ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**Product name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Austria	Cephalon GmbH Landsberger Straße 94 80339 München, Germany	Modasomil 100 mg - Tabletten	100 mg	tablets	oral use
Austria	Teva Pharma B.V. Computerweg 10, 3542 DR Utrecht The Netherlands	Modafinil TEVA 100 mg Tabletten	100 mg	tablet	oral use
Belgium	Teva Pharma B.V. Computerweg 10, 3542 DR Utrecht The Netherlands	MODAFINIL TEVA 100MG	100 mg	tablets	oral use
Belgium	N.V. Organon Kloosterstraat 6, 5349 AB Oss The Netherlands	PROVIGIL	100 mg	tablets	oral use
Cyprus	GENESIS PHARMA (CYPRUS) LTD, 2 Amfipoleos, 1st floor, P.O.Box 23638, 2025 Strovolos, Lefkosia, Cyprus	MODIODAL	100MG	tablets	oral use
Czech Republic	Teva Pharmaceuticals CR, s.r.o. Anděl City Radlická 1c 150 00 Praha 5 Czech Republic	Modafinil-Teva 100 mg	100mg	tablets	oral use
Czech Republic	Torrex Chiesi CZ, s.r.o. Na Květnici 33 140 00 Praha 4 Czech Republic	Vigil	100mg	tablets	oral use

Member State	**Marketing Authorisation Holder**	**Product name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Denmark	Cephalon France, 20, rue Charles Matigny, 94700 Maisons-Alfort, France	Modiodal	100 mg	tablets	oral use
Denmark	Teva Denmark A/S, Parallelvej 10, 2800 Kongens Lyngby, Denmark	Modafinil "Teva"	100 mg	tablets	oral use
Finland	ORCHID EUROPE LTD Building 3, Chiswick park 556, Chiswick High Road London W4 5YA United Kingdom	MODAFINIL	100 mg	tablets	oral use
Finland	ORCHID EUROPE LTD Building 3, Chiswick park 556, Chiswick High Road London W4 5YA United Kingdom	MODAFINIL	200 mg	tablets	oral use
France	CEPHALON France 20, rue Charles Martigny 94701 Maisons-Alfort Cedex France	MODIODAL 100 mg, comprimé	100 mg	tablets	oral use
France	CEPHALON France 20, rue Charles Martigny 94701 Maisons-Alfort Cedex France	MODAFINIL LAFON 100 mg, comprimé	100 mg	tablets	oral use

Member State	**Marketing Authorisation Holder**	**Product name**	**Strength**	**Pharmaceutical form**	**Route of administration**
France	TEVA SANTE Le Palatin 1 1, cours du Triangle 92936 Paris la Défense Cedex France	MODAFINIL TEVA 100 mg, comprimé	100 mg	tablets	oral use
Germany	Cephalon Pharma GmbH Fraunhoferstr. 9a D-82152 Martinsried Germany	Vigil 100 mg Tabletten	100. mg	tablets	oral use
Greece	GENESIS PHARMA Kiffissias Avenue 274 Halandri Athens 152 32 Greece	MODIODAL	100MG/TAB	tablets	oral use
Hungary	TORREX Chiesi Kft. 1052 Budapest Kristóf tér 4. III/1-3. Hungary	VIGIL	100mg	tablets	oral use
Iceland	Cephalon France 20, rue Charles Martigny 94700 Maisons Alfort France	Modiodal	100 mg	tablets	oral use
Ireland	Cephalon UK Limited 1 Albany Place Hyde Way Welwyn Garden City Hertfordshire AL7 3BT United Kingdom	PROVIGIL 100 mg tablets	100 MG	tablets	oral use

Member State	**Marketing Authorisation Holder**	**Product name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Ireland	Cephalon UK Limited 1 Albany Place Hyde Way Welwyn Garden City Hertfordshire AL7 3BT United Kingdom	PROVIGIL 200 mg tablets	200 MG	tablets	oral use
Ireland	Teva Pharma B.V. Computerweg 10 3542DR Utrecht The Netherlands	Modafinil Teva 100mg tablet	100 MG	tablets	oral use
Italy	CEPHALON SRL Piazza G. Marconi, 25 00144 ROMA Italia	PROVIGIL	100 mg	tablets	oral use
Italy	TEVA ITALIA S.R.L. Via Messina, 38 20154 Milano Italia	MODAFINIL TEVA	100 mg	tablets	oral use
Luxembourg	ORGANON N.V Kloosterstraat 6 NL-5349 AB Oss The Netherlands	PROVIGIL	100 mg	tablets	oral use
Netherlands	Cephalon France, 20 rus Charles Martigny, 94700 Maisons-Alfort, France	Modiodal, 100 mg tabletten	100 mg	tablets	oral use
Poland	Torrex Chiesi Pharma GmbH, Gonzagagasse 16/16, A-1010 Vienna, Austria	Vigil	100 mg	tablets	oral use

Member State	**Marketing Authorisation Holder**	**Product name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Portugal	Cephalon France 20, Rue Charles Martigny 94700 Maisons-Alfort France	Modiodal	100 mg	tablets	oral use
Portugal	Generis Farmacêutica, S.A. Office Park da Beloura, Edifício 4, Quinta da Beloura 2710-444 Sintra Portugal	Modafinil Generis	100 mg	tablets	oral use
Slovakia	Teva Pharmaceuticals CR, s.r.o., Radlická 3185/1c 150 00, Prague, Czech Republic	Modafinil-Teva 100 mg	100 mg	tablets	oral use
Slovakia	Torrex Chiesi Pharma GmbH, Gonzagagasse 16/16, 1010, Vienna, Austria	VIGIL 100 mg	100 mg	tablets	oral use
Spain	CEPHALON FRANCE, 20, Rue Charles Martigny 94700 Maisons Alfort France	MODIODAL	100 mg	tablets	oral use
Spain	TEVA GENERICOS ESPAÑOLA, S.L Guzmán el Bueno 133, Edificio Britania 4ºIzq.. 28003 Madrid Spain	MODAFINILO TEVA	100 mg	tablets	oral use
Sweden	Cephalon France, 20, rue Charles Martigny 94700 Maisons Alfort France	Modiodal®	100 mg	tablets	oral use

Member State	**Marketing Authorisation Holder**	**Product name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Sweden	Teva Sweden AB, Box 1070 251 10 Helsingborg, Sverige	Modafinil Teva	100 mg	tablets	oral use
United Kingdom	Cephalon UK Limited 1 Albany Place Hyde Way Welwyn Garden City Hertfordshire AL7 3BT United Kingdon	Provigil 100mg Tablets	100mg	tablets	oral use
United Kingdom	Cephalon UK Limited 1 Albany Place Hyde Way Welwyn Garden City Hertfordshire AL7 3BT United Kingdom	Provigil 200mg Tablets	200mg	tablets	oral use
United Kingdom	Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex BN22 9AG United Kingdom	Modafinil 100mg Tablets	100mg	tablets	oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET PRESENTED BY THE EMA

SCIENTIFIC CONCLUSIONS

Overall summary of the scientific evaluation of modafinil-containing products (see Annex I)

1. Introduction

Modafinil is a wakefulness promoting agent. It is currently licensed in 21 countries in Europe, and the approved indications vary between Member States. 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. Efficacy

Narcolepsy

In the two phase 3 randomised, double blind, placebo-controlled, multicenter 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 phase 3 randomised, double blind, placebo-controlled, multicenter 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. Statistically significant differences were seen in the subjective parameters (ESS and CGI-C).

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 phase 3 randomised, double-blind, placebo-controlled study), 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.

3. Safety

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.

4. 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.

5. 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 Marketing Authorisation Holder

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, the CHMP convened a Scientific Advisory Group (SAG) CNS during the re-examination procedure.

Having considered the data presented, 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. In addition modafinil does not address the underlying cause of the obstruction and, 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.

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 in 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 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 Committee considered that further risk minimisation measures would not adequately address the concern as the magnitude of the risk is not fully determined. As the Committee's assessment of the safety information did not change following re-examination, the Product Information remained unchanged.

Grounds for amendment of the summary of product characteristics and package leaflet

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, as amended, for medicinal products containing modafinil.
- The Committee considered all the available data submitted on the safety and the efficacy of modafinil-containing products.
- The Committee considered that there are significant risks associated to modafinil use, including risk of serious cardiovascular disorders, neuropsychiatric disorders and skin and hypersensitivity disorders.
- 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.
- The Committee therefore considered that the benefit risk balance:
  - Is positive under normal conditions of use for excessive sleepiness associated to narcolepsy
  - Is not positive under normal conditions of use for excessive sleepiness associated to obstructive sleep apnoea
  - Is not positive under normal conditions of use for excessive sleepiness associated to shift work sleep disorder
  - Is not positive under normal conditions of use for excessive sleepiness associated to idiopathic hypersomnia

As a consequence, the CHMP has recommended the maintenance of the Marketing Authorisations, subject to the conditions set out in annex IV, for which the amendments to the Summary of Product Characteristics and Package Leaflet are set out in Annex III for modafinil-containing products (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

Note: This SPC and package leaflet is the version valid at the time of Commission Decision.

After the Commission Decision the Member State Competent Authorities, in liaison with the Reference Member State, will update the product information as required. Therefore, this SPC and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Modafinil - containing medicinal products (see Annex I) products 100 mg tablets
Modafinil - containing medicinal products (see Annex I) products 200 mg tablets
See Annex I – To be completed nationally.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Modafinil- containing medicinal products is indicated in adults for the treatment of 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.

4.2 Posology and method of administration

Treatment should be initiated by or under the supervision of a physician with appropriate knowledge of indicated disorders (see section 4.1).

A diagnosis of narcolepsy should be made according to the International Classification of Sleep Disorders (ICSD2) guideline.

Patient monitoring and clinical assessment of the need for treatment should be performed on a periodic basis.

Posology
The recommended starting daily dose is 200 mg. The total daily dose may be taken as a single dose in the morning or as two doses in the morning and at noon, according to physician assessment of the patient and the patient's response.

Doses of up to 400mg in one or two divided doses can be used in patients with insufficient response to the initial 200mg modafinil dose.

Long-term use
Physicians prescribing modafinil for an extended time should periodically re-evaluate the long-term use for the individual patients as the long-term efficacy of modafinil has not been evaluated (> 9 weeks).

Patients with renal impairment
There is inadequate information to determine safety and efficacy of dosing in patients with renal impairment (see section 5.2).

Patients with hepatic impairment
The dose of modafinil should be reduced by half in patients with severe hepatic impairment (see section 5.2).

Elderly
There are limited data available on the use of modafinil in elderly patients. In view of the potential for lower clearance and increased systemic exposure, it is recommended that patients over 65 years of age commence therapy at 100 mg daily.

Paediatric population
Modafinil should not be used in children aged less than 18 years old because of safety and efficacy concerns (see section 4.4).

Method of administration
For oral use. Tablets should be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Uncontrolled moderate to severe hypertension and in patients with cardiac arrhythmias.

4.4 Special warnings and precautions for use

Diagnosis of sleep disorders
Modafinil should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of narcolepsy, has been made in accordance with ICSD diagnostic criteria. Such an evaluation usually consists, in addition to the patient's history, sleep measurements testing in a laboratory setting and exclusion of other possible causes of the observed hypersomnia.

Serious rash, including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Drug Rash with Eosinophilia and Systemic Symptoms
Serious rash requiring hospitalisation and discontinuation of treatment has been reported with the use of modafinil occurring within 1 to 5 weeks after treatment initiation. Isolated cases have also been reported after prolonged treatment (e.g., 3 months). In clinical trials of modafinil, the incidence of rash resulting in discontinuation was approximately 0.8% (13 per 1,585) in paediatric patients (age <17 years); this includes serious rash. No serious skin rashes have been reported in adult clinical trials (0 per 4,264) of modafinil. **Modafinil should be discontinued at the first sign of rash and not re-started** (see section 4.8).

Rare cases of serious or life-threatening rash, including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have been reported in adults and children in worldwide post-marketing experience.

Paediatric use
Because safety and effectiveness in controlled studies in children have not been established and because of the risk of serious cutaneous hypersensitivity and psychiatric adverse reactions, the use of modafinil is not recommended

Multi-organ hypersensitivity reaction
Multi-organ hypersensitivity reactions, including at least one fatality in post-marketing experience, have occurred in close temporal association to the initiation of modafinil.

Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalization or be life-threatening. There are no factors that are known to predict the risk of occurrence or the severity of multi-organ hypersensitivity reactions associated with modafinil. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively,

presented with fever and rash associated with other organ system involvement. Other associated manifestations included myocarditis, hepatitis, liver function test abnormalities, haematological abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritus, and asthenia.

Because multi-organ hypersensitivity is variable in its expression, other organ system symptoms and signs, not noted here, may occur.

If a multi-organ hypersensitivity reaction is suspected, modafinil should be discontinued.

Psychiatric disorders
Patients should be monitored for the development of *de novo* or exacerbation of pre-existing psychiatric disorders (see below and Section 4.8) at every adjustment of dose and then regularly during treatment. If psychiatric symptoms develop in association with modafinil treatment, modafinil should be discontinued and not restarted. Caution should be exercised in giving modafinil to patients with a history of psychiatric disorders including psychosis, depression , mania, major anxiety, agitation, insomnia or substance abuse (see below).

Anxiety
Modafinil is associated with the onset or worsening of anxiety. Patients with major anxiety should only receive treatment with modafinil in a specialist unit.

Suicide-related behaviour
Suicide-related behaviour (including suicide attempts and suicidal ideation) has been reported in patients treated with modafinil. Patients treated with modafinil should be carefully monitored for the appearance or worsening of suicide-related behaviour. If suicide-related symptoms develop in association with modafinil, treatment should be discontinued.

Psychotic or manic symptoms
Modafinil is associated with the onset or worsening of psychotic symptoms or manic symptoms (including hallucinations, delusions, agitation or mania). Patients treated with modafinil should be carefully monitored for the appearance or worsening of psychotic or manic symptoms. If psychotic or manic symptoms occur, discontinuation of modafinil may be required.

Bipolar disorders
Care should be taken in using modafinil in patients with co-morbid bipolar disorder because of concern for possible precipitation of a mixed/manic episode in such patients.

Aggressive or hostile behaviour
The onset or worsening of aggressive or hostile behaviour can be caused by treatment with modafinil. Patients treated with modafinil should be carefully monitored for the appearance or worsening of aggressive or hostile behaviour. If symptoms occur, discontinuation of modafinil may be required.

Cardiovascular risks
An ECG is recommended in all patients before Modafinil treatment is initiated. Patients will abnormal findings should receive further specialist evaluation and treatment before Modafinil treatment is considered.
Blood pressure and heart rate should be regularly monitored in patients receiving modafinil. Modafinil should be discontinued in patients who develop arrhythmia or moderate to severe hypertension and not restarted until the condition has been adequately evaluated and treated.
Modafinil tablets are not recommended in patients with a history of left ventricular hypertrophy or cor pulmonale and in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. This syndrome may present with ischaemic ECG changes, chest pain or arrhythmia.

Insomnia
Because modafinil promotes wakefulness, caution should be paid to signs of insomnia.

Maintenance of sleep hygiene
Patients should be advised that modafinil is not a replacement for sleep and good sleep hygiene should be maintained. Steps to ensure good sleep hygiene may include a review of caffeine intake.

Patients using steroidal contraceptives
Sexually active women of child-bearing potential should be established on a contraceptive programme before taking modafinil. Since the effectiveness of steroidal contraceptives may be reduced when used with modafinil, alternative or concomitant methods of contraception are recommended, and for two months after discontinuation of modafinil (also see 4.5 with respect to potential interaction with steroidal contraceptives).

Abuse, misuse, diversion
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 history of alcohol, drug or illicit substance abuse.

4.5 Interaction with other medicinal products and other forms of interaction

Modafinil may increase its own metabolism via induction of CYP3A4/5 activity but the effect is modest and unlikely to have significant clinical consequences.

Anticonvulsants: Co-administration of potent inducers of CYP activity, such as carbamazepine and phenobarbital, could reduce the plasma levels of modafinil. Due to a possible inhibition of CYP2C19 by modafinil and suppression of CYP2C9 the clearance of phenytoin may be decreased when modafinil is administered concomitantly. Patients should be monitored for signs of phenytoin toxicity, and repeated measurements of phenytoin plasma levels may be appropriate upon initiation or discontinuation of treatment with modafinil.

Steroidal contraceptives**:** The effectiveness of steroidal contraceptives may be impaired due to induction of CYP3A4/5 by modafinil. Alternative or concomitant methods of contraception are recommended for patients treated with modafinil. Adequate contraception will require continuation of these methods for two months after stopping modafinil.

Antidepressants**:** A number of tricyclic antidepressants and selective serotonin reuptake inhibitors are largely metabolised by CYP2D6. In patients deficient in CYP2D6 (approximately 10% of a Caucasian population) a normally ancillary metabolic pathway involving CYP2C19 becomes more important. As modafinil may inhibit CYP2C19, lower doses of antidepressants may be required in such patients.

Anticoagulants**:** Due to possible suppression of CYP2C9 by modafinil the clearance of warfarin may be decreased when modafinil is administered concomitantly. Prothrombin times should be monitored regularly during the first 2 months of modafinil use and after changes in modafinil dosage.

Other medicinal products**:** Substances that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol and omeprazole may have reduced clearance upon co-administration of modafinil and may thus require dosage reduction. In addition, *in vitro* induction of CYP1A2, CYP2B6 and CYP3A4/5 activities has been observed in human hepatocytes, which were it to occur *in vivo*, could decrease the blood levels of drugs metabolised by these enzymes, thereby possibly decreasing their therapeutic effectiveness. Results from clinical interaction studies suggest that the largest effects may be on substrates of CYP3A4/5 that undergo significant presystemic elimination, particularly via CYP3A enzymes in the gastrointestinal tract. Examples include ciclosporin, HIV-protease inhibitors, buspirone, triazolam, midazolam and most of the calcium channel blockers and statins. In a case report, a 50% reduction in ciclosporin concentration was observed in a patient receiving ciclosporin in whom concurrent treatment with modafinil was initiated.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited data on the use of modafinil in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Modafinil is not recommended for use during pregnancy or in women of childbearing potential unless they are using effective contraception. As modafinil may reduce the effectiveness of oral contraception alternative additional methods of contraception are required (see section 4.5).

Breastfeeding

Available pharmacodynamic/toxicological data in animals have shown excretion of Modafinil/metabolites in milk (for details see 5.3).

Modafinil should not be used during breast feeding.

Fertility
No data on fertility are available.

4.7 Effects on ability to drive and use machines

Patients with abnormal levels of sleepiness who take modafinil should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking modafinil should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Undesirable effects such as blurred vision or dizziness might also affect ability to drive (see section 4.8).

4.8 Undesirable effects

The following adverse reactions have been reported in clinical trials and/or post-marketing experience. The frequency of adverse reactions considered at least possibly related to treatment, in clinical trials involving 1561 patients taking modafinil were as follows: very common (≥1/10), common (≥1/100 to ≤1/10), uncommon (≥1/1000 to ≤1/100), unknown (cannot be estimated from the available data).
The most commonly reported adverse drug reaction is headache, affecting approximately 21% of patients. This is usually mild or moderate, dose-dependent and disappears within a few days.

Infections and infestations
Uncommon: pharyngitis, sinusitis

Blood and lymphatic system disorders
Uncommon: eosinophilia, leucopenia

Immune system disorders
Uncommon: minor allergic reaction (e.g., hayfever symptoms)
Unknown: Angioedema, urticaria (hives).Hypersensitivity reactions (characterised by features such as fever, rash, lymphadenopathy and evidence of other concurrent organ involvement)

Metabolism and nutrition disorders
Common: decreased appetite
Uncommon: hypercholesterolaemia, hyperglycaemia, diabetes mellitus, increased appetite,

Psychiatric disorders
Common: nervousness, insomnia, anxiety, depression, abnormal thinking, confusion.
Uncommon: sleep disorder, emotional lability, decreased libido, hostility, depersonalisation, personality disorder, abnormal dreams, agitation, aggression, suicidal ideation.
Rare: hallucinations, mania, psychosis
Unknown: delusions

Nervous system disorders
Very common: headache
Common: dizziness, somnolence, paraesthesia
Uncommon: dyskinesia, hypertonia, hyperkinesia, amnesia, migraine, tremor, vertigo, CNS stimulation, hypoaesthesia, incoordination, movement disorder, speech disorder, taste perversion

Eye disorders
Common: blurred vision
Uncommon: abnormal vision, dry eye

Cardiac disorders
Common: tachycardia, palpitation
Uncommon: extrasystoles, arrhythmia, bradycardia

Vascular disorders
Common: vasodilatation
Uncommon: hypertension, hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea, increased cough, asthma, epistaxis, rhinitis

Gastrointestinal disorders
Common: abdominal pain, nausea, dry mouth, diarrhoea, dyspepsia, constipation
Uncommon: flatulence, reflux, vomiting, dysphagia, glossitis, mouth ulcers

Skin and subcutaneous tissue disorders
Uncommon: sweating, rash, acne, pruritis
Unknown: serious skin reactions, including erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

Musculoskeletal and connective tissue disorders
Uncommon: back pain, neck pain, myalgia, myasthenia, leg cramps, arthralgia, twitch

Renal and urinary disorders
Uncommon: abnormal urine, urinary frequency

Reproductive system and breast disorders
Uncommon: menstrual disorder

General disorders and administration site conditions
Common: asthenia, chest pain
Uncommon: peripheral oedema, thirst

Investigations
Common: abnormal liver function tests, dose related increases in alkaline phosphatase and gamma glutamyl transferase have been observed.
Uncommon: abnormal ECG, weight increase, weight decrease

4.9 Overdose

Symptoms most often accompanying modafinil overdose, alone or in combination with other drugs have included: insomnia; central nervous system symptoms such as restlessness, disorientation, confusion, excitation and hallucination; digestive changes such as nausea and diarrhoea; and cardiovascular changes such as tachycardia, bradycardia, hypertension and chest pain.

Management

Induced emesis or gastric lavage should be considered. Hospitalisation and surveillance of psychomotor status; cardiovascular monitoring or surveillance until the patient's symptoms have resolved are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptic, centrally acting sympathomimetic, ATC code: N06BA

Modafinil promotes wakefulness in a variety of species, including man. The precise mechanism(s) through which modafinil promotes wakefulness is unknown.

In non-clinical models, modafinil has weak to negligible interactions with receptors involved in the regulation of sleep/wake states (e.g., adenosine, benzodiazepine, dopamine, GABA, histamine, melatonin, norepinephrine, orexin, and serotonin). Modafinil also does not inhibit the activities of adenylyl cyclase, catechol-O-methyltransferase, glutamic acid decarboxylase MAO-A or B, nitric oxide synthetase, phosphodiesterases II-VI, or tyrosine hydroxylase. While modafinil is not a direct-acting dopamine receptor agonist, *in vitro* and *in vivo* data indicate that modafinil binds to the dopamine transporter and inhibits dopamine reuptake. The wake-promoting effects of modafinil are antagonised by D1/D2 receptor antagonists suggesting that it has indirect agonist activity.

Modafinil does not appear to be a direct α_1-adrenoceptor agonist. However, modafinil binds to the norepinephrine transporter and inhibits norepinephrine uptake, but these interactions are weaker than those observed with the dopamine transporter. Although modafinil-induced wakefulness can be attenuated by the α1-adrenoceptor antagonist, prazosin, in other assay systems (e.g. vas deferens) responsive to α-adrenoceptor agonists, modafinil is inactive.

In non-clinical models, equal wakefulness-promoting doses of methylphenidate and amphetamine increase neuronal activation throughout the brain, whereas modafinil unlike classical psychomotor stimulants, predominantly affects brain regions implicated in regulating arousal, sleep, wake and vigilance.

In humans, modafinil restores and/or improves the level and duration of wakefulness and daytime alertness in a dose-related manner. Administration of modafinil results in electrophysiological changes indicative of increased alertness and improvements in objective measures of ability to sustain wakefulness.

The efficacy of modafinil in patients with obstructive sleep apnoea (OSA) exhibiting excessive day time sleepiness despite treatment with continuous positive airways pressure (CPAP) has been studied in short term randomised controlled clinical trials. Although statistically significant improvements in sleepiness were noted, the magnitude of effect and response rate to modafinil was small when assessed by objective measurements and limited to a small sub-population of the treated patients. In light of this, and because of its known safety profile, the demonstrated benefit is outweighed by the risks.

5.2 Pharmacokinetic properties

Modafinil is a racemic compound, and the enantiomers have different pharmacokinetics where the elimination t1/2 of the R-isomer is three times that of the S-isomer in adult humans.

Linearity/non-linearity
The pharmacokinetic properties of modafinil are linear and time-independent. Systemic exposure increases in a dose proportional manner over the range of 200-600 mg.

Absorption

Modafinil is well-absorbed with peak plasma concentration reached approximately two to four hours after administration.
Food has no effect on overall modafinil bioavailability; however, absorption (tmax) may be delayed by approximately one hour if taken with food.

Distribution
Modafinil is moderately bound to plasma protein (approximately 60%), primarily to albumin, which indicates that there is a low risk of interaction with strongly bound drugs.

Biotransformation
Modafinil is metabolized by the liver. The chief metabolite (40 – 50% of the dose), modafinil acid, has no pharmacological activity.

Elimination
The excretion of modafinil and its metabolites is chiefly renal, with a small proportion being eliminated unchanged (< 10% of the dose).
The effective elimination half-life of modafinil after multiple doses is about 15 hours.

Renal impairment
Severe chronic renal failure (creatinine clearance up to 20 mL/min) did not significantly affect the pharmacokinetics of modafinil administered at 200 mg, but exposure to modafinil acid was increased 9-fold. There is inadequate information to determine safety and efficacy of dosing in patients with renal impairment.

Hepatic impairment
In patients with cirrhosis, the oral clearance of modafinil was decreased by approximately 60%, and the steady-state concentration doubled, compared with values in healthy subjects. The dosage of modafinil should be reduced by half in patients with severe hepatic impairment.

Elderly population
There are limited data available on the use of modafinil in elderly patients. In view of the potential for lower clearance and increased systemic exposure, it is recommended that patients over 65 years of age commence therapy at 100 mg daily.

Paediatric Population
For patients 6 to 7 years of age, the estimated half-life is approximately 7 hours and increases with increase in age until half-life values approach those in adults (approximately 15 hours). This difference in clearance is partially offset by the younger patients' smaller size and lower weight which results in comparable exposure following administration of comparable doses. Higher concentrations of one of the circulating metabolites, modafinil sulfone, are present in children and adolescents as compared to adults.

In addition, following repeat-dose administration of modafinil to children and adolescents, a time-dependent reduction in systemic exposure, which plateaus by approximately week 6 is observed. Once steady-state is reached, the pharmacokinetic properties of modafinil do not appear to change with continued administration for up to 1 year.

5.3 Preclinical safety data

Toxicology studies by single and repeated dosing have revealed no particular toxic action in animals.

Modafinil is not considered to be mutagenic or carcinogenic.

Reproductive toxicity studies conducted in rats and rabbits showed an 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Modafinil containing medicinal products 100 mg Tablets
Modafinil containing medicinal products 200 mg Tablets
Modafinil

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects which worry you, talk to your doctor, pharmacist or nurse.

In this leaflet:

1. WHAT MODAFINIL CONTAINING MEDICINAL PRODUCTS IS AND WHAT IT IS USED FOR

The active ingredient in the tablets is modafinil.

Modafinil can be taken by adults who suffer from narcolepsy to help them to stay awake. Narcolepsy is a condition that causes excessive daytime sleepiness and a tendency to fall asleep suddenly in inappropriate situations (sleep attacks). Modafinil may improve your narcolepsy and reduce the likelihood that you will have sleep attacks but there may still be other ways that you can improve your condition and your doctor will advise you.

2. BEFORE YOU TAKE MODAFINIL CONTAINING MEDICINAL PRODUCTS

Do not take Modafinil containing medicinal products if you:
- Are **allergic** (hypersensitive) to modafinil, or to any of the other ingredients of these tablets (see section 6 'What Modafinil containing medicinal products contains').
- Have an **irregular heartbeat**.
- Have **uncontrolled**, **moderate to severe high blood pressure** (hypertension).

Take special care with Modafinil containing medicinal products if you
- Have any **heart problems** or **high blood pressure**. Your doctor will need to check these regularly while you are taking Modafinil containing medicinal products.
- Have ever had **depression**, **low mood**, **anxiety**, **psychosis** (loss of contact with reality) or **mania** (over-excitement or feeling of extreme happiness) or **bipolar disorder** because Modafinil containing medicinal products may make your condition worse.
- Have **kidney** or **liver problems** (because you will need to take a lower dose).
- Have had **alcohol** or **drug problems** in the past.

Children aged less than 18 years should not take this medicine.

Other things to talk to your doctor or pharmacist about

- Some people have reported having **suicidal** or **aggressive thoughts** or **behaviour** while taking this medicine. **Tell your doctor straight away** if you notice that you are becoming **depressed**, **feel aggressive or hostile** towards other people or have **suicidal thoughts** or other changes in your behaviour (see section 4). You may want to consider asking a family member or close friend to help you look out for signs of depression or other changes in your behaviour.
- This medicine has the potential for you to become reliant (dependent) on it after long-term use. If you need to take it for a long time your doctor will check regularly that it is still the best medicine for you.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription. Modafinil containing medicinal products and certain other medicines can affect each other and your doctor may need to adjust the doses that you are taking. It is especially important if you are taking any of the following medicines as well as Modafinil containing medicinal products:

- Hormonal **contraceptives** (including the contraceptive pill, implants, intrauterine devices (IUDs) and patches). You will need to consider other birth control methods while taking Modafinil containing medicinal products, and for two months after stopping treatment, because Modafinil containing medicinal products reduces their effectiveness.
- **Omeprazole** (for acid reflux, indigestion or ulcers).
- Antiviral medicines to treat HIV infection (protease inhibitors e.g. indinavir or ritonavir).
- **Ciclosporin** (used to prevent organ transplant rejection, or for arthritis or psoriasis).
- Medicines for **epilepsy** (e.g. carbamazepine, phenobarbital or phenytoin).
- Medicines for **depression** (e.g. amitriptyline, citalopram or fluoxetine) or **anxiety** (e.g. diazepam).
- Medicines for thinning the blood (e.g. **warfarin**). Your doctor will monitor your blood clotting times during treatment.
- Calcium channel blockers or beta-blockers for **high blood pressure** or heart problems (e.g. amlodipine, verapamil or propranalol).
- Statin medicines for lowering **cholesterol** (e.g. atorvastatin or simvastatin).

Pregnancy and breast-feeding

If you are pregnant (or think that you may be), are planning to become pregnant, or are breast feeding, you should not take Modafinil containing medicinal products. It is not known if your medicine may harm your unborn baby.

Talk to your doctor about the birth control methods that will be right for you while you are taking Modafinil containing medicinal products (and for two months after stopping) or if you have any other concerns.

Driving and using machines
Modafinil containing medicinal products can cause blurred vision or dizziness in up to 1 in 10 people. If you are affected or you find that while using this medication you still feel very sleepy, do not attempt to drive or operate machinery.

Important information about some of the ingredients of Modafinil containing medicinal products
[To be completed nationally].

3. HOW TO TAKE MODAFINIL CONTAINING MEDICINAL PRODUCTS

Always take Modafinil containing medicinal products exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Tablets should be swallowed whole with water.

Adults
The usual dose is 200 mg a day. This can be taken once daily (in the morning) or divided into two doses a day (100 mg in the morning and 100 mg at midday).

Your doctor in some cases may decide to increase your daily dose up to 400 mg.

Elderly patients (over 65 years of age)
The usual dose is 100 mg a day. This can be taken once daily (in the morning) or divided into two doses a day (50 mg in the morning and 50 mg at midday).

Your doctor will only increase your dose (up to the maximum 400 mg a day) provided that you do not have any liver or kidney problems

Adults with severe kidney and liver problems
The usual dose is 100 mg a day.

Your doctor will review your treatment regularly to check that it is right for you.

If you take more Modafinil containing medicinal products than you should
If you take too many tablets you may feel sick, restless, disorientated, confused or excited. You may also have difficulty sleeping, diarrhoea, hallucinations (sensing things that are not real), chest pain, a change in the speed of your heart beat or an increase in blood pressure.

Contact your nearest hospital casualty department or tell your doctor or pharmacist immediately. Take this leaflet and any remaining tablets with you.

If you forget to take Modafinil containing medicinal products If you forget to take your medicine take the next dose at the usual time, do not take a double dose to make up for the forgotten one.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Modafinil containing medicinal products can cause side effects, although not everybody gets them.

Stop taking this medicine and **tell your doctor straight away** if

- You have sudden difficulty breathing or wheeziness or your face, mouth or throat begins to swell.
- You notice a skin rash or itching (especially if it affects your whole body). Severe rashes may cause blistering or peeling of the skin, ulcers in your mouth, eyes, nose or genitals. You may also have a high temperature (fever) and abnormal blood test results.
- You feel any change in your mental health and wellbeing. The signs may include:
    - o mood swings or abnormal thinking,
    - o aggression or hostility,
    - o forgetfulness or confusion,
    - o feeling of extreme happiness,
    - o over-excitement or hyperactivity,
    - o anxiety or nervousness,
    - o depression, suicidal thoughts or behaviour**,**
    - o agitation or psychosis (a loss of contact with reality which may include delusions or sensing things that are not real), feeling detached or numb, or personality disorder.

Other side effects include the following:

Very common side effects (affecting more than 1 in 10 people):

- Headache

Common side effects (affecting fewer than 1 in 10 people):

- Dizziness
- Sleepiness, extreme tiredness or difficulty sleeping (insomnia)
- Awareness of your heart beat, which may be faster than normal.
- Chest pain
- Flushing.
- Dry mouth.
- Loss of appetite, feeling sick, stomach pain, indigestion, diarrhoea or constipation
- Weakness. Numbness or tingling of the hands or feet ('pins and needles').
- Blurred vision.
- Abnormal blood test results showing how your liver is working (increased liver enzymes).

Uncommon side effects (affecting fewer than 1 in 100 people):

- Back pain, neck pain, muscle pain, muscle weakness, leg cramps, joint pain, twitching or tremor.
- Vertigo (spinning sensation).
- Difficulty moving muscles smoothly or other movement problems, muscle tension, coordination problems.
- Hayfever symptoms including itchy/runny nose or watery eyes.
- Increased cough, asthma or shortness of breath.
- Skin rash, acne or itchy skin.
- Sweating.
- Changes in blood pressure (high or low), abnormal heart trace (ECG), and irregular or unusually slow heart beat.
- Difficulty swallowing, swollen tongue or mouth ulcers.
- Excess wind, reflux (bringing back fluid from the stomach), increased appetite, weight changes, thirst or taste alteration.
- Being sick (vomiting)
- Migraine.
- Speech problems.
- Diabetes with increased blood sugar.
- High blood cholesterol.
- Swollen hands and feet.
- Disrupted sleep or abnormal dreams,
- Loss of sex drive.
- Nose bleed, sore throat or inflamed nasal passages (sinusitis).
- Abnormal vision or dry eyes.
- Abnormal urine or more frequent urination.
- Abnormal periods.
- Abnormal blood test results showing that the numbers of your white blood cells have changed.

If any of these side effects become troublesome or you experience any side effects not listed, please tell your doctor pharmacist or nurse.

5. HOW TO STORE MODAFINIL CONTAINING MEDICINAL PRODUCTS

Keep out of the reach and sight of children.

Do not take this medicine after the expiry date which is stated on the blister strip and the outer pack after 'Exp'. The expiry date refers to the last day of the month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Modafinil containing medicinal products contains

Each tablet contains modafinil (either 100 mg or 200 mg) as the active ingredient. The tablets also contain [to be completed nationally] as inactive ingredients.

What Modafinil containing medicinal products looks like and the contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and manufacturers

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

National Competent Authorities, coordinated by the Reference Member State where applicable, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

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 is intended to be initiated 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.