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Assessment report for Alli

Review under Article 20 of **Regulation (EC) No 726/2004**

International Non-proprietary Name: orlistat

Procedure number: EMEA/H/C/854/A-20/0029

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

Orlistat is an inhibitor of gastrointestinal (especially gastric and pancreatic) lipases which are essential for fat digestion. It impairs the metabolism of nutrients in the intestinal lumen and prevents lipid absorption without affecting appetite. Orlistat exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine site of the gastric and pancreatic lipases. The inactivated enzyme is thus unavailable to hydrolyse dietary fat, in the form of triglycerides, into absorbable free fatty acids and monoglycerides. 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. Orlistat is poorly absorbed (less than 2%) and is mostly excreted in unchanged form through the faeces.

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 and is marketed by F. Hoffmann-La Roche Ltd. In January 2009, a marketing authorisation was granted to Glaxo Group Limited for Alli (orlistat 60 mg, capsules). The third formulation, Alli 27 mg, chewable tablets, was authorised in November 2010. Orlistat is available 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.

- 120 mg orlistat is indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a body mass index (BMI) greater or equal to 30kg/m^2, or overweight patients (BMI >_28kg/m^2) with associated risk factors. Treatment with orlistat should be discontinued after 12 weeks if patients have been unable to lose at least 5% of the body weight as measured at the start of therapy.

- 27 mg and 60 mg orlistat is indicated for weight loss in adults who are overweight (body mass index, BMI, >28 kg/m^2) and should be taken in conjunction with a mildly hypocaloric, lower-fat diet.

In May 2010 the US food and drug administration (FDA) communicated the conclusions of its review on reports of severe liver injury in patients taking orlistat. The FDA was of the opinion that at this time, a cause and effect relationship of severe liver injury with orlistat use had not been established. However, because of the seriousness of severe liver injury, the FDA added information about reported cases of severe liver injury to the product information of Xenical and Alli, in order to educate the public about the signs and symptoms of liver injury and the need to see a physician promptly should they occur. The section on warnings was revised accordingly.

In the EU the risks of orlistat, including liver reactions, have been kept under close review. The undesirable effects “hepatitis that may be serious” and “increase in transaminases and alkaline phosphatases” were added to section 4.8 of the Xenical Summary of Product Characteristics (SmPC) in May 2001, while the product information (PI) for Alli has reflected the risks of liver reactions since its initial marketing authorisation in January 2009. The risks were addressed in the Risk Management Plans (RMP) of both products.

Cumulative reviews of orlistat-induced liver disorders were previously assessed by the Committee for Medicinal Products for Human Use (CHMP) in 2009 and 2010 and no additional changes to the PI were considered necessary. In a recent review, concerns were raised regarding the number of reported cases of liver disorders. The analysis of Xenical, covering the period 8 August 2009 to 31 January 2011, identified a total of 21 hepatic events of which 4 were cases of serious liver toxicity (one fatal case of hepatic failure, one case of hepatic failure leading to liver transplantation, one case of exacerbation of hepatitis and one case of hepatitis). Overall, since 1997 until January 2011, 21 cases of serious liver toxicity have been reported, for which causality cannot be excluded. For Alli, a total of 9 reports of hepatic failure/liver transplant (one case of acute hepatic failure considered related to orlistat by the reporter despite confounding factors, five cases with possible confounding factors/alternative aetiologies and three cases with limited data to allow causality) 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 for Alli and Xenical, referring the matter to the CHMP on 08 August 2011. The European Commission requested the CHMP to assess the above concerns and their impact on the risk-benefit balance of all centrally authorised 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. A procedure under Article 31 of Directive 2001/83/EC, as amended was also triggered for mutual recognition/decentralised products and nationally authorised products which had either already been or were in the process of being authorised at national level. In its assessment, the CHMP therefore considered the total body of available data on orlistat.

The CHMP consulted its Pharmacovigilance working party (PhVWP) as applicable.

After reviewing all the available data submitted by the Marketing Authorisation Holders (MAHs) to address the concerns discussed, the CHMP adopted an opinion on 16 February 2012.

2. Scientific discussion

2.1. Clinical aspects

Overweight and obesity is recognised as the most prevalent metabolic disease worldwide. The economic implications and the burden of obesity on national health costs are substantial and represent a major worldwide health concern. A Body Mass Index (BMI) of 25 kg/m² and above conventionally defines overweight, while a BMI of 30 kg/m² and above defines obesity. Overweight and obesity are considered important risk factors for mortality and morbidity from cardiovascular diseases, diabetes, cancers and are responsible for about 80% of cases of type 2 diabetes, 35% of ischaemic heart disease and 55% of hypertensive disease among adults in Europe. The aim of an obesity treatment is to achieve a clinically relevant and maintained weight loss which is susceptible to decrease cardiovascular risk factors in order to prevent morbidity and mortality. It has been demonstrated that a weight loss of 10% of the initial body weight had a positive influence on cardiovascular risk factors such as arterial blood pressure, lipaemia and glycaemia. The use of obesity drugs may be prescribed after assessment of both the clinical and economic potential benefits and risks.

Concerns regarding the safety of orlistat, in particular of orlistat-induced liver disorders, were addressed in this article 20 review. The discussion focuses on the data relevant to the identified concerns.

2.1.1. Efficacy

Data from randomised clinical trials and other studies are available. When used in conjunction with a mildly hypocaloric, lower-fat diet, orlistat has been shown to significantly reduce body weight, compared to placebo. A reduction in body weight could translate into clinically meaningful improvements of risk factors for diabetes and cardiovascular disease. Treatment may need to be discontinued after 12 weeks, if patients have been unable to lose weight. The CHMP considered that the demonstrated efficacy has not changed since the initial authorisations of the products.

2.1.2. Safety

2.1.2.1. Pre-clinical data

The MAHs provided a summary overview of the orlistat pre-clinical toxicity study results relating to hepatic effects. In the rat, hepatic lipid accumulation, in the form of fatty change and/or positive fat staining, was observed in rats following intravenous (i.v.) administration of orlistat doses ranging from 5 to 100 mg/kg/day for 2 weeks and following oral administration of orlistat doses of 1000 and 2500 mg/kg/day for 13 weeks. No evidence of hepatic lipid accumulation was observed in rats following i.v. administration of orlistat doses up to 4.48 mg/kg/day for 2 weeks, or following oral administration at doses up to 500 mg/kg/day for 13 weeks or 125 mg/kg/day for 52 weeks. Single cell hepatic necrosis was observed in a single study following i.v. administration of 100 mg/kg/day orlistat to rats for 2 weeks. It was not observed in rats following i.v. administration of orlistat at doses up to 25 mg/kg/day for 2 weeks, or following oral administration of orlistat at doses up to 2500 mg/kg/day for 13 weeks, or 125 mg/kg/day for 52 weeks. In the dog, the results of a single 2-week i.v. study with orlistat revealed increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin following administration of 25 or 125 mg/kg/day and yellow

coloured livers and multifocal hepatitis with marked fatty change following administration of 125 mg/kg/day (mean AUC of 302,7000 ng.hr/ml). However, in another 2-week i.v. study in dogs, in which lower dose levels of 1.16, or 4.46 mg/kg/day orlistat were administered, there was no evidence of adverse hepatic effects. Similarly, 3 oral toxicity studies in which orlistat was administered to dogs at doses up to 1000 mg/kg/day for periods up to 52 weeks revealed no adverse hepatic effects. In the mouse, there was no evidence of adverse hepatic effects in a study in which doses up to 2500 mg/kg/day were administered orally in the diet for 13 weeks.

The metabolites designated as M1 (Ro 42-3988) and M3 (Ro 42-2556) have been shown to be the main metabolites of orlistat in human plasma following oral administration. The results of oncogenicity studies in mice and rats demonstrated plasma levels of orlistat and its M1 (Ro 42-3988) and M3 (Ro 42-2556) metabolites that exceeded those observed in clinical studies. Additionally, the results of a 1-year chronic oral toxicity study in dogs demonstrated plasma levels of orlistat and its M1 metabolite that exceeded those observed in clinical studies. The results of these animal studies revealed no major adverse effects (including no adverse hepatic effects) associated with orlistat and it M1 and M3 metabolites for periods of 1 to 2 years at doses that were significantly greater than the intended clinical dose. Finally, a recent literature search did not reveal additional pre-clinical information indicative of hepatotoxicity of orlistat that is relevant to humans.

The CHMP noted that orlistat exerts its therapeutic activity by forming a covalent bond with the active serine site of gastric and pancreatic lipases in the lumen of the stomach and small intestine. Orlistat is not selective for GI lipases but inhibits a broad range of lipases including gastric, pancreatic, lipoprotein, hepatic and hormone sensitive lipases. However, at therapeutic doses the interference with systemic lipid metabolism is avoided, as absorption of the drug following oral administration is negligible in animals and humans, with less than 1% systemic availability of intact orlistat. In the chronic toxicity studies, the exposure of animals (mouse, rat and dog) to orlistat and its main metabolites at the no-adverse hepatic effect level were considerably higher than levels seen in humans under therapeutic conditions. In the rat, hepatic effects such as fatty infiltration and fatty change were only seen at very high oral doses of 1000 and 2500 mg/kg/day. Toxicity studies in which orlistat was administered orally to dogs at doses up to 1000 mg/kg/day for periods up to 52 weeks revealed no adverse hepatic effects and in the mouse there was no evidence of adverse hepatic effects at doses up to 2500 mg/kg/day for 13 weeks.

Intravenous dosing studies were conducted in rats and dogs which produced more severe hepatic effects than observed with higher oral doses. In the rat, single cell hepatic necrosis was present in a number of high dose animals. In dogs, marked hepatic toxicity and clinical pathological alterations such as increased plasma transaminase activity and hyperbilirubinemia were seen. High doses produced yellow-coloured livers and multifocal hepatitis with marked fatty change. Findings at 25mg/kg day were confined to increased transaminases. However, the CHMP considered the systemic exposures in these studies to be too far in excess of normal human therapeutic exposures for the hepatic effects to be considered relevant. The CHMP stated that for idiosyncratic hepatotoxicity to occur, rare combinations of poorly characterised exposure conditions, host and genetic defects are required and conventional pre-clinical toxicity studies have limited ability to predict these reactions. The CHMP noted that the possibility of haptenization is one of many potential risk factors that have been associated with idiosyncratic hepatotoxicity, due to the covalent binding mechanism of action of orlistat. The safety of orlistat derives from its very low bioavailability and makes a systemic pharmacological effect of orlistat (or metabolites) unlikely. The CHMP therefore concluded that the pre-clinical studies are not suggestive of an increased risk of hepatotoxicity following normal human therapeutic exposures.

2.1.2.2. Clinical data

Clinical Pharmacology

In a high dose clinical pharmacokinetic study in obese subjects, oral doses of 400 mg t.i.d. (more than 3 times the recommended dose of Xenical and approximately 7 times the recommended dose of Alli) for 10 days resulted in most plasma concentrations of orlistat being either non-measurable or below 10 ng/ml, with an assay sensitivity of 1ng/ml. Peak concentrations were maintained for less than two hours and no accumulation of orlistat was observed. Liver function tests (transaminases, bilirubin, gamma-glutamyl transpeptidase, alkaline phosphatase, prothrombin time, partial thromboplastin time, protein and albumin) were monitored before, during and after treatment, and all values remained within normal limits. Compared to i.v. doses of 125 mg/kg/day to dogs in which hepatic events were observed, the systemically available dose in this pharmacokinetic study would be equivalent to a

human dose of 0.34 mg/kg/day assuming 2% absorption and a body weight of 70 kg. Systemic exposure in humans receiving therapeutic doses is unlikely to have a toxic effect on the liver.

Clinical trials

Liver function tests were assessed in the Phase III clinical trials, enrolling approximately 6,000 middle-age patients with obesity, obesity related risk factors and diabetes. There was no statistically significant difference between the orlistat 60mg and 120mg treatment groups and the placebo group. From approximately 2,500 patients treated with orlistat for up to two years during Phase III trials, a total of 18 (0.4%) patients presented with an ALT abnormality at or above 3 times the upper limit of normal (ULN). The ALT abnormalities appeared unrelated to either the dose of the active treatment or the allocation to the active or the placebo groups. None of these marked abnormalities was associated with serious damage or persistent deviation. Out of a total of 3,245 gastrointestinal system disorders reported, the incidence of hepatobiliary events varied from 1.0% to 2.1%, depending on group and duration of treatment. Differences between treatment groups were not significant.

In a Phase IV multicentre, double-blind, placebo-controlled, randomised trial, 3,304 patients received orlistat 120mg for up to 4 years. Marked ALT abnormalities occurred with incidences of 2.9%, 2.2%, 2.0% and 2.5% (years 1, 2, 3 and 4 respectively) for the orlistat group, compared to 1.7%, 2.4%, 2.6% and 3.5% (years 1, 2, 3 and 4 respectively) for the placebo group. There was no significant difference between the orlistat and placebo groups. Hepatobiliary adverse events consisted mostly of cholelithiasis and/or cholecystitis, with 47 cases (3%) in the orlistat versus 30 cases (2%) in the placebo groups.

Meta-analysis of liver function tests in clinical trials

The MAHs submitted a meta-analysis of liver function test data from previously completed randomised clinical trials of orlistat. This study primarily used data from internal clinical trials but also included externally performed studies identified from the literature. Studies had to meet the following criteria for selection: randomised and placebo-controlled trial, orlistat dose 60mg or 120mg, available data on ALT or bilirubin and the nominal treatment period must be 16 weeks or longer (this was later widened to include studies ≥ 4 weeks but no further data was identified). The meta-analysis focused on serum ALT and BIL (total bilirubin), as these may be useful diagnostic tests of potential drug-induced liver injury (DILI). Only the first year's data from long studies was analysed as the onset of DILI is very likely to eventuate within this period and only data from the first period of cross-over studies was used. The primary analysis was a comparison between orlistat 120 mg and placebo, while the analyses comparing orlistat 60 mg with placebo were considered secondary.

The results indicated that the occurrence of two successive abnormal ALT measurements was slightly higher for the orlistat patients compared to placebo but that this difference was not statistically significant: 7.4% compared to 6.9% (odds ratio 1.09 and 1.10 from the fixed- and random-effects analyses, p=0.27 and 0.32, respectively). The analysis of individual abnormal ALT measurements was similar to that of two successive abnormal measurements, with odds ratios of 1.05 and 1.04. Analyses for 60 mg and 120 mg doses separately gave similar results. The average occurrence of two successive abnormal bilirubin levels was 5.6% for orlistat compared to 4.6% for placebo, with odds ratio 1.24 from the fixed-effect analysis (p=0.02) and 1.21 from the random-effects analysis (p=0.21). The analysis of individual abnormal measurements gave an average occurrence of 11% for orlistat compared to 10% with placebo, with an odds ratio of 1.13, which was at the limit of significance at 5%. For all measurements, the differences may be explained by the higher number of measurements carried out on orlistat patients, due to higher withdrawal rates for placebo patients. A patient-level analysis was carried out analysing ALT and bilirubin simultaneously, using the individual patient data from the same trials. Generally, there was no striking distinction between placebo and orlistat. A Kaplan-Meier analysis of these data showed little difference between treatments.

A number of limitations of the meta-analysis were acknowledged, including a number of excluded studies for which the MAHs were unable to access data, the quality of individual studies, the fact that potential biases were not evaluated (there is a potential for reporting bias with orlistat as blinding may be hindered by its gastrointestinal side-effects), differences in the populations being studied (e.g. some studies included obese diabetic patients, or patients with different severities of obesity) and no attempt to model for covariates such as BMI and concomitant medication.

Other epidemiological data

Results from seven studies investigating an association between obesity and liver disease were provided. The studies showed that non-alcoholic steatohepatitis (NASH) is seen in approximately 30% of obese patients, with 5-30% of these progressing to cirrhosis (*Caldwell et al*, 2002) and that non-alcoholic fatty liver disease (NAFLD) is higher in the obese population (58%-75%) compared to the general population (10-24%) (*Rutherford et al*, 2006). The prevalence of elevated aminotransferase may also be increased in overweight (7.3%) and in obese (12.0%) subjects compared to normal weight subjects (4.4%) (*Erbey et al*, 2000). Increased alcohol intake may also be associated with an increased prevalence of elevated aminotransferase amongst the overweight and the obese (*Ruhl et al*, 2003). A nested case control study in the UK General Practice Research Database (GPRD) identified 2,718 cases of newly diagnosed liver disorder. Of these 1,524 had known predisposing conditions. The overall incidence rates per 1,000 person years were 2.48 for the normal weight subjects, 2.91 for pre-obese subjects and 3.83 for obese subjects. In the nested case-control analysis, the adjusted odds ratio for obese, as compared to normal weight subjects, was 1.2 (95% CI 1.1-1.4). The overall risk for obese vs. non-obese for idiopathic cases (without known risk factors for liver disorders) was 1.3 (95% CI 1.1-1.6). The study concluded that the risk of both overall liver disorders and idiopathic cases may be increased in obese patients compared to normal weight patients (*Meier et al*, 2002). No observational studies of the incidence of acute liver failure in the obese are available, however one study showed that some patients with undiagnosed NASH had silent progression to cirrhosis which progressed to subacute liver failure.

In addition, a large US study with over 170,000 diabetic patients and 650,000 non-diabetic patients revealed that the incidence rate of acute liver failure was significantly higher in diabetic patients (incidence rates of 2.3 per 10,000 person years compared to 1.4 for non-diabetics). The relative risk was 1.44 (95%CI: 1.26-1.63) after adjusting for age, gender, race and the presence of chronic liver disease. Another study, investigating the outcome of 573 patients with (acute liver failure (ALF), showed that obese patients with ALF were 1.6 times more likely to have a transplant or die compared with non-obese patients with ALF. Obese subjects are often also prescribed potentially hepatotoxic medications for complications associated with obesity (e.g. oral hypoglycaemic agents) increasing their risk for liver injury.

The CHMP reviewed the data submitted by the MAHs, which showed that liver function tests before, during and after treatment remained within the normal limits and that there were no statistically significant differences in the occurrence of abnormal liver function tests between orlistat and placebo. Only in one Phase III study (study 14161) was there any sign of a possible dose relationship with a marked increase in the percentage of patients in the 120mg group having raised liver enzymes compared to placebo (4% vs. 1% after year 1). However, the incidence in the orlistat 60 mg group (1%) was equal to that in the placebo group. The MAHs meta-analysis of orlistat clinical trials found a small non-statistically significant increase in the occurrence of abnormal ALT and bilirubin measurements (9% and 20% increase, respectively) with orlistat compared to placebo. The CHMP was of the opinion that there is evidence from epidemiological studies that obesity may be associated with an increased risk of liver disease.

2.1.2.3. Spontaneous reports

Spontaneous reports for Alli (orlistat 60 mg)

An overview of all spontaneous reports by System Organ Class (SOC) received in association with Alli was provided. A total of 47,707 reports describing 101,530 adverse events were received between 01 May 2007 and 31 August 2011. Where gender was reported (77% of reports), the patients were overwhelmingly female (92%) and mainly in the age range 30 to 59 years. The majority of the cases were non-serious (96%). The Gastro-intestinal disorders SOC accounted for the largest proportion of cases (50.3%), followed by the General disorders and administration site disorders (18.2%), Investigations (8.2%), Nervous system disorders (4.8%) and Skin and subcutaneous tissue disorders (4%) SOCs.

The most commonly reported events in the Gastro-intestinal disorders SOC generally related to the expected gastrointestinal side effects of orlistat (e.g. diarrhoea, abdominal distension, abdominal pain and steatorrhoea/oily discharge). Constipation and nausea were also commonly reported but these events are not unexpected in subjects on reduced calorie diets. The most frequent events in the General disorders and administrations site disorders SOC involved non-specific symptoms such as ill-defined disorder, malaise or fatigue. Pain (unspecified) and hunger were also commonly reported. In the Investigations SOC, ‘weight increased’ accounted for 75% of all reported events. The next most commonly reported terms were ‘blood pressure increased’, ‘heart rate increased’ and ‘hepatic enzymes

increased'. The majority of cases in the Nervous system disorders SOC reported headache or dizziness which would not be unexpected in subjects on a reduced calorie diet. In the Skin and subcutaneous tissue disorders SOC, the majority of reports related to the listed reactions itching and rash. Hyperhydrosis was also commonly reported but this event is considered to be commonly experienced by the general population.

Serious cases (including fatal reports)
1,837 (4%) of the spontaneous reports received up to 31 August 2011 were serious. The Gastro-intestinal disorders SOC accounted for the largest proportion of serious cases (38%), followed by the Investigations (10%), Nervous system disorders (7%), Hepatobiliary disorders (5.1%) and Infections and infestations (5%) SOCs. Rectal bleeding was the most frequently reported serious event in the Gastro-intestinal disorders SOC. The other events in this SOC reflect the expected gastrointestinal events associated with orlistat. Increased hepatic enzymes/abnormal liver function tests were among the most frequently reported events in the Investigations SOC. Dizziness and headache accounted for almost a third of the reported events in the Nervous system disorders SOC and gastro-intestinal and respiratory infections accounted for the majority of the events in the Infections and infestations SOC. Fourteen reports had a fatal outcome, including one case of hepatic failure.

Hepatic events
A total of 300 reports of 'drug-related hepatic events' in association with Alli were identified, which represent 0.63% of the entire dataset of Alli spontaneous reports. The majority of reports originated from the US (85%), with 15% of the reports originating from Europe. 24% were reported by health professionals. The majority of cases (85%) met the criteria for a serious adverse event report. Seriousness was most commonly due to the inclusion of an event from the list of medically serious terms and included any report of abnormal liver function test (LFT) results. The MAHs stated that for this report, medical judgement had been used to determine the subset of cases that represent serious liver disorders. Where gender was known (n=283), 90% involved female subjects, with a median age of 52 years (range 23 to 82 years). Of the 300 reports, 76 reports were considered to involve isolated signs or symptoms of possible liver disease, but were not indicative of hepatotoxicity: 15 reports of yellow skin/eyes, 6 reports of erratic or deranged prothrombin time, 4 reports of ascites and 51 cases of liver pain, enlarged liver or unspecified liver damage/disorder. There were also a further 181 reports involving elevations/derangement in liver function tests as well as 8 reports involving a primary hepatic event of fatty liver and one report each of hepatic cyst and hepatic lesion. The remaining 33 reports were subject to detailed review by the MAHs to identify serious liver disorders and to provide a specific comment on each report.

From these 33 reports, thirteen reports described medically serious hepatic conditions and were also medically confirmed and/or well documented (7 reports of hepatic failure, 3 reports of autoimmune hepatitis, 2 reports of hepatitis and one report of drug-induced hypersensitivity syndrome). A further 4 reports involving hepatic failure either lacked objective verification of this diagnosis or provided insufficient information for assessment. In addition, there were 12 reports of hepatitis and one report of hepatic cirrhosis (6 medically confirmed). These reports were generally not well documented and did not provide a coherent picture of potential hepatotoxicity. The final 3 reports were of hepatic steatosis, hepatotoxicity and primary biliary cirrhosis. Of the 33 reports, the outcome was known in 24 cases and included 11 patients who recovered after treatment and 6 patients who recovered after stopping orlistat. In 3 cases, the outcome was stated as not recovered and a further 3 patients received a liver transplant and one case resulted in death. None of the patients were subject to rechallenge. Gender and age distribution largely reflected that of the general Alli user population, being predominantly female (88%) aged between 23 and 67 years (mean 46 years). No pattern could be observed in terms of type of liver injury and time to onset, where known, was highly variable, ranging from a few days to years. BMI was reported in fewer than half these reports but where information was provided, both persons of low weight and obese patients were identified. No patients were reported to be morbidly obese and none were underweight. Two thirds of patients were receiving concurrent medication which could have been a factor in the evolution of the events in over 50% of the 33 reports. Relevant medical history (potentially representing confounding features) was described in 70% of reports that provided this information.

The CHMP noted that the majority of spontaneous reports received in association with Alli were non-serious consumer reports in female patients and that half of all reports reported the primary reaction in the Gastrointestinal disorder SOC. The Alli SmPC states that adverse reactions to orlistat are largely gastrointestinal in nature and related to the pharmacologic effect of the medicinal product on preventing the absorption of ingested fat and that the package leaflet (PL) advises patients that eating lower-fat meals can help manage diet-related treatment effects. Apart from gastrointestinal disorders,

the only other common adverse reactions listed in the Alli SmPC was anxiety, which is possibly related to the anticipation of, or secondary to, gastrointestinal adverse reactions. Other frequently reported reactions in the spontaneous reports described event terms that are common background events in the general population such as malaise/fatigue, dizziness and headache.

Regarding hepatic events, the CHMP noted the recorded spontaneous reports and that the identified reports of 'drug-related hepatic events' account for less than one percent of the total number of spontaneous reports received in association with Alli (of note, hepatobiliary disorders accounted for 5% of reports reported by health professionals). The majority were cases of elevations in hepatic enzymes with no clinical features documented, which are already listed in the Alli SmPC as 'increase in transaminases and in alkaline phosphatase' in Section 4.8. In addition, there were also reports of non-specific terms: yellow skin eyes, abnormal prothrombin reading, ascites, liver pain, enlarged liver or unspecified liver damage/disorder, which were considered to involve isolated signs or symptoms of possible liver disease, but not indicative of hepatotoxicity. There were also additional reports of liver symptoms/disorders not considered indicative of drug-induced liver injury (fatty liver, hepatic cyst and hepatic lesion).

Overall, the CHMP noted the reports of hepatic failure received in association with Alli, 3 of which resulted in a liver transplant and one of which had a fatal outcome. In one report of hepatic failure/transplant, the transplant surgeon considered that the acute hepatic failure was related to orlistat. In this case, hepatic copper levels were indicative of Wilson's disease, although this was thought to be an incidental finding by the reporter. In the remaining cases, 6 reports had possible confounding factors or alternative aetiologies and 4 reports had limited data which did not allow full assessment or objective verification of the diagnosis of liver failure. The CHMP also noted the reports of hepatitis in association with Alli. Nine of these had possible confounding factors and the others had insufficient information for assessment. There were also 3 reports of autoimmune hepatitis for which temporal association with Alli was weak and where all 3 subjects had lost significant amounts of weight prior to the onset of symptoms. The CHMP noted that hepatitis is a listed reaction in the Alli SmPC and is listed as an identified risk in the Alli RMP. Notwithstanding this fact, the CHMP considered that the SmPC wording should be revised to reflect 'Hepatitis that may be serious'. The PL (Section 4) should be updated accordingly to ensure that patients are aware of hepatic signs and symptoms.

The CHMP was of the opinion that the available spontaneous reports do not provide convincing evidence of a causal relationship between Alli and serious hepatotoxicity and that no additional new issues with Alli were identified from the overview of spontaneous reports.

Spontaneous reports for Xenical (orlistat 120 mg)

A summary tabulation of all spontaneous events by SOC was provided for Xenical, reported cumulatively from initial authorisation until 31 August 2011, together with a summary tabulation of all cases and spontaneous events by report type (medically confirmed vs. non-medically confirmed) and a full list of all spontaneous events. A total of 36,066 cases were reported, describing 69,376 adverse events. Among these cases, 7,887 (22%) were medically confirmed and 28,179 were non-medically confirmed (78%). The majority of spontaneous cases were female (84.0%) and the predominant age group 30-60 years. The most frequently reported events were in the Gastrointestinal Disorders SOC (49.4%), followed by the General Disorders and Administration Site Conditions SOC (10.9%) and the Skin and subcutaneous tissue disorders SOC (6.6%). Within the Gastrointestinal Disorders SOC, the most frequently reported events were steatorrhoea (n=6,085) followed by diarrhoea (n=3,889). Within the General Disorders and Administration Site Conditions SOC, the most frequently reported events were 'drug ineffective' (n=1,830) followed by 'no adverse events' (n=987). Lastly, within the Skin and subcutaneous tissue disorders SOC, the events most frequently reported were rashes (n=1062) followed by pruritus (n=685). Events in the Hepatobiliary Disorders SOC accounted for 0.9% of all spontaneous events reported. The most frequent event within this SOC was cholelithiasis (30%).

Adverse events in the Renal and Urinary Disorders SOC accounted for 2.4% of all events. The most frequently reported event in this SOC was pollakiuria (23%). Adverse events in the Gastrointestinal Disorders SOC accounted for 49% of all spontaneous events reported. The most frequently reported event in this SOC was steatorrhoea (18%). Gastrointestinal adverse events have been closely monitored and presented in several cumulative case reviews. 393 events of rectal haemorrhage were identified, together with 3625 events of constipation, 1411 events of nausea and 780 events of vomiting. These events are already reflected in the Xenical PI and no changes to the SmPC were considered necessary. There have been 86 events of pancreatitis and 26 events of pancreatitis acute, which are listed events. A causal relationship between pancreatitis and treatment with orlistat was not

established. Adverse events in the Endocrine Disorders SOC account for 0.1% of all events, whilst adverse events in the Metabolism and Nutrition Disorders SOC account for 4.4% of all events. The most frequently reported event in the Endocrine Disorders SOC was hypothyroidism with 41 reports (50%), which is a listed event, together with 24 reports of 'blood thyroid stimulating hormone increased'. The most frequently reported event in the Metabolism and Nutrition Disorders SOC was 'weight loss poor' (70%). There were also 100 reported events of hypoglycaemia, which is listed as a very common adverse event.

The Neoplasms Benign, Malignant and Unspecified SOC accounted for 0.2% of all reported events. The most frequently reported event in this SOC was breast cancer (21%). There were 2 reported events of colon adenoma, 9 reported events of colon cancer, one reported event of colon cancer stage 1, and one reported event of colon neoplasm. Colorectal cancer in patients taking orlistat was reviewed in a report published jointly by Roche and GSK on 03 August 2006, which included a comprehensive assessment of pre-clinical and clinical trials data as well as spontaneous case reports. Adverse events in the Vascular Disorders SOC accounted 0.9% of all spontaneous events. The most frequently reported event within this SOC was hypertension (29%). There were 5 reported events of vasculitis. Two cases of cutaneous vasculitis were also reported under the Skin and Subcutaneous Tissue Disorders SOC, which accounted for 6.6% of all spontaneous events reported. The most frequently reported events within this SOC were rash (23%) and pruritis (15%). There were 7 events of erythema multiforme and one case of toxic epidermal necrolysis. No events of Stevens Johnson syndrome were reported. Adverse events in the Psychiatric Disorders SOC accounted for 2.1% of all spontaneous events. The most frequently reported events within this SOC were insomnia (19%), depression (17%) and anxiety (16%). 29 events of overdose were also reported. Regarding misuse and off-label use, there was 1 reported event of binge eating, 2 of bulimia nervosa and 6 of eating disorder. The MAH also reviewed 258 events of drug interaction, including drug interactions with antidepressants, anti-epileptics, antihypertensives, lithium, antipsychotics, fat soluble vitamins, cyclosporine, oral contraceptives, and clozapine.

Regarding hepatic events, hepatobiliary adverse events are continuously monitored since March 2000, covering the complete review time from initial launch to 31 August 2011. Several drug safety reports (DSR) have been submitted with detailed analyses of all relevant case reports concerning hepatic disorders. A cumulative DSR (DSR 1036542) up to 07 August 2009 and a 1st Addendum DSR (DSR 1043544) covering the period 08 August 2009 to 31 January 2011 had been previously submitted, while a 2nd Addendum DSR (DSR 1046850) covering the additional period from 01 February 2011 to 31 August 2011 was submitted in the context of this procedure. Adverse events in the Hepatobiliary Disorders SOC accounted for 0.9% of all reports. The most frequent event within this SOC was cholelithiasis (30%). DSR 1036542 was based on a search performed using the SMQs `Liver related investigations, signs and symptoms', `Hepatic failure, fibrosis and cirrhosis and other liver damage related conditions', 'Hepatitis, non-infectious', `Cholestasis and jaundice of hepatic origin'. A total of 555 cases including 810 hepatic events were received, of which 252 were reported as serious. Seven patients died, and 5 patients required liver transplant. Of 312 cases reporting laboratory findings only, 67 were serious and 249 were non serious cases. Of those 67 serious cases, 34 had alternative explanations for the events, 16 provided insufficient information for a causality assessment and in 9 cases, the laboratory findings were co-manifestations of other serious adverse events. Of 212 cases reporting hepatic pathology, 161 had alternative explanations and 46 provided insufficient information for a causality assessment. DSR 1043544 identified a total of 21 cases with 30 hepatic events, 18 of them serious adverse events were identified. Hepatic failure was reported in 3 cases (with fatal outcome in 2 cases and liver transplant in one case), unspecified liver injury in one case, increased liver enzymes in 10 cases, hepatitis in 2 cases, hepatic steatosis in 4 cases and unspecified increased hepatic echogenicity in one case. None of these cases provided evidence of a causal association with orlistat and all presented either alternative explanations (e.g. concurrent diseases, co-medications), temporal relationships which made a causal role of orlistat very unlikely, or limited information which precluded an adequate assessment. Finally, DSR 1046850 identified an additional 5 cases. Of those, 4 were reported 'Liver enzymes increased' (all non-serious) and 1 `Cholestasis and jaundice of hepatic origin' (reported as serious). Of the 4 cases with liver enzymes increased, one had alternative explanations for the event, one had mild elevations of ALT and AST occurring 8 years after stopping orlistat and in 2 cases there was insufficient information for an adequate assessment. In the patient with cholestasis and jaundice, the events appear to have occurred in the context of pancreatitis, although there is insufficient information for an adequate assessment (i.e. no laboratory or imaging data).

The CHMP noted the total 36,066 cases representing 69,376 adverse events (of which 5,151 were serious) reported for Xenical, the majority of which were non-medically confirmed (78%). The most

frequently reported events were from the Gastrointestinal Disorders SOC (49.4%), followed by the General Disorders and Administration Site Conditions (10.9%), and the Skin and subcutaneous tissue disorders (6.6%) SOC. The CHMP considered that the Xenical SmPC already describes various adverse effects including in particular the following listed as very common: abdominal pain/discomfort, oily spotting from the rectum, flatus with discharge, faecal urgency, fatty/oily stool, flatulence, liquid stools, oily evacuation and increased defecation. Pancreatitis has already been listed in Section 4.8 of the Xenical SmPC based on nearly 86 cases of pancreatitis, including a certain number of reports where no confounding factors were retrieved. Based on the GRPD, the MAH provided an estimate of the incidence rate of pancreatitis of 54.4 per 100,000 person-years for Xenical. The CHMP noted that obesity is associated with an increased risk of several types of cancers including "colorectal cancer" and "breast cancer" after menopause but that the available pre-clinical data including genotoxicity, carcinogenicity and exploratory studies on colonic cell proliferation do not support a causal relationship between orlistat and the occurrence of such malignancies.

Regarding hepatotoxicity, the CHMP reviewed the provided Drug Safety reports and concluded that cumulatively, a total of 581 cases with 846 hepatic events (271 serious) have been recorded from an estimated exposure of 39.76 million patients. Nine patients died and six required a liver transplantation. Among the 846 hepatics events, 536 were listed in the Investigations SOC. Among these, a total of 21 cases of serious hepatotoxicity where the role of orlistat cannot definitively be excluded were identified, including 5 cases of hepatic failure (2 cases with a fatal outcome and 3 cases leading to liver transplant), one case of liver injury, one case of cholestatic hepatitis, one case of acute hepatitis, 2 cases of toxic hepatitis, and 10 cases of hepatitis, and one case of exacerbation of hepatitis. The CHMP also noted a retrospective study carried out by France, reviewing all cases of hepatic transplant for fulminant hepatitis in France, in order to identify possible cases related to orlistat intake and not reported in the national pharmacovigilance system. Using the French National Transplant Database "Cristal", all registered cases of hepatic transplant for fulminant hepatitis from 2008 (launch of Xenical in France) until 14 October 2011 were considered and cases from exclusively paediatric transplant centres or from a foreign transplant centres were excluded. A total of 561 cases of hepatic transplant for fulminant hepatitis were retained, 248 of which were selected for further review. None of these 248 cases suggested a causal association with orlistat.

The CHMP noted that 'Hepatitis that may be serious' is a listed reaction in the Xenical SmPC and is listed as an identified risk in the Xenical RMP. The CHMP considered that the PL (section 4) should be updated accordingly in order to ensure that patients are aware of hepatic signs and symptoms.

Based on the analysis of all submitted spontaneous reports, the CHMP was of the opinion that there was no convincing evidence of a causal relationship between Xenical and serious hepatotoxicity and that no additional new issues with Xenical were identified from the overview of spontaneous reports.

2.1.2.4. Expected versus observed analysis

At the request of the CHMP, the MAHs carried out 'observed versus expected' analyses for Alli and Xenical, using global exposure data and background rates of serious liver events calculated among obese subjects in the GPRD.

The expected number of serious liver events in subjects exposed to Alli was estimated by applying the age- and gender- specific background hepatic event rates calculated among obese subjects in GPRD. The analysis was based on the estimated total of 13.5 million subjects exposed to Alli and assumed that each subject was exposed for 78 days, resulting in a total of 2,880,074 person years. The MAHs also assumed that 80% of users were women and that the proportion of subjects in each age group was 36.5% < 40 years, 29% 40-49 years, 19% 50-59 years, 11% 60-69 years, 4% 70-79 years and 0.4% 80+ years. Based on these assumptions, the expected number of cases among 13.5 million subjects exposed to Alli was estimated to be 195. To date, a total of 18 serious liver disorders have been reported. Since these were spontaneous ADR reports, under-reporting should be considered. Assuming that only 20% of all serious liver cases were reported, the adjusted number of cases observed would be 90 and if assuming that only 10% of all cases were reported, the adjusted number of observed cases would be 180. The limitations of this analysis were acknowledged, as the number of patients using the product, their age/gender profile and the duration of use was based on observational data that preceded the European launch of the product. In addition, the selected serious hepatic events reported in GPRD may not precisely match those reported among Alli users.

The analysis for Xenical was based on an estimated global use of approximately 39.8 million patients since launch. Using the distribution of gender derived from over 40,000 spontaneous reports on Xenical, the MAHs estimated that 86% of patient population is female. Since launch, 21 reports of serious or potentially serious liver conditions (SLC) associated with Xenical have been received. In order to provide a context to the observed number of cases relative to the number of patients exposed to Xenical, the MAHs used the GPRD database to define and follow a cohort of obese patients in order to estimate the expected background incidence rate of SLC in obese individuals. The GPRD obese cohort comprised of 163,752 patients and during the time followed, 18 females and 24 males reported a SLC, yielding incidence rates of 7.6 and 15.3 per 100,000 patient years respectively. To estimate the background expected number of cases amongst Xenical users, the MAHs defined a risk period associated with Xenical (i.e. exposure period to the drug plus a follow up period during which events could be reported in association with the drug) of 6 months, based on an average duration of use of 3 months and a 3 months follow-up period. Based on this exposure period, a risk period of 17.1 million person years for females and 2.8 million person years for males was calculated. Applying the estimated GPRD rates to the Xenical risk periods yields background expected rates of approximately 1,300 cases amongst females and 428 amongst males, in total 1,728 expected cases. The MAHs calculated the observed/expected ratio to be 21/1,728 = 0.012. While agreeing that spontaneous reports in general are known to under-estimate the true incidence of adverse events, the MAHs considered it unlikely that SLC would be subject to the same magnitude of under reporting. Nevertheless, assuming that only 10% of SLC cases were reported (i.e. that the true number of SLC is around 210) the observed/expected ratio would then be 0.12. The MAHs further investigated sensitivity by assuming that only events occurring during drug therapy are reported, thus reducing the risk period to 3 months. This resulted in an observed/expected ratio of 0.24. The Proportional Reporting Ratios (PRR) which compare the reporting of livers conditions for Xenical with that for all others drugs in the MAHs spontaneous reports database were submitted. The PRRs for hepatic events provided no evidence of an increased reporting of these events for Xenical

The CHMP reviewed both analyses and identified several limitations, including the inherent limitations and biases of spontaneous case reports and the use of an external source for expected incidence rates, as well as the lack of accurate overall exposure and of age-stratified exposure data. Nevertheless, the CHMP considered that the results 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 that the number of reports of serious hepatic reactions may reflect background events in a very large population of users. The CHMP therefore concluded that the results from the analyses do not support a causal relationship between orlistat and serious hepatotoxicity.

2.1.2.5. Possible mechanism

Pharmacokinetic data in human subjects show that orlistat is minimally absorbed, low in bile, and is primarily excreted unchanged in the faeces. The systemic and biliary exposures to orlistat and its metabolites are extremely low. The CHMP considered that rare idiosyncratic drug-induced liver injury (DILI) may be a potential explanation. The common features of these reactions are the unpredictability of susceptible individuals and the lack of a dose-response relationship.

There are 2 pathological categories to consider for idiosyncratic DILI: allergic and non-allergic, however the CHMP considered that the spontaneous case reports received do not point towards a single patho-physiological mechanism.

The CHMP noted that the possible 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 (*Lau & Chan*, 2002) or an immunoallergic reaction (*Umemura et al*, 2006). The CHMP agreed that idiosyncratic DILI may be the mechanism for the potential causal relationship between orlistat and hepatotoxicity but also considered that the strength of evidence from suspected cases of severe hepatotoxicity and from the observed/expected analysis is very weak. It has been proposed that the risk of DILI may be related to the daily dose of drug and the extent of hepatic metabolism (*Lammert et al*, 2008, *Lambert et al*, 2010). Other potential factors in the development of DILI may include mitochondrial toxicity, reactive metabolites, immune-response pathways and biliary transporters. The CHMP noted that faecal excretion is the major route of elimination (approximately 97% of the administered dose), although orlistat and its 2 major metabolites are also subject to biliary excretion.

2.1.2.6. Overall discussion on safety

For Alli, the CHMP noted the 47,707 spontaneous case reports identified between 01 May 2007 and 31 August 2011, describing 101,530 adverse events. Where gender was reported (77% of reports), the patients were overwhelmingly female (92%) and mainly in the age range 30 to 59 years. The majority of the cases were non-serious (96%). Gastro-intestinal disorders SOC accounted for the largest proportion of cases (50.3%), followed by General disorders and administration site disorders (18.2%), Investigations (8.2%), Nervous system disorders (4.8%) and Skin and subcutaneous tissue disorders (4%). The CHMP noted that these identified risks are already mentioned in the SmPC. Close observation through routine pharmacovigilance was deemed sufficient for all identified and potential risks and no additional risk minimisation was considered to be necessary.

Regarding hepatic events in association with Alli, the CHMP noted that the review of spontaneous reports of 'drug-related hepatic events', account for less than one percent of the total number of spontaneous reports received. The majority were cases of elevations in hepatic enzymes with no clinical features documented (181 reports, 60% of all reported hepatic reactions), which are already listed in Section 4.8 of the Alli SmPC as 'increase in transaminases and in alkaline phosphatase' in. In addition, there were also 76 reports of non-specific terms: yellow skin eyes, abnormal prothrombin reading, ascites, liver pain, enlarged liver or unspecified liver damage/disorder, which were considered to involve isolated signs or symptoms of possible liver disease, but not indicative of hepatotoxicity. The CHMP assessed 11 reports of hepatic failure received in association with Alli as well as 14 reports of hepatitis. The CHMP noted that hepatitis is a listed reaction in the Alli SmPC and is listed as an identified risk in the Alli RMP. Nevertheless, based on the data, the CHMP decided that the statement should be revised to reflect "Hepatitis that may be serious". The CHMP also updated Section 4 of the PL in order to ensure that patients are aware of hepatic signs and symptoms. The CHMP was of the opinion that the reported spontaneous reports do not provide convincing evidence of a causal relationship between Alli and serious hepatotoxicity and that no additional new issues were identified for Alli. The CHMP also noted that interaction with acarbose and the risk of oxalate nephropathy were mentioned in the Alli SmPC but not in the PL and therefore revised the PL to align the wording for acarbose and oxalate nephropathy.

Overall, the CHMP considered that once the revisions regarding hepatitis, acarbose and oxalate nephropathy have been implemented, the Alli product information will adequately reflect the available data from clinical trials and spontaneous reports of suspected adverse drug reactions.

For Xenical, the CHMP noted the 36,066 spontaneous case reports identified cumulatively until 31 August 2011, describing 69,376 adverse events of which 5,151 were serious events from an estimated exposure of 39.76 million patients. The majority of the cases were non-medically confirmed (78%). The most frequently reported events were in the Gastrointestinal Disorders SOC (49.4%), followed by the General Disorders and Administration Site Conditions SOC (10.9%) and the Skin and subcutaneous tissue disorders SOC (6.6%). Within the Gastrointestinal Disorders SOC, the most frequently reported events were: steatorrhoea followed by diarrhoea. Within the General Disorders and Administration Site Conditions SOC, the most frequently reported events were "drug ineffective" followed by "no adverse events". Lastly, within the Skin and subcutaneous tissue disorders SOC, the events the most frequently reported were rash followed by pruritus. The CHMP noted that these identified risks are already mentioned in the SmPC. Close observation through routine pharmacovigilance was deemed sufficient for all identified and potential risks and no additional risk minimisation was considered to be necessary.

Regarding hepatic events in association with Xenical, the CHMP noted the 581 cases of 846 hepatic events (271 of which were serious) analysed in the 3 Drug Safety Reports. Nine patients died and six required a liver transplant. Among the 846 hepatics events, 536 events concerned the Investigations SOC. A total of 21 cases of serious liver toxicity where the role of orlistat cannot definitively be excluded have been identified, including 5 cases of hepatic failure (2 cases with a fatal outcome and 3 cases leading to liver transplant), one case of liver injury, one case of cholestatic hepatitis, one case of acute hepatitis, 2 cases of toxic hepatitis, and 10 cases of hepatitis, and one case of exacerbation of hepatitis. The CHMP noted that "Hepatitis that may be serious" is listed in section 4.8 of the SmPC of Xenical since 2001 but updated Section 4 of the PL in order to ensure that patients are aware of hepatic signs and symptoms. Given the low number of relevant cases up to now where the causality of the drug cannot be formally excluded compared to the population exposed (>39 million patients), the CHMP considered that spontaneous reports do not currently provide evidence confirming orlistat-induced serious hepatotoxicity. The CHMP noted that interaction with acarbose and the risk of oxalate nephropathy were mentioned in the Xenical SmPC but not in the PL and therefore revised the PL to align the wording for acarbose and oxalate nephropathy.

Overall, the CHMP considered that once the revisions regarding hepatitis, acarbose and oxalate nephropathy have been implemented, the Xenical product information will adequately reflect the available data from clinical trials and spontaneous reports of suspected adverse drug reactions.

The CHMP also assessed the results of the 'expected versus observed' analyses, which 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, even when assuming a reporting rate for spontaneous events of 10%. While the CHMP identified limitations to the analyses, it concluded that the number of reports of serious hepatic reactions may reflect background events in a very large population of users. The CHMP also noted the pre-clinical evidence submitted for orlistat and considered that no evidence of a causal relationship between orlistat and serious hepatotoxicity was identified.

2.2. Risk management plan

The MAHs submitted risk management plans for their products, which were considered during this review. The CHMP was of the opinion that the identified and potential risks and the proposed pharmacovigilance activities and risk minimisation activities associated with each of these safety concerns are adequately reflected in the RMPs of orlistat-containing products.

Further to the assessment and discussion of the data submitted by the MAHs, the CHMP considered whether a case-control study could provide further evidence of a causal association between an increased risk of serious hepatotoxicity and orlistat. The CHMP noted a publication by *Fontana et al*, 2010 (*Fontana RJ*. Approaches to the study of drug-induced liver injury. Clin Pharmacol Ther. 2010 Sep;88(3):416-9), indicating that drug-induced liver injuries are very rare. In addition, diagnosing DILI is difficult as it is largely a diagnosis of exclusion based on circumstantial evidence. The CHMP also noted that prospective multicentre registry studies allow for more accurate phenotyping of individual patients with DILI, as well as for collection of biological samples for mechanistic studies. This was supported by *Bell & Chalasani*, 2009 (*Bell & Chalasani*. Epidemiology of idiosyncratic drug-induced liver injury. Semin Liver Dis. 2009 Nov;29(4):337-47), who stated that the high variability in the estimated frequency of DILI in retrospective studies reflects not only the difficulty in diagnosing this condition, but also the need for prospectively designed clinical studies investigating DILI. The CHMP noted that prospective registries such as the US DILI Network, the US Acute Liver Failure Study Group or the Spanish Drug Induced Liver Injury Network could be considered for prospective studies. However, the CHMP questioned the feasibility of a case-control study. Given the low incidence of the observed hepatotoxicity events and the expected difficulties of identifying exposure-positive or exposure-negative subjects (due to the availability of a non-prescription orlistat product), the CHMP concluded that a study would not provide further adequate evidence of a causal association between an increased risk of serious hepatotoxicity and orlistat. The CHMP concluded that no further study was required for orlistat.

The CHMP therefore considered that further risk minimisation measures are not required beyond the agreed revisions to the PIs and that the RMPs do not need to be revised.

2.3. Product information

Based on the assessment of the data submitted by the MAHs as well as the overall total available data, the CHMP was of the opinion that a small number of revisions to the SmPC and the PL were necessary. The CHMP noted that hepatitis is a listed reaction in the Alli SmPC but considered that the SmPC wording should be revised to reflect 'Hepatitis that may be serious'. The PL (Section 4) should be updated accordingly to ensure that patients are aware of hepatic signs and symptoms. In addition, 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. The CHMP also clarified the recommendation on how to take Alli.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

- *Section 4.8 - "Hepatitis that may be serious"*

PACKAGE LEAFLET (PL)

- *Section 2 - Before you take [Product name]*
    - *"- acarbose (an anti-diabetic drug used to treat type 2 diabetes mellitus). [Product name] is not recommended for people taking acarbose."*
    - For Alli 60 mg hard capsules: *"Taking [Product name] with food and drink" "[Product name] can be taken immediately before, during a meal or up to one hour after a meal. The capsule should be swallowed with water."*
    - For Alli 27 mg chewable tablets: *"Taking [Product name] with food and drink" "[Product name] can be taken immediately before, during a meal or up to one hour after a meal. The tablet should be chewed."*

- *Section 4 - Possible side effects*
    - *"Hepatitis (inflammation of the liver). Symptoms 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 on your right hand side), sometimes with loss of appetite."*
    - *"oxalate nephropathy (build up of calcium oxalate which may lead to kidney stones) See Chapter 2, take extra care with [Product name]"*

3. Overall discussion and benefit-risk assessment

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 Section 4.8 of the SmPCs of all orlistat-containing products. The CHMP also considered that the PL (Section 4) 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.

4. Conclusion and grounds for the recommendation

Having considered the overall submitted data provided by the MAHs in writing and taking into account the discussions during the Committee plenary meetings, the CHMP concluded that the benefits of orlistat-containing products outweigh the associated risks in their current indication and that the benefit-risk balance of Alli is therefore positive under normal conditions of use.

On the basis of the above, the Committee recommended the variation to the terms of the marketing authorisation for Alli and for which the amendments to the summary of product characteristics and package leaflet are set out in annex I and IIIB of the opinion.

The scientific conclusions and the grounds for the amendment of the SmPC and PL are set out in Annex IV of the opinion.