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Press Office

Press release

European Medicines Agency confirms positive benefit-risk balance of orlistat-containing medicines

Existing information on potential very rare liver-related side effects to be harmonised

Finalising its review on orlistat-containing medicines and the possible risk of severe liver injuries, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefit of these medicines continue to outweigh their risks in the treatment of obese or overweight patients with a body mass index of 28 kg/m² or above. The Committee recommended that the product information for these products should be harmonised to ensure that the information on possible very rare liver-related side effects is the same for all orlistat-containing medicines.

This review included the centrally authorised medicines Xenical and Alli (available 'over the counter' at a lower dose) and nationally authorised orlistat-containing generics.

The risk of very rare liver-related side effects in association with orlistat has been under close review by the CHMP since 2001 for Xenical, when the product information was updated to reflect post-marketing reports of liver reactions in association with orlistat. The current product information for orlistat-containing medicines lists hepatitis, cholelithiasis and a change in liver enzyme levels as potential liver-related side effects.

The review of orlistat-containing medicines was initiated in August 2011 at the request of the European Commission, following spontaneous reports of severe liver injuries that have been received over a number of years. Recent safety monitoring showed that from August 2009 to January 2011, 4 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 between May 2007, when it was first marketed, and January 2011, although in some cases there were other possible explanations and in some cases there was insufficient information to assess the cause. The number of cases needs to be considered in the context of cumulative usage of Xenical and Alli. Xenical and Alli together are

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estimated to have been used by over 53 million people worldwide, with over 20 million in the European Union (EU).

The CHMP reviewed all 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, and results of an 'expected versus observed' analysis of reports of severe liver injuries conducted by the marketing authorisation holders at the request of the Committee.

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 Committee considered that while there may be very rare cases of serious liver injury for which causality with orlistat cannot be excluded, the cases do not provide good evidence of a causal association. The CHMP also noted that published population-based studies suggest that obesity may be associated with a higher risk of liver disease.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of orlistat-containing medicines continue to outweigh their risks, and recommended that the product information for these products should be harmonised to ensure that the information on possible very rare liver-related side effects is the same for all orlistat-containing medicines.

Notes

1. This press release, together with all related documents, is available on the Agency's website.
2. 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'). More information about Alli and Xenical can be found in the European public assessment reports (EPARs) available on the Agency's website.
3. 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.
4. The European review of the centrally authorised orlistat-containing medicines Xenical and Alli was conducted in the context of a formal review, initiated at the request of the European Commission under Article 20 of Regulation (EC) No 726/2004, on 8 August 2011.
5. The European review of the nationally authorised orlistat-containing generics was conducted in the context of a formal review under Article 31 of Directive 2001/83/EC, initiated on 16 September 2011 at the request of the European Commission.
6. Spontaneous case reports of suspected adverse reactions alone are rarely sufficient to prove that a certain suspected reaction has been caused by a specific medicine. The suspected reaction may have been caused by the medicine, but there may be alternative or contributing causes to be considered. These may be for example the disease treated or an additional disease the patient has

developed, or another medicine the patient is taking. The information in the case reports is often not sufficient to conclude upon the causality with high certainty.

Any individual case report should be seen as a piece of a jigsaw puzzle, with consideration given to all available data to complete the picture. These data include spontaneous reports worldwide, clinical trials, epidemiological studies and toxicological investigations.

7. The CHMP's opinions have been sent to the European Commission for the adoption of a binding decision throughout the European Union.
8. A question-and-answer document on this review is available on the Agency's website.
9. More information on the work of the European Medicines Agency can be found on its website: www.ema.europa.eu

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