20th February 2012

Circular No. P06/2012

Dear Healthcare Professional,

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

The Medicines Authority would like to inform you that the European Medicines Agency (EMA) has finalised its review on orlistat-containing medicines and the possible risk of severe liver injuries and 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/m^2 or above. The EMA's Committee for Human Medicines (CHMP) 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 had been described by the Medicines Authority in Circular **P12/2011** and included the centrally authorised medicines Xenical and Alli (available 'over the counter' at a lower dose). 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

Medicines Authority
203 Level 3, Rue D'Argens, Gzira, GZR 1368 – Malta.
Tel. (+356) 23439000 Fax. (+356) 23439161 www.medicinesauthority.gov.mt

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 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.

Medicines Authority
203 Level 3, Rue D'Argens, Gzira, GZR 1368 – Malta.
Tel. (+356) 23439000 Fax. (+356) 23439161 www.medicinesauthority.gov.mt

The Medicines Authority is in agreement with the full **press release** and **question-and-answer document** issued by the EMA, attached here for your perusal. Healthcare professionals are encouraged to maintain vigilance on orlistat medicinal products. Suspected Adverse Drug Reactions may be reported using the Medicines Authority yellow card scheme or online at **http://www.medicinesauthority.gov.mt/pub/adr.doc** or to the marketing authorisation holder or their local representatives.

Healthcare professionals are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Medicines Authority
203 Level 3, Rue D'Argens, Gzira, GZR 1368 – Malta.
Tel. (+356) 23439000 Fax. (+356) 23439161 www.medicinesauthority.gov.mt