Hypersomnias	4%
		Sleep apnoea	3%
		Disturbed-sleep wake schedule	4%
		Sleep disorder unspecified	4%
		Multiple sclerosis	27%
		Disorder of Brain unspecified	14%
		Parkinson's disease	4%
		Malaise and fatigue	3%
		Unspecified	32%

2.3.2. Discussion

Skin and hypersensitivity reactions

A total of 16 cases of Stevens Johnson Syndrome/Toxic Epidermal Necrolysis/Erythema Multiforme have been reported in a post-marketing setting. Three of these had a fatal outcome, and for the majority, causality could not be excluded. In clinical trials, another 3 cases of Serious Cutaneous Adverse Reactions (SCARs) have been observed, which is of particular concern given the rare background incidence rate of such events. The fact that all 3 serious SCARs observed in the modafinil clinical trials have occurred in children is indicative of a higher incidence of these reactions in the paediatric population.

A causal association between hypersensitivity reactions and modafinil is supported both by post-marketing data and data from clinical trials. In clinical trials, all the hypersensitivity related terms were

reported more commonly in association to modafinil than to placebo. Temporal association also contributes to the confirmation of causality.

Despite the lack of a clear definition of multi-organ hypersensitivity, reports of allergic reactions involving multiple organs (including a well documented case with a fatal outcome) are of particular concern. Because this type of event is considered to be rare, to have observed cases in a clinical trial setting is unexpected and considered indicative of an incidence higher than previously thought.

Nervous system disorders

Serious adverse reactions affecting the nervous system have been reported spontaneously in association with modafinil, including cerebrovascular disorders, convulsions and extrapyramidal symptoms. This type of events was also observed in clinical trials, and frequently time to onset was suggestive of a temporal association with the product. Positive re-challenge or de-challenge is also reported on a number of cases. In clinical trials, with the exception of headache, dizziness and cataplexy, all other nervous system related terms occurred almost exclusively in the modafinil treated patients.

Psychiatric disorders

A significant number of adverse reactions relating to psychiatric disorders have been reported spontaneously. There are 517 cases of hostility/aggression (4 of which with a fatal outcome), 331 cases of psychosis/psychotic disorders (of which 1 had a fatal outcome), 330 cases of depression and 118 cases of suicide/self-injury (15 with a fatal outcome). The majority of the spontaneous reports reviewed indicated that onset of events was within the first few months of initiating modafinil, and positive de-challenge or re-challenge was also reported.

The percentage of patients experiencing a psychiatric adverse event in clinical trials is also significant, particularly when compared to placebo. In clinical trials, the most commonly reported events leading to study discontinuation were insomnia, anxiety, depression and agitation. In addition, there were reports of suicidal ideation, hostility/aggression and psychotic episodes.

Cardiovascular disorders

A review of the MAH's pharmacovigilance database identified 873 spontaneous reports of cardiovascular disorders, of which 171 were serious and 17 had a fatal outcome. This includes 69 events of torsades de pointes/QT prolongation, 405 of cardiac arrhythmia, 74 of cardiac failure, 205 of hypertension, 462 of cardiomyopathy and 57 of ischemic heart disease. Positive de-challenge and/or re-challenge was reported in some cases.

In the placebo controlled studies, various cardiovascular events occurred almost exclusively in the modafinil treated group. This included serious cases of moderate chest pain linked to symptomatic mitral valve prolapse, increased heart rate, congestive heart failure, cardiomegaly, palpitations, syncope and bradycardia. A fatal outcome was reported in 3 cases (cardiomyopathy, cardiac failure and syncope).

It is noted that in a number of cases leading to discontinuation there was a very tight temporal association between modafinil and the events, and that in many cases the patients were young and had no known risk factors. The large number of spontaneous reports seems to support this association. Despite the fact that the majority of the spontaneous reports seem to be poorly documented, many included information on de-challenge or re-challenge further supporting a causal role of modafinil in increasing cardiovascular risk.

The higher rate of adverse events observed in the modafinil group during the OSA trials is of particular concern, given the known cardiovascular risks in this population. In placebo controlled studies in this indication, 6 patients withdrew from the modafinil group due to a cardiovascular adverse event while only one patient withdrew in the placebo group. The cardiovascular co-morbidities in OSA lead to difficulties in interpreting this observation. However, a higher incidence of cardiovascular adverse events when compared to placebo was observed in the modafinil clinical trials, seems to be consistent across the indications and is not seen exclusively in OSA patients.

Paediatric use

While modafinil is not currently approved for paediatric use, a number of serious adverse reactions have been reported in children. Particularly for serious skin disorders, data is indicative of a higher incidence in the paediatric population.

Pregnancy and lactation

While some of the pre-clinical studies have shown reproductive toxicity, the available human data are insufficient to establish whether toxicity occurs in humans during pregnancy and lactation.

Potential risk of abuse, misuse and diversion

A search of the MAH's pharmacovigilance database revealed a total of 485 reports related to abuse, misuse, dependency and tolerance associated to modafinil use. A monitoring programme to assess the abuse and misuse potential of modafinil was conducted between 1999 and 2007, and consisted of online monitoring of modafinil references and messages. Misuse and illicit use accounted for less than 3% of posted messages online. However, there have been reports of modafinil being used as a performance enhancer.

While the data presented by the MAH on abuse, misuse and diversion does not allow a conclusion on the abuse/misuse potential of the product, these results may have been influenced by the fact that relevant populations (such as students) have not have been included.

Off label use

Almost half of all the adverse events reported for modafinil appear to be reported in use outside of the approved indications.

2.4. Risk management plan

The MAH submitted a risk management plan, which included a risk minimisation plan.

Table 17 - Summary of the activities proposed in the risk management plan

Safety concern	Proposed pharmacovigilance activities
Serious skin reactions	• Routine pharmacovigilance • Additional activities A pharmacoepidemiologic study will be conducted in the United States using large-linked medical claims databases to further assess the incidence of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). Surveillance of severe skin reactions in the German Severe Cutaneous Adverse Reactions (SCAR) registry will continue.
Cardiovascular disorders Psychiatric disorders Nervous system disorders Hypersensitivity	• Routine pharmacovigilance
Misuse Diversion	• Routine pharmacovigilance • Additional activity Cephalon will have access to data from a study, which will be undertaken to assess misuse (including recreational use) and diversion of modafinil among British university students. The study will be conducted by the Substance Use Epidemiology, Centre for Public Health, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University.
Off-label use	• Routine pharmacovigilance • Additional activity Off-label use will be further assessed with a Drug Utilization Study (DUS) of the use of modafinil in the primary care setting, with data retrieved and analyzed from the United Kingdom (UK) General Practice Research Database (GPRD) and The Health Improvement Network (THIN).
Pregnancy	• Routine pharmacovigilance • Additional activity Cephalon is implementing a pregnancy registry, in the United States, to systematically collect data on the effect of modafinil exposure in women of childbearing potential during pregnancy, labor, and delivery.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for a safe and effective use of the medicinal product:

Communication

The MAHs should inform healthcare professionals on the outcome of this review on modafinil via a Direct Healthcare Professional Communication (DHPC) to be distributed the Monday after 5 days have passed from the adoption of the European Commission Decision. The key messages have been agreed with CHMP and each Member State will ensure that the relevant information is included in the translation in their National Language, as applicable.

Cardiovascular effects

The MAHs will provide, within 3 months of the Commission Decision, a feasibility analysis of an epidemiological cardiovascular safety study. The outcomes of this study should be: first occurrence of myocardial infarction, cardiovascular death, cardiovascular hospitalisation and all cause mortality. If the feasibility analysis shows that a scientifically valid, well-designed and suitable powered study is viable, then the MAHs commit to submit a detailed protocol within 2 months and to present the final study report within 6 months of completion of the study.

Off-label use

The MAHs will conduct a retrospective drug utilisation study of the use of modafinil in the primary care setting, with data retrieved and analysed at least from the UK General Practice Research Database (GPRD). Further consideration will be given to the use of databases in other EU countries, such as the

Institute for Drug Outcomes Research (PHARMO) in the Netherlands and Cegedim in France. The study should be started within 2 months of the Commission Decision, and the final report should be submitted within 6 months of study initiation.

Skin and hypersensitivity reactions

The MAHs will conduct a pharmacoepidemiological study using large-linked claims databases in the United States to further assess the incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis. The study will initiate in September 2010 and the final report will be submitted in 4Q2011.

The MAHs will continue to perform surveillance of severe skin reactions in the German Severe Cutaneous Adverse Reactions (SCAR) registry. Data will be presented in future modafinil PSURs.

Abuse, misuse and diversion

The MAHs will access and submit data on the study on recreational use and diversion among university students in the UK, being developed by the Centre for Public Health, School of Pharmacy and Biomolecular Sciences - Liverpool John Moores University. Data should be submitted once it is available from the investigators. Updates on data from the study should be presented in future modafinil PSURs.

Pregnancy and lactation

One MAH has implemented a pregnancy registry in the United States to systematically collect data on the effect of modafinil exposure in women of childbearing potential during pregnancy, labour and delivery. Updates on data from the registry will be presented in future modafinil PSURs.

Once the Commission Decision is issued, the MAHs must submit an updated version of the Risk Management Plan to the National Competent Authorities, taking into account all recommendations made by the CHMP during the procedure and including all the studies described as conditions of the marketing authorisation.

2.5. Overall benefit/risk assessment

Having considered the data presented, it is the Committee's view that modafinil is associated to a rare risk of serious, life-threatening skin reactions. This risk appears to be higher in children.

Serious nervous system and psychiatric related events such as suicidal ideation, psychotic episodes, and depression have also been identified in association to modafinil.

Cardiovascular adverse events such as hypertension and arrhytmias are documented in association with modafinil. The cardiovascular profile of modafinil is of particular concern in the OSA population given the already elevated baseline risk.

The Committee considered that the evidence for clinically significant efficacy of modafinil-containing products in excessive sleepiness associated with obstructive sleep disorder, shift work sleep disorder and idiopathic hypersomnia is very limited, and therefore any potential benefit for patients is outweighed by the identified risks.

In narcoplesy, however, the benefits of modafinil have been clearly and significantly demonstrated in double blind controlled clinical trials, both in objective and subjective measurements. The benefit-risk balance in this indication is therefore considered to be positive under the normal conditions of use.

However, in view of the safety concerns identified during this review, risk minimisation measures are considered necessary to ensure a safe and effective use of the product. It is therefore recommended that the Summary of Product Characteristics be updated to reflect the skin, hypersensitivity, neuropsychiatric and cardiovascular adverse reactions observed. In addition, a contraindication in patients with uncontrolled hypertension or cardiac arrhythmia is deemed necessary to prevent serious complications in patients with such co-morbidities.

The development of skin and hypersensitivity reactions, as well as neuropsychiatric reactions seems to be closely correlated to the modafinil dose. It is therefore appropriate that treatment with modafinil

always starts with the lowest recommended dose (200 mg) and be increased up to 400 mg only in patients with insufficient response.

The Summary of Product Characteristics should also clearly mention that modafinil is not recommended for use in children and during pregnancy and lactation.

Significant safety issues identified during this review (skin and hypersensitivity reactions, cardiovascular events) require further study. Further information should also be collected on use in pregnancy and lactation, potential for abuse/misuse and diversion and off-label use.

2.6. Communication plan

As part of this referral procedure, the MAH and the CHMP agreed the wording of a Dear Healthcare Professional Communication designed to inform prescribers of the deletion of therapeutic indications, the identified risks associated with modafinil-containing products and the recommendation to always start treatment with the 200 mg dose, to be sent to relevant health care professionals after the Commission Decision is issued.

2.7. Changes to the product information

As part of the referral procedure, the CHMP recommended that all the clinical and preclinical sections of the SPC be amended and harmonised in the EU. The key amendments are described below:

Narcolepsy (with or without cataplexy) is the only indication for the product in section 4.1.

In section 4.3 there should be a contraindication in patients with uncontrolled moderate to severe hypertension and in patients with cardiac arrhythmia.

Section 4.4 should contain warnings on the skin and hypersensitivity, neuropsychiatric and cardiovascular risks identified during the procedure. Section 4.4 should also include a warning that the safety and efficacy in children has not been established and therefore paediatric use is not recommended.

In section 4.6 it is stated that modafinil should not be used during pregnancy and lactation, and information on the relevant preclinical findings is included in section 5.3.

2.8. Re-examination procedure

Following the CHMP conclusion and recommendations for modafinil-containing medicinal products, one MAH submitted detailed grounds for the re-examination of the CHMP opinion.

Detailed grounds for re-examination submitted by the applicant

One MAH expressed its disagreement with the CHMP opinion, focusing its grounds for re-examination on the following points:

- The opinion did not accurately reflect the data supporting the efficacy of Modafinil in the indication excessive sleepiness associated with obstructive sleep apnoea. In particular, the MAH discussed in their detailed grounds:
    - the clinical relevance of the differences observed on objective measures of wakefulness
    - whether the entry criteria of the studies were appropriate
    - the lack of supportive evidence of possible unblinding
    - the benefit for a specific subpopulation of patients
- Misinterpretation of the risks associated to modafinil
- The opinion adopted a Product Information which did not fully reflect the safety information for modafinil

Following a request from the MAH at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) CNS inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the MAH's response. The MAH presented their grounds in writing and at an oral explanation.

Report from the SAG CNS

The SAG recognised that a small number of OSA patients (approx 6%) will continue to complain of sleepiness despite CPAP therapy. There is however no established or widely accepted criterion which defines under which situation a patient is considered to be unresponsive to CPAP in terms of residual sleepiness. Patients in this population should only be given modafinil if they have been evaluated by a sleep expert and when other medical and psychiatric disorders that could contribute to sleepiness have been excluded. It must also be clarified that the use of CPAP has been satisfactory.

When asked specifically if an ESS score above 10 is sufficient to define refractoriness to CPAP treatment, the group noted that there is no single ESS score that can be used to define refractoriness to CPAP treatment. The upper limit of normal for the ESS has not been definitively established. For definition of unresponsiveness, it is recommended to use ESS score in conjunction with clinical judgement. The SAG considered that the proposed ESS score of 10 is too low, and that a score of 12 would probably be more accurate. The question was raised whether the approximately 6% of the OSA patients on CPAP who were reported in one study to have an ESS >10 merely reflected the distribution of sleepiness in the general population rather than disease.

Regarding the clinical significance of differences observed in trials 303 and 402 in short-term efficacy, the group considered that the improvement in the ESS was of small magnitude (2.5-3 units on a 24 unit scale) and that no direct measurement of clinical meaningfulness, for example impact on the frequency of road accidents, had been provided. It was not considered possible to specify a minimal difference that can be deemed as clinically relevant. The scales measured selected aspects of sleepiness but were not designed to provide information on the clinical relevance of the changes in measurements. In the case of modafinil, as there is no strong correlation between objective and subjective measures, the SAG considered that subjective measures need to be taken into account since they reflect patient experience.

The group found it difficult to draw conclusions on the long-term efficacy of modafinil in OSA associated sleepiness with the existing uncontrolled data. Patients in the long-term extension study were a selected population (about 70 % of the initial population). This population included also previously placebo-treated patients. Although there seems to be some evidence of maintenance of effect over the 12 months open label extension, approximately 70% of patients increased the dose during this period, which may be indicative of development of tolerance.

The SAG also considered that dose escalation should be done with caution given the identified risks and the absence of proof of increased efficacy with higher doses. The MAH should consider which criteria should be used for recommending a dose escalation. A reasonable timeframe to decide that a patient is unresponsive to modafinil would be 4 weeks, with the assessment of a response to treatment including an assessment of ESS and CGI-C changes and evaluation by a specialist in sleep disorders.

Experts also emphasized the increased risk for cardiovascular disease in patients with OSA compared to other treated patient groups. Regular clinical assessment of cardiovascular status was considered important and patients should be informed of such risks before initiating treatment. Minor changes were suggested to the PI wording to clarify the contraindication related to severe hypertension and cardiac arrhythmias.

CHMP conclusion on grounds for re-examination

Having considered all of the above, the CHMP recognises the existence of a consistent short-term effect of modafinil in all variables measured. However the effect size is small and does not necessarily reflect a clinically significant benefit. Even if the effect size of modafinil is considered as comparable to that of CPAP therapy, it is noted that CPAP therapy addresses the underlying obstruction, whilst modafinil will have an effect of symptomatic relief by minimising the impact of diurnal somnolence. It is further considered by CHMP that, in a clinical setting where treatments are expected to be long lasting, the lack of controlled long-term efficacy data is a cause for concern and the possibility of development of tolerance cannot be excluded.

When discussing the entry criteria for studies, the CHMP noted that not only CPAP-compliant patients (≥4 hours per night on ≥70% objectively monitored nights), but also partially CPAP-compliant patients (≥4 hours per night on ≥30% objectively monitored nights) were included. The validity of ESS as a measure of sleep propensity is not questioned, but clinical judgement should also have been considered as part of the inclusion criteria as there is not a unique diagnostic test for excessive daytime sleepiness. In fact, when comparing baseline data among variables, the mean ESS in these studies indicate moderate levels of excessive sleepiness, whereas mean MWT values show no excess of somnolence for the same population (see table 4).

Patients exposed to modafinil in placebo-controlled studies experienced adverse events more frequently than those on placebo, but the majority of neuropsychiatric events were non-specific and also reported in the placebo arm. It is therefore agreed that the impact of a potential bias favouring modafinil is unlikely.

The CHMP considered the responder analysis submitted and agreed that no differences between subgroups can be observed for the presented variables.

The MAH considered, in their grounds for re-examination, that the CHMP misinterpreted the safety data and submitted an overview of its own interpretation of causality for some of the adverse events identified during the review. The limitations of adverse event reports are well recognised, particularly in the postmarketing setting, however in the absence of enough information to dismiss causality, a conservative approach should be taken when assessing safety data.

It is the CHMP's view that the risk minimisation measures agreed in relation to cutaneous and neuropsychiatric safety concerns (pharmacoepidemiological study to further assess the incidence of serious skin reactions, product information changes and routine pharmacovigilance) adequately address the concerns.

The cardiovascular profile of modafinil remains the most relevant concern in the OSA population given the already elevated baseline risk. Appropriate data on the cardiovascular safety of modafinil on OSA patients continues to be considered necessary to assess the magnitude of the concern. It is noted during the discussion with the MAH that, in the clinical trials, there was an average blood pressure increase of 2-3 mmHg of systolic blood pressure during the long term extension of pivotal studies. This may seem a small absolute increase but it in view of the cardiovascular risk associated to this population, and the fact that it is an asymptomatic consequence of treatment, it cannot be dismissed. The MAH proposed additional risk minimisation measures to address this concern, including a patient information sheet to be provided to the patients by the prescriber and revised SPC warnings. However the Committee considered that these risk minimisation measures would not sufficiently minimise the cardiovascular risk and address the safety concerns.

Divergent positions were expressed by members of the Committee for the following reasons:

Short-term efficacy of modafinil in the small population of patients (around 5 % of the OSA population) with residual excessive daytime sleepiness despite compliance to CPAP was demonstrated in two double blind placebo controlled clinical studies. It was shown both in subjective and objective parameters and supported by other secondary endpoints that overall support the clinical relevance. Clinical use of modafinil does not indicate that the efficacy would decline with time. It is also noted that there are no alternative treatment available. Although patients with OSA have an increase risk of cardiovascular events, risk minimisation measures included in the SPC such as contra indications, warnings and close monitoring would be adequate to ensure a safe use of modafinil. The benefit/risk is therefore positive in this indication. As the Committee's assessment of the safety information did not change following re-examination, the Product Information remained unchanged.

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanation, the CHMP concluded the benefit-risk balance is:

- Positive under normal conditions of use for excessive sleepiness associated with narcolepsy;
- Not positive under normal conditions of use for excessive sleepiness associated with obstructive sleep apnoea;
- Not positive under normal conditions of use for excessive sleepiness associated with shift work sleep disorder;
- Not positive under normal conditions of use for excessive sleepiness associated with idiopathic hypersomnia.

The CHMP also concluded that the cardiovascular risk profile of modafinil needs to be further characterised, but the existing information warrants the introduction of a specific contraindication in patients with uncontrolled moderate to severe hypertension and in patients with cardiac arrhythmia.

Furthermore, significant risks have been identified for development of skin and hypersensitivity reactions, as well as neuropsychiatric reactions. The risk of development of a serious adverse reaction seems to increase with higher doses. At least for skin and hypersensitivity reactions, the risk appears to be higher in children than in adults, so modafinil should not be recommended for use in children.

Existing human data is insufficient to conclude that the product can be safely used in pregnancy and lactation. In view of the reproductive toxicity observed in pre-clinical studies, the product should not be recommended in pregnancy and lactation.

The potential for abuse/misuse of modafinil should continue to be monitored.

Therefore, the CHMP recommended the variation to the terms of the marketing authorisations for the medicinal products referred to in Annex I, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III to the opinion.

The conditions affecting the marketing authorisations are set out in Annex IV.

Having considered the detailed grounds for re-examination submitted by the MAH in writing and in the oral explanation, the CHMP considered that the benefit-risk of the indication ‘excessive sleepiness associated with obstructive sleep apnoea’ continues to be negative and that the scientific conclusions of its 22 July 2010 opinion should be maintained.