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Questions and answers on the review of orlistat-containing medicines

Outcome of procedures under Article 20 of Regulation (EC) No 726/2004 and Article 31 of Directive 2001/83/EC

The European Medicines Agency has completed a review of orlistat-containing medicines, following concerns about the possible risk of severe liver injury with these medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of orlistat continue to outweigh its risks, and recommended that the marketing authorisations be maintained with minor amendments to the product information to ensure the same information on very rare liver-related side effects is provided for all orlistat-containing medicines.

What is orlistat?

Orlistat is an anti-obesity medicine, which does not affect appetite. Orlistat blocks the action of gastrointestinal lipases (enzymes that digest fat). When these enzymes are blocked, they cannot digest some fats in the diet, and this allows about a quarter of the fat eaten in the meal to be passed out in the stools undigested. The body does not absorb this fat and this helps the patient reduce their weight.

Two orlistat-containing medicines hold an EU-wide marketing authorisation. Xenical was authorised in 1998 and is available as capsules (120 mg) which can only be obtained with a prescription. Alli was authorised in 2007 and is available as capsules (60 mg) and chewable tablets (27 mg) which can be obtained without a prescription ('over-the-counter').

A number of generic orlistat-containing medicines have also been authorised via national procedures in Belgium, Bulgaria, Denmark, Estonia, Latvia, Lithuania, Norway, Portugal, Slovakia, the Netherlands, and the United Kingdom.

Why was orlistat reviewed?

Since 2001 it has been recognised that some patients taking orlistat could experience very rare liver-related side effects. This risk has been closely monitored by the CHMP and measures to manage the

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known risks were put in place. The product information for orlistat-containing medicines lists hepatitis, cholelithiasis (gall stones) and a change in liver enzyme levels as potential liver-related side effects.

Xenical and Alli are together estimated to have been used by over 53 million people worldwide, with over 20 million in the EU. Since authorisation, there have been some reports of severe liver problems in users of these medicines. Recent safety monitoring showed that from August 2009 to January 2011 four cases of severe liver injury were reported in patients using Xenical where the role of orlistat could not be excluded, including one fatal case of liver failure and one case leading to liver transplantation. Overall, from 1997 to January 2011, 21 cases of severe liver toxicity were reported where Xenical was considered a possible cause, although other factors that could have caused the liver injury were present. There were 9 reports of liver failure in people using Alli since it was marketed in May 2007 until January 2011, although in some cases there were other possible explanations and in some cases there was insufficient information to assess the cause.

Therefore, the CHMP considered it necessary to assess whether the evidence gathered over time on the risk of severe liver problems had altered the benefit-risk balance of orlistat-containing medicines. Consequently, the European Commission asked the CHMP to issue an opinion on orlistat and on whether the marketing authorisation for orlistat-containing medicines should be maintained, varied, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The CHMP reviewed the available data on the risk of liver injury and other side effects with orlistat, including post-marketing surveillance, data from the studies supporting the marketing authorisations and population-based studies in the published literature. The Committee also reviewed information requested from the companies that market orlistat-containing medicines, including the estimated number of people using these medicines and an analysis of the observed number of reports of severe liver problems compared with the expected background rate of liver problems in these people.

What are the conclusions of the CHMP?

The CHMP considered that there was no strong evidence that orlistat increased the risk of severe liver injury, and there was no known mechanism by which orlistat was expected to cause liver disorders. The Committee concluded that the number of reported severe liver reactions in orlistat users was low and below the background rate expected in these people, given the large number of users. A pattern was not seen in the type of liver problems reported, and in most cases there were other factors which were likely to increase the risk of liver injury such as existing health problems or the use of other medicines. The CHMP also noted that published population-based studies suggest that obesity may be associated with a higher risk of liver disease. The Committee considered that while there may be very rare cases of serious liver injury for which orlistat cannot be excluded as a possible cause, the cases do not provide good evidence of a causal link.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of orlistat continue to outweigh its risks, and therefore recommended that the marketing authorisations be maintained for orlistat-containing medicines. It noted that the product information for Xenical already listed ‘hepatitis that may be serious’ as a side effect of unknown frequency, and recommended that the product information for all orlistat-containing medicines should be harmonised to include this information. The product information for Alli, which currently lists ‘hepatitis’, will be updated accordingly. The Committee also agreed on minor amendments to the package leaflet for all orlistat-containing medicines to ensure they

give the same information, including a description of the symptoms of hepatitis to alert patients to these symptoms.

The amended information to doctors and patients are detailed here.

What are the recommendations for patients and prescribers?

- Patients and prescribers are reminded that the benefits of orlistat-containing medicines continue to outweigh the risks. These medicines should continue to be used as before.
- Patients and prescribers should be aware that certain liver-related problems, including very rare serious reactions such as hepatitis, have been reported and are listed in the product information for orlistat-containing medicines as possible side effects. There remains no clear evidence that orlistat causes these reactions.
- Patients should note that symptoms of hepatitis can include yellowing skin and eyes, itching, dark coloured urine, stomach pain and liver tenderness (indicated by pain under the front of the rib cage), sometimes with a loss of appetite. Patients should stop taking orlistat and inform their doctor if they experience any of these symptoms.
- Patients who have any questions should speak to their doctor or pharmacist at a routine appointment.

The European Commission issued a decision for Orlistat Art. 31 on 24 April 2012.

The current European public assessment report for Alli can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.

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