European Medicines Agency

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QUESTIONS AND ANSWERS ON RECOMMENDATION FOR THE REFUSAL OF THE MARKETING AUTHORISATION
for
RAMELTEON

International non-proprietary name (INN): ***ramelteon***

On 30 May 2008, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Ramelteon 4 mg and 8 mg tablets intended for the treatment of primary insomnia in adult patients. The company that applied for authorisation is Takeda Global Research and Development Centre (Europe) Ltd. They may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Ramelteon?
Ramelteon is a medicine that contains the active substance ramelteon (4 mg or 8 mg). It was to be available as tablets.

What was Ramelteon expected to be used for?
Ramelteon was expected to be used to treat primary insomnia (difficulty in falling and staying asleep, and poor quality of sleep) in patients aged 18 years or over. 'Primary' means that the insomnia does not have any identified cause, including other medical, mental or environmental causes.

How is Ramelteon expected to work?
The active substance in Ramelteon, ramelteon, is a melatonin-receptor agonist. This means that it works by attaching itself to the receptors that melatonin normally attaches itself to. Melatonin is a naturally occurring hormone that is involved in co-ordinating the body's sleep cycle by acting on receptors in specific areas of the brain. Ramelteon was expected to work in the same way as melatonin in promoting sleep.

What documentation did the company present to support its application to the CHMP?
The effects of Ramelteon were first tested in experimental models before being studied in humans. The effectiveness of Ramelteon was compared with that of placebo (a dummy treatment) in a total of about 5,400 patients. Most of the studies were carried out in sleep laboratories, but the three main studies in a total of 2,807 patients were carried out in a natural setting (at home).
All of the studies except one were short-term studies that lasted five weeks or less. The one long-term study lasted six months, during which patients spent some nights in a sleep laboratory. The main measure of effectiveness was the time taken for the patient to fall asleep.

What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?
The CHMP was concerned that the company had not demonstrated the effectiveness of Ramelteon, which was measured considering only one aspect of insomnia, the time to fall asleep. In addition, in only one of the three studies in a natural setting there was a difference in time to fall asleep between patients taking Ramelteon and those taking placebo, and this difference was considered too small to be relevant. When other aspects of sleep were considered, Ramelteon did not have any effect. The

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Committee was also concerned that the company had not demonstrated the long-term effectiveness of Ramelteon.
At that point in time, the CHMP was of the opinion that the benefits of Ramelteon in the treatment of primary insomnia did not outweigh its risks. Hence, the CHMP recommended that Ramelteon be refused marketing authorisation.

What are the consequences of the refusal for patients in clinical trials/compassionate use programmes using Ramelteon?
The company informed the CHMP that there are no ongoing clinical trials or compassionate use programs with Ramelteon in Europe.