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**QUESTIONS AND ANSWERS ON RECOMMENDATION FOR REFUSAL OF MARKETING
AUTHORISATION
for
VALDOXAN/THYMANAX**

International Non-proprietary Name (INN): *agomelatine*

On 27 July 2006 the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of a marketing authorisation for the medicinal product Valdoxan/Thymanax, 25 mg film-coated tablets intended for the treatment of major depressive disorder. The company that applied is Les Laboratoires Servier. They may request re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Valdoxan/Thymanax?

Valdoxan/Thymanax are orange-yellow tablets containing 25 mg of the active substance agomelatine.

What was Valdoxan/Thymanax expected to be used for?

Valdoxan/Thymanax was expected to be used in adult patients to treat major depressive disorder. In major depressive disorder, patients have disturbances of mood that interfere with their everyday life. They may suffer from deep sadness, feelings of worthlessness, loss of interest in favourite activities, sleep disturbances, feeling of being slowed down, feelings of anxiety, changes in weight. The key symptoms are depressed mood and loss/diminished interest or pleasure. Patients often suffer relapses (when the disease comes back after it has been treated).

How is Valdoxan/Thymanax expected to work?

The active substance in Valdoxan/Thymanax, agomelatine, is a 'melatonergic agonist' and a '5-HT_{2C} antagonist'. This means that agomelatine stimulates the melatonin receptors MT1 and MT2 (these receptors are normally activated by a natural hormone, melatonin) and it blocks the 5-HT_{2C} receptors (these receptors are normally activated by a chemical messenger, serotonin).

What documentation has been presented by the company to support the application to the CHMP?

The effects of agomelatine were first tested in experimental models before being studied in humans. The main studies involved more than 2,400 patients that took Valdoxan/Thymanax. They looked at the short- and long-term effectiveness of the medicine (short-term studies lasting 6-8 weeks and the long-term studies lasting up to a year). All patients treated suffered from a major depressive disorder as assessed using a standard questionnaire (the Hamilton Rating Scale for Depression, HAM-D). Valdoxan/Thymanax was compared with a placebo (a dummy treatment). Some studies included a control group where patients were treated with fluoxetine or paroxetine (other medicines used in depression). The effectiveness was measured by looking at the score in the HAM-D questionnaire before and at the end of the study.

What were the major concerns that led to the CHMP to recommend a refusal of the marketing authorisation?

The major concern of the CHMP was that the effectiveness of Valdoxan/Thymanax had not been sufficiently shown:

- The long-term study did not show that the medicine was effective .
- The short-term studies showed that the medicine has an effect, but the extent of this did not allow the Committee to draw a firm conclusion on the medicine's effectiveness

The CHMP had no special concerns regarding the side effects associated with Valdoxan/Thymanax, as these could have been managed using the standard risk management tools.

At this point in time, the CHMP was of the opinion that the benefits of Valdoxan/Thymanax did not outweigh its risks. Hence, the CHMP recommended that Valdoxan/Thymanax be refused marketing authorisation.

What are the consequences of the refusal for patients undergoing clinical trials/compassionate use programmes with Valdoxan/Thymanax?

The Company has informed the CHMP that there are no consequences on patients currently included in clinical trials or compassionate use programmes with Valdoxan/Thymanax. The trials and programmes will continue as planned.

If you are in a clinical trial or compassionate use programme and need more information about your treatment, contact the doctor who is giving it to you.