ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS PRESENTED BY THE EMA

Scientific conclusions

Overall summary of the scientific evaluation of orlistat-containing medicinal products

Orlistat impairs the metabolism of nutrients in the intestinal lumen and prevents lipid absorption without affecting appetite. This allows about 30% of the fat ingested in a meal to pass through the gut undigested. As a result, the body cannot use this dietary fat for energy or convert it into fat tissue, which helps weight reduction.

Three formulations of orlistat are currently authorised in the European Union through the centralised procedure. Xenical (orlistat 120 mg, capsules) was authorised in July 1998. In July 2007, a marketing authorisation was granted for Alli (orlistat 60 mg, capsules). The third formulation, Alli 27 mg, chewable tablets, was authorised in November 2010. Orlistat is available in Europe as both a prescription only medicine (Xenical) and a non-prescription medicine (Alli). Generic formulations of 60 mg and 120 mg orlistat are also authorised nationally in different member states.

The risks of liver reactions with orlistat have been kept under close review since the first signal in May 2001. The risks are addressed in the Risk Management Plans (RMP) of both products. In June 2009, the Committee for Medicinal Products for Human Use (CHMP) requested the Marketing Authorisation Holders (MAHs) of Xenical and Alli to submit cumulative reviews of orlistat-induced liver disorders. For Xenical, 21 cases of serious liver toxicity were reported between 1997 and January 2011, for which causality cannot be excluded. For Alli, a total of 9 reports of hepatic failure/liver transplant were reported during the period May 2007 to January 2011. In view of the above, the European Commission initiated procedures under Article 20 of Regulation (EC) No 726/2004 and under Article 31 of Directive 2001/83/EC, as amended, referring the matter to the CHMP on 08 August 2011. The European Commission requested the CHMP to assess the risk of serious hepatotoxicity and its impact on the risk-benefit balance of all orlistat-containing medicinal products and to give its opinion on measures necessary to ensure the safe and effective use of these products and on whether the marketing authorisations for these products should be maintained, varied, suspended or withdrawn.

Benefit

The CHMP assessed the data submitted by the MAHs as well as the total available body of data and concluded that a clinically relevant degree of weight loss was demonstrated for orlistat-containing products, which could translate into clinically meaningful improvements of risk factors for diabetes and cardiovascular disease.

Risks

Hepatotoxicity

The focus of this review was on the strength of the evidence relating to serious hepatotoxicity with orlistat. The evidence available from pre-clinical studies is not suggestive of the possibility of liver toxicity following normal human therapeutic exposures. Clinical trials showed no significant differences in the occurrence of abnormal liver function tests between orlistat and placebo. However, a meta-analysis of some orlistat clinical trials identified a small non-statistically significant increase in the occurrence of abnormal alanine aminotransferase and bilirubin measurements with orlistat compared with placebo. This may provide some evidence of an adverse effect of orlistat on hepatic function but does not provide evidence of serious

hepatotoxicity. It was noted that evidence from epidemiological studies suggests that obesity per se may be associated with an increased risk of liver disease.

The CHMP noted a total of 881 reports of 'drug-related hepatic events' received in association with orlistat-containing products since July 1998, from an estimated exposure of 53 million patients. The majority of cases were non-serious. For Alli, 60% of the reports described elevations in hepatic enzymes with no clinical features while a further 25% described isolated signs and symptoms of possible liver disease but were not indicative of hepatotoxicity. A total of 18 cases of serious liver disorder were identified, the majority of which had possible confounding factors, alternative aetiologies or limited data prohibiting a full assessment. For Xenical, nine cases involved fatalities and six involved a liver transplant and a total of 21 cases of serious hepatotoxicity where the role of orlistat cannot definitively be excluded were identified. The CHMP considered that the spontaneous reports provide only very weak evidence of a causal relationship between orlistat and serious hepatotoxicity. It is notable that there is no specific pattern regarding the nature of reported hepatotoxicity or any particular pattern in relation to time to onset of events, and in many cases, alternative explanations are present. The potential mechanism for hepatic disorders in association with orlistat is not known, however published case reports of hepatic injury in association with orlistat have suggested that this may be a rare idiosyncratic reaction. The CHMP considered the number of reports received in association with orlistat to be small in the context of the cumulative usage of this medicine.

Furthermore, the CHMP considered that the results of the 'expected versus observed' analyses of reports of serious hepatotoxicity indicated that the observed number of cases of serious hepatic reactions reported in association with orlistat is within the expected number of cases in an obese population and concluded that the number of reports of serious hepatic reactions may reflect background events in a very large population of users.

The risk of hepatitis and increases in transaminases and alkaline phosphatase have been included in the product information and risk management plan (RMP) of orlistat-containing medicinal products. In view of the evidence available, the CHMP considered that "hepatitis that may be serious" should be reflected under the 'Undesirable effects' section of the Summary of Product Characteristics (SmPCs) of all orlistat-containing products. The CHMP also considered that the package leaflet (PL) should be updated accordingly to ensure that patients are aware of hepatic signs and symptoms. The CHMP concluded that no additional risk minimisation measures were necessary to address the issue of serious liver reactions with orlistat.

Other risks

In addition to the risk of hepatotoxicity, the CHMP also reviewed other orlistat safety concerns, including hepatobiliary events (cholelithiasis), pancreatitis, oxalate nephropathy, acute kidney injury, gastrointestinal events, hypersensitivity reactions, hypoglycaemia, hypokalaemia, drug interactions, misuse, and off-label use. Gastro-intestinal reactions were the most frequently reported side-effects with orlistat and are related to its pharmacological effects. At the time of CHMP approval, the gastro-intestinal safety profile for orlistat 60 mg was considered to be better than that of orlistat 120 mg, causing milder gastrointestinal adverse effects. The CHMP noted that interaction with acarbose and the risk of oxalate nephropathy were mentioned in the SmPC but not in the PL and therefore revised the PL to align the wording for acarbose and oxalate nephropathy.

Risk management plan

The CHMP was of the opinion that all safety concerns are adequately reflected in the risk management plans of orlistat-containing products and therefore considered that these do not need to be revised.

Benefit-risk balance

Overall, the CHMP considered that the benefits of orlistat-containing products outweigh the associated risks in their current indication. The CHMP recommended that the current wording of the approved SmPCs should be revised to include the risk of 'Hepatitis that may be serious' in Section 4.8 and that the PLs should be harmonised and revised to include additional symptoms of liver injury as well as statements on interaction with acarbose and the risk of oxalate nephropathy.

Grounds for amendment of the summary of product characteristics and package leaflet

The Committee reviewed the totality of the available data on orlistat-containing products, including pre-clinical and clinical data, epidemiological data and spontaneous reports as well as observed versus expected analyses.

The CHMP considered that a clinically relevant degree of weight loss was demonstrated for orlistat-containing products, which could translate into clinically meaningful improvements of risk factors for diabetes and cardiovascular disease.

The Committee considered that the available data from clinical trials and spontaneous report with regard to the risk of serious hepatotoxicity events associated with orlistat provided only very weak evidence of a causal relationship between orlistat and serious hepatotoxicity.

The Committee considered that the results from the 'observed versus expected' analyses of serious hepatotoxicity indicated that the observed number of cases of serious hepatic reactions reported in association with orlistat is within the expected number of background cases in obese patients and did not further support a causal association between orlistat and serious hepatotoxicity.

The Committee considered that with the revisions proposed to the SmPC regarding the risk of hepatitis that may be serious and to the package leaflet, raising awareness of the symptoms of hepatitis, the product information adequately reflects the identified risks of orlistat-containing medicinal products.

Overall, the CHMP considered that the benefits of orlistat outweigh the associated risks in its current indications. The Committee therefore concluded that the benefit-risk of orlistat-containing medicinal products remains positive under normal conditions of use.

The Committee agreed that the current risk management plans adequately reflect the identified and potential risks of orlistat and therefore considered that they do not need to be revised.

In view of the above, the CHMP recommended the variation of the terms of the marketing authorisations for orlistat-containing medicinal products (see Annex I), for which the revised Summary of Product Characteristics and Package Leaflet are set out in Annex III of the opinion.

To the extent that other orlistat-containing medicinal products not included in Annex I could be currently authorised in the EU, or are subject to future authorisation procedures by the member

states, the CHMP recommends that the concerned member states take due consideration of the scientific conclusions in Annex II.