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**QUESTIONS AND ANSWERS ON RECOMMENDATION FOR THE REFUSAL OF A
CHANGE TO THE MARKETING AUTHORISATION
for
ZAVESCA**

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

On 18 October 2007, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of a change to the marketing authorisation for the medicinal product Zavesca 100 mg capsules. The change concerned an extension of indication to add the treatment of neurological manifestations in patients with Niemann Pick type C disease. The company that applied for authorisation is Actelion Registration Ltd. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Zavesca?

Zavesca is a hard white capsule, which contains the active substance miglustat. It is used for the treatment of mild to moderate type 1 Gaucher disease. Gaucher disease is a rare, inherited disease that affects the way the body handles fats. In patients with this disease, a fatty substance called glucosylceramide builds up in different parts of the body, such as the spleen, liver, and bones.

What was Zavesca expected to be used for?

Zavesca was expected to be used to treat the 'neurological' symptoms of Niemann Pick type C disease (affecting the brain and nervous system). This is another rare inherited disease that affects the way the body handles fats. In patients with this disease, fatty substances called glycosphingolipids build up within cells in the brain, as well as elsewhere in the body. Symptoms include a progressive loss of co-ordination, problems with rapid eye movements that can lead to impaired vision, delayed development, difficulty swallowing, increased muscle tone, fits, and learning difficulties. The disease can result in dementia and is usually fatal before the patient has reached adulthood. Zavesca was designated as an orphan medicinal product on 16 February 2006 for Niemann Pick disease, type C.

How is Zavesca expected to work?

Miglustat, the active substance in Zavesca, prevents an enzyme called 'glucosylceramide synthase' from working. This enzyme is involved in the first step of the production of glycosphingolipids. By preventing the enzyme from working, miglustat can reduce the production of glycosphingolipids in cells. This is expected to reduce the symptoms of the disease.

What documentation did the company present to support its application to the CHMP?

The effects of Zavesca were first tested in experimental models before being studied in humans. The effectiveness of Zavesca has been studied in one main study involving 29 patients aged 12 years and over with Niemann Pick type C disease. The study compared the effects of adding Zavesca taken at a dose of 200 mg three times a day to standard care with the effects of standard care alone. The medicine was also studied in 12 patients aged less than 12 years. The main measure of effectiveness was the change in the speed at which the patients made 'saccadic' (rapid) horizontal eye movements after a year's treatment.

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

The CHMP acknowledged that there are no alternative treatments for Niemann Pick type C disease, but it was concerned that a benefit of Zavesca in the treatment of the neurological symptoms of Niemann Pick type C disease had not been sufficiently demonstrated. The medicine showed a very limited benefit in the main study: there was only a marginal difference in the change in the speed of eye movements between the patients taking Zavesca and those receiving standard care, and there were uncertainties over whether looking at eye movements was the best way to measure the medicine's effectiveness. Zavesca was also linked to side effects affecting the stomach and gut, as well as cases of weight loss and thrombocytopenia (low blood platelet counts).

Therefore, at that point in time, the CHMP was of the opinion that the benefits of Zavesca in the treatment of neurological manifestations in Niemann Pick type C disease did not outweigh its risks. Hence, the CHMP recommended that the change to the marketing authorisation be refused.

What are the consequences of the refusal for patients in clinical trials or compassionate use programmes using Zavesca?

The company informed the CHMP that there are no consequences for patients currently included in clinical trials or compassionate use programmes with Zavesca. 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.

What is happening for Zavesca for the treatment of type 1 Gaucher disease?

There are no consequences on the use of Zavesca in its authorised indication, for which the balance of benefits and risks remains unchanged.