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Questions and answers on the review of medicines containing modafinil

Indications restricted following review procedure under Article 31 of Directive 2001/83/EC as amended

The European Medicines Agency has completed a review of the safety and effectiveness of modafinil. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of modafinil-containing medicines continue to outweigh their risks but that their use should be restricted to the treatment of narcolepsy. The CHMP also recommended further changes to the product information to ensure that the medicines are used appropriately, and asked the manufacturers to put in place risk minimisation measures. After re-examination, the Committee confirmed these recommendations on 18 November 2010.

What is modafinil?

Modafinil is used to promote wakefulness (help people stay awake). The exact way modafinil works is not fully understood, but it most likely interacts with some chemicals in the brain called neurotransmitters such as dopamine and norepinephrine. Modafinil-containing medicines are used in patients who suffer from excessive sleepiness. Excessive sleepiness can be caused by narcolepsy, a disease that causes the person to fall asleep during the day, or it can be due to disturbed night-time sleeping patterns leading to daytime sleepiness. This can be seen in people who work a shift-pattern or in those who suffer from obstructive sleep apnoea (a condition in which pauses in breathing occur repeatedly during the night, disturbing sleep). Excessive sleepiness can also happen with no known causes (idiopathic hypersomnia).

Medicines containing modafinil were first marketed in Europe in 1992. They are available in Austria, Belgium, Cyprus, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Poland, Portugal, Slovakia, Spain, Sweden and the United Kingdom. They are available under the following invented names: Modasomil, Modiodal, Provigil and Vigil, and as generic medicines.

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Why was modafinil reviewed?

In 2007, the CHMP's Pharmacovigilance Working Party (PhVWP) reviewed the safety of modafinil-containing medicines because of concerns that the medicines were associated with serious psychiatric disorders (suicidal thoughts, mania and symptoms of psychosis such as delusion) and with skin reactions, including severe reactions such as Stevens-Johnson syndrome, a life-threatening type of allergic reaction affecting the skin and mucous membranes. This led to an update of the product information for modafinil-containing medicines across Europe to strengthen the warnings about these risks. The PhVWP also asked the companies that make modafinil-containing medicines to provide all information they had to assess if further measures were needed.

Once the PhVWP had received and started its assessment of the data, the working party had further concerns about the medicines, and consequently, on 14 May 2009, the UK medicines regulatory agency asked the CHMP to carry out a full assessment of the benefit-risk balance of modafinil-containing medicines, and to issue an opinion on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the European Union.

Which data has the CHMP reviewed?

The Committee looked at all the data from the clinical trials of modafinil in narcolepsy, obstructive sleep apnoea, shift-work sleep disorder and idiopathic hypersomnia, and at articles from the published literature. The CHMP also reviewed all the side effects reported with modafinil-containing medicines. A group of experts on clinical neurosciences was also convened to provide advice.

What are the conclusions of the CHMP?

Looking at the data from the clinical trials, the Committee noted that the effectiveness of modafinil in narcoleptic patients had been shown. However, the data from the trials in other disorders did not provide strong evidence to support the use of the product.

Looking at the safety data, the Committee noted that modafinil is strongly linked to a risk of serious, life-threatening skin reactions, and this risk appears higher in children. The Committee also noted a link between modafinil and psychiatric adverse reactions, such as suicidal thoughts, depression, psychotic episodes, and between modafinil and cardiovascular adverse reactions, such as hypertension (high blood pressure) and irregular heart beat.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of modafinil-containing medicines continue to outweigh their risks only in the treatment of narcolepsy. For obstructive sleep apnoea (including in patients with excessive sleepiness despite correctly using a Continuous Positive Airway Pressure machine), shift-work sleep disorder and idiopathic hypersomnia, the CHMP concluded that the data on the effectiveness were not sufficient to outweigh the risks, and that therefore the benefit-risk balance was negative. The Committee recommended that these indications be removed from the product information. In addition the Committee also recommended that modafinil-containing medicines not be used in patients with uncontrolled hypertension or irregular heart beat. The Committee also noted the increased risk of serious life-threatening skin reactions with modafinil in children and advised against its use in children.

The CHMP has also asked the companies that make modafinil-containing medicines to put in place measures to minimise the risks. These include informing healthcare professional of the changes to the product information triggered by this latest review, and putting in place studies looking at the cardiovascular and skin safety of modafinil. Because the Committee noted in its review that modafinil

has often been used for conditions for which it is not indicated, the companies have also been asked to carry out further studies, including a 'drug utilisation study' to look at why family doctors prescribe the medicines. In addition, data on the misuse of modafinil by university students, currently being collected, will be analysed once available.

The CHMP confirmed the above conclusions after re-examining its opinion. The full changes made to the information to doctors and patients are detailed here.

What are the recommendations for prescribers and patients?

- Doctors prescribing modafinil-containing medicines should keep in mind the change in the indication: modafinil is only indicated to treat narcolepsy.
- Modafinil should **no longer** be used to treat:
  - Obstructive sleep apnoea;
  - Shift work sleep disorder;
  - Idiopathic hypersomnia.
- Doctors should also be aware of the safety profile of modafinil-containing medicines, and they should monitor their patients appropriately.
- Patients who are receiving modafinil-containing medicines should contact their doctors at a convenient time to check that they should continue receiving it.
- There is no need for patients to stop treatment with modafinil immediately, but patients who wish to stop can do so at any time.
- Patients who have any questions should speak to their doctor or pharmacist.

The European Commission issued a decision on 27 January 2011.