European Medicines Agency

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ASSESSMENT REPORT
FOR
alli

International Nonproprietary Name:
orlistat

Procedure No. EMEA/H/C/854/X/0001

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

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1. Introduction

Obesity is recognised by the World Health Organization (WHO) as one of the greatest public health challenges for the 21st century with alarming trends in several parts of the world, including Europe [World Health Organization, 2005a]. It is a condition where there is excess body fat, resulting from a positive energy balance. Obesity occurs when an individual's energy intake exceeds energy expenditure from physical activity and metabolic processes over a long period of time. Being overweight is invariably a precursor to being obese, and as such it is the greatest risk factor for obesity. The adverse health consequences of overweight and obesity are numerous and well documented [World Health Organization, 2002], and in Europe it is known that overweight and obesity (along with raised cholesterol and hypertension) are among the risk factors associated with the greatest loss of healthy life [Lopez, 2006].

Currently in Europe, almost 400 million adults are estimated to be overweight and about 130 million to be obese [World Health Organization, 2005a]. The average BMI (Body Mass Index) in Europe is now 26.5 kg/m^2 and overweight affects between 25% and 75% of the adult population among the different countries within Europe [World Health Organization, 2005a].

Data on the prevalence of overweight and obesity among adults have been reported from most countries in the European Union (EU), although the age range and dates of the surveys differ[International Association for the Study of Obesity, 2007]. Prevalence varies markedly between countries with the proportion of males with a BMI ≥25 kg/m^2 ranging from 45.7% (Estonia) to 75.4% (Germany), and for females ranging from 34.5% (Italy) to 58.9% (Germany).

Risks of coronary heart disease, ischaemic stroke, type 2 diabetes mellitus and certain cancers increase steadily with increasing BMI [World Health Organization, 2002]. Obesity is a major risk factor for osteoarthritis [Woolf, 2006] and is also associated with obstructive sleep apnoea [Kopelman, 2000], atrial fibrillation, and asthma [Malnick, 2006]. However, it should not be assumed that the health consequences are limited to the severely obese population: risks to health increase progressively from well below the overweight threshold [International Obesity Task Force, 2005]. According to the World Health Report, 58% of diabetes globally, 21% of ischaemic heart disease and between 8% and 42% of certain cancers were attributable to BMI >21 kg/m2 [World Health Organization, 2002].

alli (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 30 kg/m^2, or overweight patients (BMI > 28 kg/m^2) with associated risk factors.

The currently approved formulation is presented as 120 mg hard capsules.

In this Annex II application, the applicant applied for the introduction of a lower strength, orlistat 60 mg hard capsules indicated *'for weight loss in adults who are overweight (body mass index, BMI, ≥25 kg/m^2) and should be taken in conjunction with a mildly hypocaloric, lower-fat diet.'* and proposed the classification for supply of orlistat 60 mg hard capsules to 'medicinal product not subject to medical prescription'.

2. Quality aspects

Introduction

alli is currently presented as 120 mg hard capsules in PVC/PE/PVDC blister packs and glass bottles of 21, 42 and 84 capsules. The applicant introduced a new strength of 60 mg hard capsules packaged in high-density polyethylene (HDPE) bottles with a foil induction seal cap liner with polypropylene child resistant caps using a push down and turn opening mechanism.
The composition of the additional strength of alli 60 mg capsules is essentially similar to the currently approved alli 120 mg capsules and has been well defined.

Drug Substance

The applicant confirmed that no further changes were made in the documentation already submitted for the active substance (orlistat 120mg). The applicant has taken into account the quality information of active substance which has been assessed previously. In other words, the active substance used in this Line Extension, is identical to that used in the manufacture of the approved alli 120 mg capsule (EU/1/07/401/001-006)

Drug Product

- **Pharmaceutical Development**

The primary aim of the applicant was to develop an additional strength (60 mg) of orlistat for the use of the anti-obesity agent as a non-prescription medicine. As already mentioned that new dosage (60 mg) is compositionally identical to alli 120 mg capsules : therefore, the quantitative compositions of the granulation and bulk pellet blend are the same for the two strengths. Additionally, a gelatin band is added in order to distinguish both strengths. It was agreed that the data from the basis of approval for alli 120 mg capsules was considered suitable to support the current 60 mg capsules application, in relation to: Formulation development (including justification for excipient selection and composition); Manufacturing process development (including identification of critical processing steps, process scale-up and optimisation, and establishment of appropriate process controls); bioequivalence/pharmacological equivalence studies supporting the final formulation. In this context, it was agreed that no changes would be necessary to alli 60mg capsules, which will require further development activities. Therefore, the development was focussed on capsule banding and its effect on the dissolution profile. It is important to underline that further studies confirmed that there are no significant differences between the dissolution profiles for the banded and unbanded capsules of alli 60 mg. Furthermore, it was demonstrated that there are no significant differences between the dissolution profiles of both strengths (60 mg & 120 mg).

- **Adventitious Agents**

Neither the excipients nor the active substance is derived from human or animal origin. Certificates of Suitability have been provided for the gelatine capsule which is of ruminant origin.

- **Manufacture of the Product**

This manufacturing process is based upon the manufacturing process already authorised for alli 120 mg. Therefore, it involves standard technology using standard manufacturing processes such as blending, wet granulation, drying, sieving and blending, followed by encapsulation in hard gelatin capsules, and finally the addition of gelatin bands. It was noticed that the equipment used is commonly available in the pharmaceutical industry. The proposed commercial process was validated by a number of studies for the major critical steps of the manufacturing process. The batch analysis data show that these additional strengths can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of the capsules.

- **Product Specification**

The proposed release and shelf life specifications provided contain the quality relevant characteristics required for this pharmaceutical form. Furthermore, the specifications were established according the ICH guidelines and include the following tests: appearance, assay, identity test (HPLC/IR), impurities (HPLC), uniformity of dosage units, dissolution, microbial quality (Ph Eur).
Following a length discussion it was agreed that the specifications for the proposed product would be identical to the already authorised strength product.

All analytical procedures that were used for testing the drug product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines. 9 batches of product stored in the proposed marketing containers (with desiccant) for periods up to 36 months at 25°C/60%RH, 30°C 60%RH., 30°C /65%RH and 40°C /75%RH. It is important to underline that Orlistat has poor chemical stability at 40°C due to a low melting range (42 - 44°C) of the active substance.
Based on the available stability data, the proposed shelf life as stated in the SPC is acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The active substances' manufacture and control is essentially the same as that reviewed for the already authorised strength.
The development of the formulation and manufacturing process for the finished product is essentially the same and has been performed with a view to the main variables that could compromise the efficacy and safety of the product. The information presented indicates consistency and uniformity of the finished product.

3. Non-clinical aspects

Introduction

Substantial pharmacodynamic, pharmacokinetic and toxicological data for orlistat and its metabolites have previously been reported for orlistat 120 mg capsules (Xenical). Based on this available data and established clinical experience with orlistat 120 mg capsules (Xenical), the pharmacological, toxicological and safety-in-use profile of orlistat, when used as recommended, is well characterised.
No additional non-clinical testing has been undertaken.

A revised environmental risk assessment (ERA) has been submitted in accordance with the CHMP guidance for the environmental risk assessment of medicinal products for human use [EMEA/CHMP/SWP/4447/00, June 2006].

Ecotoxicity/environmental risk assessment
The ERA indicated that the proposed use of orlistat 60mg will result in an increased environmental exposure in the EU from 29.4 Metric tons of orlistat to 57 Metric tons which is effectively a doubling of the environmental exposure to orlistat. This, however, is a worst case estimate because the applicant expects there to be a reduction in the sales of the prescription product following the launch of orlistat 60 mg.

The increased exposure will mainly affect the terrestrial compartment, and any effects in the aquatic compartment would be marginal. Available data (e.g. tests conducted on earthworms and soil micro-organisms) have indicated that ecotoxicity in the terrestrial compartment is unlikely to be a concern however the applicant has initiated studies to further investigate potential effects in the terrestrial and aquatic compartment.

Discussion on the non-clinical aspects

Since orlistat 60 mg and orlistat 120 mg capsules are dose proportional, the available pharmacodynamic, pharmacokinetic and toxicological data with orlistat 120 mg capsules (Xenical) are supportive of the lower strength, orlistat 60 mg. On the basis of this information, the CHMP considered acceptable that no additional non-clinical testing has been undertaken with orlistat 60 mg.

With respect to the ERA, the CHMP considered that it has been adequately addressed. A number of studies (OECD 218/219, OECD 307 and OECD 210) are expected to be submitted as part of a follow–up-measure.

4. Clinical aspects

Introduction

This extension of the marketing authorisation concerns a new strength, orlistat 60 mg to be indicated in:
'alli is indicated for weight loss in adults who are overweight (body mass index, BMI, ≥25 kg/m^2) and should be taken in conjunction with a mildly hypocaloric, lower-fat diet.'

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics
The pharmacokinetic data provided for orlistat 120 mg are supportive of orlistat 60 mg, the proposed new strength. Orlistat acts locally in the gastrointestinal (GI) tract with minimal systemic absorption and the proportion of orlistat that is absorbed, and its metabolites, are subject to biliary excretion. Due to its minimal systemic absorption, the potential for systemic adverse reactions and pharmacokinetic interactions with other medicines is limited.

Pharmacodynamics
No new pharmacodynamic studies have been performed for alli 60mg. The pharmacodynamic data provided for orlistat 120 mg are supportive of orlistat 60 mg, the proposed new strength.

Orlistat acts locally in the gastrointestinal tract inhibiting gastrointestinal lipases and has very limited systemic pharmacodynamic activity. The potential for pharmacodynamic drug interaction is secondary to orlistat's effect on lipid absorption so that there is a theoretical risk of reduction in the absorption of lipid soluble drugs and vitamins.
Few pharmacodynamic studies have been performed but the study by *Zhi et al* demonstrated a statistically significant reduction in the AUC and C_{max} of amiodarone. Other lipid soluble drugs with a low therapeutic index may be affected to a clinically relevant extent (e.g with ciclosporin, warfarin and oral contraceptives).

Clinical efficacy

Data from the following studies have been submitted in support of this application:

Table 1. Description of the clinical studies

Study number (location)	Type of study	No of Subjects Age/Gender	Duration	BMI (kg/m^2)	Dose (t.i.d.)
Three pivotal efficacy studies (data from BM14149 and NM14161 are presented individually and pooled)					
NM17247 (US) DB, R, PC, PG	Phase III weight loss study in overweight subjects in a primary care setting	Placebo (N=195) 60 mg tds (N=196 Placebo; 46.5 yrs Orlistat; 45.8yrs 94% Female	4 months	25-28	Placebo 60 mg
BM14149 (Europe)	Phase III weight loss study [a, b]	Placebo (N=237) Orlistat 60mg (N=239) Orlistat 120mg (N= 242) Mean age 43 yrs ~80% female	2 years	28-43	Placebo 60 mg 120 mg
NM14161 (US) DB, R, PC, PG	Phase III weight loss study using primary care providers [a, b]	Placebo (N=212) Orlistat 60mg (N=213) Orlistat 120mg (N= 210) Mean age 43 yrs ~80% female	2 years	30-43	Placebo 60 mg 120 mg
Supportive efficacy studies					
BM14150 (Europe; Brazil) DB, R, PC, PG	Phase II weight loss study [b]	Orlistat 60mg (N=123)	6 months	28-43	Placebo 30 mg 60 mg 120 mg 240 mg
Behavioural studies					
NM17285 (US) Open label	Phase III, actual use study in pharmacies	Orlistat 60mg (N=262) Mean age 45 yrs 85% Female	3 months	No restriction	60 mg[c]
RCH-ORL-002 (US) Open label	Phase III study, based in shopping malls	162 enrolled Mean age 36.72 84% female	1 month	≥27	60 mg

[a.] Weight loss evaluated in year 1; weight maintenance in year 2
[b.] One month placebo lead-in on mild hypocaloric diet
[c.] Recommended dosage was one to two capsules t.i.d.
DB – double-blind; R – Randomised; PC – placebo-controlled; PG – parallel group
tds or tid :three times daily

Dose response studies

A dose-response relationship was established for orlistat in study BM14150 (previously submitted for the original marketing authorisation application (MAA) for orlistat 120 mg) based on change in body weight. Orlistat 60 mg (N=123) was the lowest dose tested that was statistically significant based on least squares mean change in body weight (from the start to the end of the double-blind treatment period at week 24). The least squares mean difference from placebo was -1.86 kg for orlistat 60 mg (p=0.002) at the end of treatment. The categorical analysis for subjects losing >10% of initial body weight showed a similar relationship to orlistat dose.

Main clinical studies

The pivotal studies from the original marketing authorisation application for orlistat 120 mg (studies BM14149 and NM14161) are supportive clinical data for orlistat 60 mg, the proposed new strength. These studies were double-blind, double-dummy, randomised, parallel-group, placebo-controlled, multicentre studies and included a 60mg arm as well as the 120mg arm. The main objective of these studies was to determine the weight loss effect of 60 mg orlistat, 120 mg orlistat, or placebo administered t.i.d (three times daily) in combination with a mildly hypocaloric diet, during the first year of treatment.

Study NM17247 was a multi-centre, double-blind, randomized, placebo-controlled, parallel-group study conducted in overweight patients with a BMI of ≥ 25 and < 28 kg/m^2. The main objective of this study was to assess the efficacy of orlistat 60 mg tid plus diet as compared with placebo plus diet on change in the body weight over 16 weeks in subjects with BMI ≥25 to < 28 kg/m^2 .

alli 60mg has been shown to increase weight loss in overweight and obese subjects compared to placebo. The weight loss increases with increased baseline BMI measurements such that the obese subject benefits more than the overweight or normal weight subject.

Data from the original MAA (**studies BM14149, NM14161**) demonstrate efficacy of the 60mg strength in subjects with a BMI of ≥28 with 45% achieving a weight loss of ≥5% of baseline body weight and 21% achieving a weight loss of ≥10% of baseline body weight (compared to 29.3% and 11.5% respectively in the placebo group). This degree of weight loss is clinically relevant in regard to the risk factors for diabetes and cardiovascular disease.

There are, however, fewer data on the efficacy of the 60 mg dose in subjects with a BMI of 25 to 28. Only four months data in this population have been submitted in the present application (**study NM17247**) and over this time period only 13% of subjects in the orlistat group achieved a weight loss ≥10% baseline body weight. Forty-four% achieved a weight loss of ≥5% of baseline body weight and 67% achieved a weight loss of ≥3%. Only the percentage losing ≥3% baseline body weight was statistically significantly greater than placebo and the clinical relevance of a 3% weight loss has not been clearly demonstrated (see Table 2).

Table 2 Categorical Analysis of Percent Body Weight Loss from Baseline, ITT Population

Visit/ %BW Change		Placebo n (%)	Orlistat n (%)	p-value* (orlistat – placebo)
Day 113				
<5%	LOCF	132 (71.7)	124 (63.9)	
	Observed	88 (63.8)	87 (56.5)	
≥5%	LOCF	52 (28.3)	70 (36.1)	0.104
	Observed	50 (36.2)	67 (43.5)	0.206
Day 113				
<3%	LOCF	107 (58.2)	84 (43.3)	
	Observed	67 (48.6)	51 (33.1)	
≥3%	LOCF	77 (41.8)	110 (56.7)	0.004
	Observed	71 (51.4)	103 (66.9)	0.007

*P values are based on between treatment group CMH Test
BW = Body weight; CMH = Cochran Mantel Haenszel, ITT= Intention To Treat

While it may be appropriate to extrapolate from these results to 6 months or 12 months, the CHMP considered that it is not known if, in this population (BMI 25-28) the rate of weight loss will continue with continued treatment. In these subjects the actual weight loss was small (3-4.5 kg over 3-4 months) and only 1.15kg more than the placebo group on average but appeared to continue while the medication is taken and not to plateau after a short time.

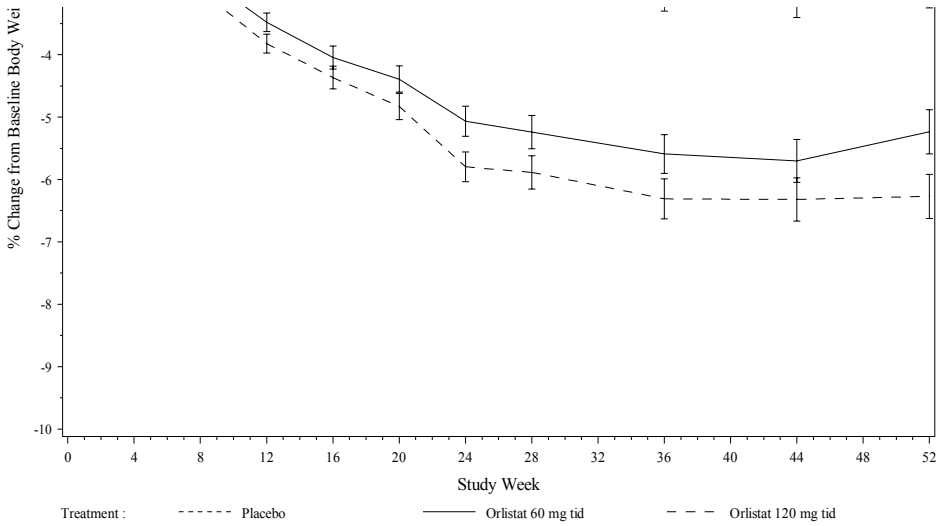
Clinical studies in special populations

No clinical studies have been performed in special populations. The proposed indication for alli 60 mg does not include the use in children and adolescents under 18 years of age.

Analysis performed across trials

A pooled analysis of the data from the two pivotal studies of the original MAA were presented in the dossier. This analysis demonstrated a similar efficacy of the 60mg orlistat to that seen with 120mg orlistat in patients with a BMI of ≥28 (see Figure 1).

Figure 1. Relative change from baseline weight pooled data from studies BM14149 and NM14161



ITT population, observed data; mean ± SE

Based on the pooled analysis, the adjusted mean change from baseline after 6 months of treatment was -2.09 kg, -4.40 kg and -5.18 kg for placebo, 60 mg and 120 mg, respectively in the ITT population ($p<0.001$ for the comparisons with placebo). There was some further weight loss in all three groups over the next 6 months of treatment. Adjusted mean change from baseline after 12 months of treatment was -2.32 kg, -4.78 kg and -5.56 kg for placebo, 60 mg and 120 mg, respectively, in the ITT population ($p<0.001$ for the comparisons with placebo). Based on the comparison of the adjusted mean change from baseline for the 60 mg dose, 92% of the efficacy at 12 months was achieved at the 6 month time-point.

Supportive studies

The supportive studies include studies of the use of orlistat in the real-life situation in the United States (US), ie behavioural studies NM17285 and RDH-ORL-002.

- NM17285

In the actual use study NM17285, customers were invited to decide whether orlistat was appropriate for them with very little input from the pharmacist. Fewer than 50% of patients with excluded conditions made an appropriate selection decision based on the product information alone (see Table 3).

Table 3 Subjects with unconditional labelled exclusions: appropriate initial selection decision Eligible subjects

Unconditional Labelled Exclusion	Number of Subjects[1]	Appropriate Initial Selection Decision n (%)[2]
Allergic to Ingredients	0	N/A
Taking Cyclosporine	2	1 (50.0)
Taking Warfarin	14	7 (50.0)
Taking Medicine for Diabetes	46	16 (34.8)

1 Total number of subjects who reported the specific condition
2 This percentage is based on total number of subjects who reported the specific condition

Table 4 Subjects with conditional labelled exclusions: appropriate use decision Eligible Subjects

Conditional Labelled Exclusion	Number of Subjects[1]	Purchaser n (%)[2]	Appropriate Use Decision n (%)[3]
Problems Absorbing Food	12	1 (8.3)	0
Gall Bladder Problems	25	7 (28.0)	2 (28.6)
Have High Blood Pressure	166	54 (32.5)	21 (38.9)
Have High Cholesterol / Triglyceride Levels	147	49 (33.3)	21 (42.9)
More than 30 Pounds to Lose	346	114 (32.9)	27 (23.7)
On a Diet Recommended by a Doctor	48	10 (20.8)	5 (50.0)
Taking Another Weight Loss Medication	33	12 (36.4)	3 (25.0)

1 Total number of subjects who reported the specific condition
2 This percentage is based on total number of subjects who reported the specific condition
3. This percentage is based on total number of subjects who purchased orlistat and who talked to a healthcare professional about the labelled condition or orlistat before use.

Table 4 showed the subjects who actually purchased and used the product. Fewer than 50% made the appropriate decision to talk to a physician prior to using this product when they had a condition that would possibly exclude them from using the product. However they were given only minimal guidance at the point of sale.

Following the results of this study, some labelling changes were made by the applicant to ensure more appropriate self-selection and were considered acceptable by CHMP. In addition, the labelling was further amended to emphasise key safety messages at the CHMP's request. A positive user-testing confirmed that the packaging and the leaflet for alli 60mg was both readable and easily understood.

Weight loss according to baseline BMI

Subjects with an initial BMI of <25 had a mean weight loss of 2 pounds, subjects with an initial BMI of 25-29.9 had a mean weight loss of approximately 5 pounds, and subjects with an initial BMI of ≥ 30 had a mean weight loss of about 8 pounds. Measured weight loss according to different times of measurement are showed in Table 5.

Table 5 Measured weight loss (Users Group, N=237)

Measured Weight Loss	Time of Measurement[a] 1 - 30 Days (N=37) n (%)	31-60 Days (N=77) n (%)	>60 Days (N=60) n (%)	Final Return Visit[b] (N=106) n (%)
Gained weight	3 (8.1)	12 (15.6)	7 (11.7)	15 (14.2)
Lost no weight	0	2 (2.6)	2 (3.3)	4 (3.8)
≤5 pounds	18 (48.6)	29 (37.7)	12 (20.0)	33 (31.1)
6 - 10 pounds	8 (21.6)	21 (27.3)	10 (16.7)	28 (26.4)
11 - 15 pounds	1 (2.7)	8 (10.4)	9 (15.0)	11 (10.4)
16 - 20 pounds	2 (5.4)	3 (3.9)	5 (8.3)	5 (4.7)
21 - 25 pounds	1 (2.7)	1 (1.3)	5 (8.3)	6 (5.7)
>25 pounds	0	0	4 (6.7)	4 (3.8)
Missing	4 (10.8)	1 (1.3)	6 (10.0)	0
Mean ± SD	5.5 ± 5.70	5.1 ± 5.72	10.1 ± 11.84	7.2 ± 9.64
Median	4	5	8	6
Range	-6 - 21	-7 - 24	-8 - 52	-8 - 52
N	33	76	54	106

[a]days from enrollment to pharmacy visit; the last measurement in each interval was tabulated
[b]measurement taken at subject's final pharmacy visit, regardless of time from enrollment

Lifestyle changes

An overwhelming majority of subjects (>90%), indicated that they were very successful or somewhat successful in maintaining their diet. These results remained consistent at every interview for the duration of the study.

At study completion, approximately 32% of subjects indicated that they exercised more than they did prior to study enrolment.

- RDH-ORL-002

This study was an open, uncontrolled study based in shopping malls to determine the effect of 60mg orlistat plus diet administered for 4 weeks on weight change.

In this simple study to investigate the use of orlistat in the real-life setting subjects achieved a mean weight loss of 8 lbs based on subjects' diaries. This study was conducted in subjects with a BMI ≥27.

Withdrawal

Regarding the possibility of rebound weight gain following withdrawal of orlistat treatment, two studies conducted with orlistat 120mg demonstrated some weight gain following discontinuation of therapy. However these patients were allowed to take a eucaloric diet rather than being encouraged to continue a low calorie diet. Importantly the results did not demonstrate a 'rebound' weight gain where the weight rose to above the baseline weight. The success of any attempt to lose weight is dependent upon the consumer's willingness to change lifestyle habits in the long term and orlistat is no different from other weight loss aids in this respect. In fact because of its mode of action orlistat encourages a change to less fatty foods which may help consumers to maintain a healthier lifestyle after stopping treatment.

In the placebo-controlled studies fewer subjects dropped out of the orlistat groups compared to the placebo groups and in the 'real-life' study NM17285, the majority of subjects successfully maintained their diet while 32% increased the amount of exercise they took while taking orlistat.

Discussion on clinical efficacy

Orlistat 60mg tds taken with a hypocaloric diet has been shown to be effective in reducing weight to a greater extent than placebo in patients with a BMI ≥28.

Results from previously submitted studies BM14149 and NM14161 demonstrated efficacy of the 60mg strength in subjects with a BMI of ≥28 with 45% achieving a weight loss of ≥5% of baseline body weight and 21% achieving a weight loss of ≥10% of baseline body weight (compared to 29.3% and 11.5% respectively in the placebo group). This degree of weight loss is clinically relevant in regard to the risk factors for diabetes and cardiovascular disease.

In real-life use the majority of patients taking orlistat 60 mg were able to adhere to the low-calorie, low-fat diet and a third of patients increased the amount of exercise taken.

Although, the effect size was modest and smaller than seen with the currently approved dose of 120mg, evidence was presented that halving the dose of orlistat did not halve the efficacy; but that the efficacy of orlistat 60mg was 85% that of orlistat 120mg. At this dose, nearly 50% of patients achieved a weight loss of ≥5% of their baseline body weight and there is a body of evidence in the literature that demonstrates that this level of weight loss is beneficial to parameters of the common co-morbidities of obesity, such as hypertension, diabetes and hypercholesterolaemia. The CHMP was therefore of the opinion that the effect size of orlistat 60 mg could be considered clinically relevant.

The applicant was requested to provide further evidence of efficacy in the proposed target population (BMI 25-28) at the dose of 60mg tds.

In response, the Applicant proposed to increase the lower limit for BMI from 25 to 28 kg/m^2. The CHMP therefore considered this point resolved provided the SPC restricts use to subjects with a BMI ≥ 28 kg/m^2. It is acknowledged that the guideline on clinical investigation of medicinal products used in weight control recommends recruiting overweight subjects with risk factors. The inclusion criteria for study BM14149 only specified a BMI ≥ 28 kg/m^2 for subjects to be included in the study and therefore subjects without additional risk factors were studied.

Further sensitivity analyses for studies BM14149 and NM14161 were provided. In study NM14161, the results for the 60mg dose remain significant in all the sensitivity analyses. In study BM14149, the results remained significant at 6 months but the baseline carried forward analysis was not significant for the 60mg dose at 12 months. Overall, however, these sensitivity analyses are reassuring and show clear evidence of efficacy at one year for the 60mg dose. The responder rates for the 60mg dose were very similar to the 120mg dose responder rates.

Clinical safety

Orlistat 120mg has been on the market since 1998 and therefore there has been extensive patient exposure. The safety profile of orlistat is therefore well documented.

The following studies for orlistat 120 mg also provide safety data for orlistat 60 mg: BM14149; NM14161; NM14302; BM14150, and BM15421D (XENDOS). Three additional studies have been undertaken with orlistat 60 mg capsules in the US and provide further safety data for the current application.

Patient exposure (Table 6)

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range (60mg)	Patients with long term* safety data
Placebo-controlled	6376	3763	942	3567
Open studies	446	446	446	0
Post marketing	31,570	31,570	0	>7,775

* This refers to at least 6 months continuous or intermittent exposure.

Adverse events

The pattern of AEs was generally similar for subjects treated with orlistat 60 mg in Study NM17247 (BMI 25 to <28 kg/m^2) and in the three long-term studies included in the pooled analysis (BMI ≥28 kg/m^2), indicating that the AE profile of orlistat 60 mg is not influenced by BMI (for BMI of ≥25 kg/m^2) (Table 7).

Table 7 Adverse events (AEs) reported for orlistat 60 mg in the various studies regardless of causality

	BM14149, NM14161 NM14302, (pooled)[2]	**NM17247[1] (N=196)**	**NM17285 (N=284)**	**RCH-ORL-002 (N=162)**
Total Number of Subjects Reporting Events Total Number of Events Reported	555	137 (69.9%) 219		119 (73%) 355
Infections & Infestations	168	30	41 (14.4)	-
Neoplasms Benign & Malignant			3 (1.1)	-
Immune System Disorders			6 (2.1)	-
Endocrine Disorders			1 (0.4)	-
Metabolic/Nutrition Disorders			1 (0.4)	1 (1%)
Psychiatric Disorders	16		2 (0.7)	-
Nervous system	116 (headache)	13	29 (10.2)	3 (2%)
Eye Disorders			1 (0.4)	-
Ear & Labyrinth Disorders			1 (0.4)	-
Cardiac disorders			2 (0.7)	2 (1%)
Vascular Disorders			6 (2.1)	-
Respiratory system	201		9 (3.2)	5 (3%)
Gastrointestinal disorders	1012	171	168 (59.2)	101 (62%)
Skin& Subcutaneous Tissue Disorders			6 (2.1)	1 (1%)
Musculoskeletal System	45	5	23 (8.1)	1 (1%)
Pregnancy, Puerperium & Perinatal Conditions			1 (0.4)	-
Reproductive System & Breast Disorders	23		2 (0.7)	-
Urogenital system			7 (2.5)	7 (4%)
General Disorders & Admin. Site Conditions	38		19 (6.7	47 (29%)
Investigations			5 (1.8)	-
Injury & Poisoning			13 (4.6)	-
Surgical & Medical Procedures			1 (0.4)	-

[1] includes events with incidence in the orlistat group ≥2% and greater than that in the placebo group

[2] includes AEs with an incidence ≥3% during first 6 months of treatment

Serious adverse events and deaths

In study NM17247, 2 subjects receiving orlistat 60 mg t.i.d. experienced serious adverse events (SAEs) in this study. Both events (repair of umbilical hernia, intervertebral disc prolapse) were considered unrelated to study medication.

In study NM17285, 5 (1.8%) of the 284 safety subjects experienced a total of six SAEs during treatment with orlistat 60 mg in this uncontrolled study. Four of these SAEs were considered to be unrelated to study drug by a study physician. Two events were considered possibly related to study drug and these were abdominal pain and chest pain (secondary to oesophageal spasm).

In the pooled analysis (BM14149, NM14161 and NM14302), the incidence of cholecystitis and cholelithiasis at 6 months and 1 year was low in all three treatment groups of these studies with no evidence of increased incidence with orlistat treatment. As was also noted in the XENDOS study (placebo vs orlistat 120mg), more orlistat-treated patient had cholelithiasis, but equal numbers of patients in both treatment groups had cholecystitis.

Three deaths were reported in the pooled studies, one during the placebo lead-in (car accident; study NM14302), and two deaths from myocardial infarction (one on 60 mg t.i.d., Study BM14149, and one 120 mg t.i.d., Study NM14161). None was considered treatment related.

Laboratory findings

There is a possible trend towards increased elevated gamma-glutamyl transferase (GGT) and alanine transaminase (ALT) with orlistat 120mg compared to placebo but this was not seen in the orlistat 60mg group.

In the 3 phase III studies, the frequency of two consecutive low levels of vitamins A, D, E and beta-carotene during 1 year of treatment was low in all treatment groups. For vitamin D and beta-carotene, there was a significantly lower frequency of two consecutive low vitamin levels with the 60 mg dose compared to the 120 mg dose.

Psychiatric events

From the clinical trial data the only psychiatric event that appeared to be associated with orlistat and that gives an apparent dose response was ‘anxiety’.

Fracture risk

The data from clinical trials did not suggest a decrease in bone mineral density associated with use of orlistat.

Cancer risk
Data from investigations of a possible association between orlistat and breast cancer or colorectal cancer did not support a causal relationship between orlistat and breast cancer or colorectal cancer.

Safety in special populations

- Elderly

The discontinuation rates at 1 year among the elderly population analysed (from 7 phase III studies previously submitted in the original MAA) were 13.3% and 12.9% for the 60 mg and 120 mg doses respectively; these were lower than in the placebo group (26.2%). There was no unusual or unexpected pattern of SAEs in this elderly population, and specifically, the overall incidence of gastrointestinal AEs was similar to that seen in the general population.

Similarly, summary statistics of laboratory changes over time revealed few differences between the elderly and general populations. Any changes were small and did not appear to be clinically meaningful.

Vitamin D deficiency and the concomitant use of orlistat in the elderly is considered as a risk of osteoporosis, given that vitamin D deficiency may contributing factor. However, there was no evidence of an increased risk of bone fractures from post-marketing data. The advice to consumers using orlistat 60 mg to take a multivitamin supplement containing vitamins A, D, E and K may thus be considered sufficient to address this concern.

- Under age consumers, those of normal weight and those with eating disorders

Orlistat has been studied in a limited number of adolescent subjects. However; orlistat 60 mg is not proposed to be indicated for use in subjects under 18 years of age.

- Hepatic and renal impairment

There are no data on the use of orlistat in patients with renal or hepatic impairment. Due to the very limited absorption of orlistat such impairment is unlikely to cause an increase in plasma concentrations of orlistat and cholestasis is a contraindication due to the biliary route of excretion.

- Pregnancy and lactation

Pregnancy and breast feeding are contraindications to the use of orlistat 60 mg.

Immunological events

Orlistat is contraindicated in patients hypersensitive to orlistat.

Safety related to drug-drug interactions and other interactions

Due to the low systemic absorption of orlistat few drug-drug interactions have been observed. However the pharmacodynamic effect of orlistat on the absorption of fats may interfere with the absorption of lipid-soluble drugs.

- Fat-soluble vitamins

The results of measurements of vitamin levels in clinical trials of orlistat showed a small but statistically significant decrease in levels of vitamins D and E and betacarotene. However despite these decreases, levels of these vitamins remained within the normal range even after one year's treatment. It is proposed to include include advice to consumers that a daily multivitamin supplement should be taken while taking orlistat in the product information.

- Warfarin

A study in patients taking warfarin was conducted by the applicant in the US to ascertain if they could safely self-select the product without professional advice. A total of 54 warfarin users participated in the study. Overall, 39 of the 54 participants (72%) appropriately self-selected based on their condition (taking warfarin) by expressing an intent to contact a doctor before use. Encouragingly, more than 97% of warfarin users indicated that they discussed their concomitant medications with their physicians, and 91% said that their international normalised ratio (INR) levels were monitored routinely. However, in order to enhance compliance with this statement even further, the prominence of the warning on the US pack label was increased.
In 6 months post-marketing experience with the non prescription product in the US there was one case of a probable interaction between orlistat and warfarin in which the consumer reported that her blood was 'too thin' and that she had been advised by her physician to discontinue orlistat.

- Ciclosporin

Concomitant use of ciclosporin and orlistat is contraindicated. Following amendments to the US label to include distinct warning statements to target (a) organ transplant recipients and (b) consumers using ciclosporin for other indication the label was tested in a self-selection study. The study population was 60 subjects who were 1) organ transplant recipients currently using cyclosporine, and 2) also interested in losing weight. The majority (98.3%) of subjects made a correct selection decision and indicated that the highlighted organ transplant alert was very clear and easy to understand. The one subject who made an incorrect selection decision stated that he would not use, non prescription orlistat until he received approval from his physician.

Discontinuation due to AES

The incidence of withdrawals due to adverse events was generally low and mainly related to gastrointestinal adverse effects. In the longer term studies, the incidence of withdrawal during the second six months of treatment was lower than the incidence of withdrawal during the first six months.

The incidence of AEs leading to withdrawal during the first 6 months of treatment was greater for the orlistat treatment groups compared with placebo but less for the 60 mg dose compared with the 120 mg dose (2.1% placebo; 4.8% for orlistat 60 mg; 7.3% for orlistat 120 mg). GI AEs were the most frequent event leading to withdrawal (0.8% placebo; 3.2% orlistat 60 mg; 5.4% orlistat 120 mg).

The incidence of serious AEs during the first 6 months of treatment was similar across the treatment groups (3.5% placebo; 3.4% orlistat 60 mg; 3.5% orlistat 120 mg).

From a safety perspective, the choice of orlistat 60 mg, rather than 120 mg, for non-prescription use, is appropriate based on consideration of the withdrawal rates and the overall incidence of GI events.

Post marketing experience

Using worldwide sales data, cumulative patient exposure of orlistat 120 mg from first launch is approximately 6.37 million patient years. Up to 30 April 2007, 6,396 spontaneous reports associated with orlistat 120 mg from Healthcare Professionals and serious, unblinded, attributable clinical trial cases describing a total of 12,498 adverse events have been received. The majority of the events, 78%, were non-serious according to regulatory criteria. The majority of events reported were in the Gastrointestinal Disorders System Organ Class (SOC) (33.4%), the Skin and Subcutaneous Tissues Disorders SOC (10.5%), the General Disorders and Administration Site Conditions SOC (9.6%) and the Nervous Systems Disorders SOC (8.0%). The majority of the events resolved. The safety profile, as assessed from the 12,498 events, is similar to that seen in the clinical studies.

Additionally, data were available from two post-marketing studies conducted in the UK [Acharya, 2006] and Germany [Wirth,2005]. Overall both studies demonstrated that orlistat was generally well tolerated and that the safety profile remains unchanged. In both studies, gastrointestinal events were the most frequently reported adverse events.

The US post-marketing experience of the orlistat 60 mg (used as a non prescription product) has also been provided from 07 February 2007 to 06 November 2007. The safety data since the data lock point of the submitted report including the review of the individual adverse event cases received to date, monthly aggregate data review and routine literature searching has not identified any significant new information or safety concerns.

Discussion on clinical safety

In terms of safety, the CHMP considered that the profile of orlistat 60 mg does not raise major concerns, given the cumulative safety experience (over 9 years) of orlistat 120 mg, and the usage/postmarketing experience of orlistat 60 mg in the US.

The dose of 60mg of orlistat causes milder gastrointestinal adverse effects than 120mg and this resulted in many fewer withdrawals due to adverse events in the pivotal studies conducted on orlistat 60mg and 120mg.

Nevertheless, the CHMP had some concerns over the reporting of anxiety during clinical trials, the potential impairment of fat soluble vitamins (A,D,E and K) absorption and the reported unwanted pregnancies in patients taking oral contraceptive pills (OCP). Consequently, addition of the term 'anxiety' as an adverse reaction as well recommendation for vitamin intake and use of additional contraceptive method in case of severe diarrhoea were included in the product information and accepted by CHMP.

Another concern was the results of the self selection study performed in patients taking warfarin. Concomitant use of orlistat and anti-coagulants such as warfarin can lead to unbalanced INR measurements which may lead to reports of bleeding. Following the results of the study and one US reported case of warfarin interaction, the CHMP recommended to contraindicate the use of warfarin and other oral anticoagulants with orlistat 60 mg, intended to be used in the non prescription setting.

Having considered the introduction of this new strength (orlistat 60 mg) intended to be used in the non prescription setting, the CHMP also recommended the restart of the PSUR cycle of the product as follows: 6 monthly PSURs for one year after the Commission Decision on this extension application then yearly for 2 years and every three years thereafter.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAH submitted a risk management plan – October 2008 version.

Table 7 Summary of the Risk Management Plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified risks:		
Gastrointestinal events	Routine Pharmacovigilance	Routine activities. Warning in section 4.4 of the SPC. Listed in Section 4.8. PL will provide dietary advice and guidance to patients. The pack label will inform consumers that these events

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		may occur to enable informed self selection.
Hepatitis	Routine Pharmacovigilance Scheduled cumulative reviews of spontaneous adverse event reports at 6, 12 and 24 months.	Routine activities. Hepatitis and increases in transaminases are described in section 4.8 of SPC and included in the PL.
Interaction with ciclosporin	Routine Pharmacovigilance Scheduled cumulative reviews of spontaneous adverse event reports at 6, 12 and 24 months.	Routine activities Contraindicated in section 4.3 with cross reference in section 4.4 of the SPC and included in the PL. This interaction is also included on the pack to ensure consumers are able to self select.
Interaction with amiodarone	Routine Pharmacovigilance Scheduled cumulative reviews of spontaneous adverse event reports at 6, 12 and 24 months.	Routine activities. Warning in section 4.4 of the SPC and included in the PL. This interaction is also included on the pack to ensure consumers are able to self select.
Interaction with anticoagulants	Routine Pharmacovigilance Scheduled cumulative reviews of spontaneous adverse event reports at 6, 12 and 24 months.	Routine activities. Contraindication is included in the SPC and PL. This contraindication is also included on the pack to ensure consumers are able to self select.
Interaction with fat soluble vitamins	Routine Pharmacovigilance Scheduled cumulative reviews of spontaneous adverse event reports at 6, 12 and 24 months.	Routine activities. Warning in section 4.4, of the SPC and included in the PL. Information for the consumer is also included on the pack to advise on vitamin supplementation.

Potential Risks:		
Rectal bleeding	Routine Pharmacovigilance Scheduled cumulative reviews of spontaneous adverse event reports at 6, 12 and 24 months.	Routine activities. Warning in section 4.4 of the SPC. Listed in Section 4.8 and included in the PL.
Interaction with oral contraceptives	Routine Pharmacovigilance Scheduled cumulative reviews of spontaneous adverse event reports at 6, 12 and 24 months.	Routine activities. Warning in section 4.4 with cross reference to section 4.5 of SPC and included in the PL.
Cholelithiasis	Routine Pharmacovigilance Scheduled cumulative reviews of spontaneous adverse event reports at 6, 12 and 24 months.	Routine activities. Cholelithiasis is listed in section 4.8 of the proposed SPC and included in the PL.
Inappropriate use in: - Patients with BMI <28 kg/m^2	Survey to collect demographic data on consumers of alli 60 mg capsules.	The pack and PL provide clear guidance to enable appropriate self selection by consumers in respect of appropriate weight.
Inappropriate use in: - Children and adolescents under 18 years of age	Survey to collect demographic data on consumers of alli capsules. Scheduled cumulative reviews of spontaneous adverse event reports at 6, 12 and 24 months.	The pack and PL provide clear guidance to enable appropriate self selection by consumers in respect of age.
Use in patients with eating disorders	Routine Pharmacovigilance. Scheduled cumulative reviews of spontaneous adverse event reports at 6, 12 and 24 months.	None planned.

Important missing information		
Limited experience in non-prescription environment	Routine Pharmacovigilance. Survey to collect demographic data on consumers of alli capsules	None planned.
Use in patients aged 65 and above	Routine Pharmacovigilance.	None planned

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Legal Status

According to the European Commission guideline on '*Changing the classification for supply of medicinal product for human use'* (January 2006), the applicant proposed the classification for supply of alli 60 mg to 'medicinal product not subject to medical prescription'. The applicant considers that the criteria for medical prescription under article 71 of the Directive 2001/83/EC, as amended, are not met.

However, the CHMP had further concerns related to the proposed legal status for alli 60 mg which were addressed by the MAH during an oral explanation held on 23 September 2008, as follows:

First criterion for medical prescription under article 71 of the Directive 2001/83/EC, as amended – "Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical prescription."

1) *Increased risk that patients may not have their underlying co-morbid conditions identified (usually co-existing with obesity), thus delaying the diagnosis and definitive treatment of any underlying conditions*

Results from Consumer surveys conducted in the EU [GSK, TNS Market Research, 2008] and in the US [GSK, ACNielsen and Synovate, 2008] were presented to CHMP.
The EU survey was to characterise the usual habits of overweight and obese people in eight EU markets and demonstrated that there was a high rate of patient/physician interaction in this population. The majority of overweight patients (83%) had had their blood pressure checked in the preceding 12 months and 44% had had a test for diabetes.

Further data following the launch of alli 60 mg as a non-prescription medicine in the US demonstrated that patient/physician interaction and physicians' prescribing of weight-loss medicines had not been adversely affected by the wider availability of alli.

Finally, the applicant proposed strengthening the information on the labelling and Package Leaflet including simple and clear guidance to potential purchasers about the consequences of being overweight and directing them to see their doctor for a general health check so that co-morbidities can be assessed and managed appropriately avoiding a delay in the detection and treatment of co-morbid conditions. Patients with existing co-morbidities are also encouraged to consult their physicians during the use of orlistat so that control of co-morbidities can be maintained.

2) *Potential for incorrect use of the product, as the patient can use the product where it is not indicated, uses it for a longer period than recommended or exceeds the recommended dose (specifically, on the use of orlistat by underage adolescents and children or by patients with eating disorders)*

Data from 12 month experience in the US of alli 60 mg as a non-prescription medicine were presented. These showed that actual incorrect use of alli in the US was limited, with the majority of consumers using the product correctly and appropriately.
Adverse event reports supported the conclusion that the incidence of misuse was small and the adverse events that have been reported in inappropriate patient populations followed the known safety profile of the product, i.e., the vast majority were gastrointestinal, and have not resulted in any serious consequences.

The applicant also indicated that the majority of patients used alli 60 mg for ≤6 months although a maximum duration of use is not stated in the US labelling.

Having considered the data submitted by the applicant and the criteria for medical prescription under article 71 of the Directive 2001/83/EC, as amended, the CHMP recommended the classification of alli 60 mg to 'medicinal product not subject to medical prescription'.

7. Data exclusivity

The Applicant provided additional clinical studies (studies NM17247 and NM17285, an 'actual use' study) and Consumer Surveys conducted in the US [GSK, ACNielsen and Synovate, 2008] and the EU [GSK, TNS Market Research , 2008] in support of this application and claimed a one-year data exclusivity on these data. The CHMP reviewed the clinical data submitted, taking into account the provisions of Article 74a of Directive 2001/83/EC, as amended, in support of the classification of alli 60 mg hard capsules as 'medicinal product not subject to medical prescription'.

Whereas :

- The Consumer Surveys conducted in the US [GSK, ACNielsen and Synovate, 2008] and the EU [GSK, TNS Market Research , 2008] are not eligible for the one-year data exclusivity, taking into account the provisions of Article 74a of Directive 2001/83/EC, as amended;

- Taking into account the European Commission guideline on '*Changing the classification for the supply of a medicinal product for human use'*, the CHMP considered that studies NM17247 and NM17285 were not relevant and necessary for demonstrating efficacy of orlistat 60 mg , nor did they give more insight into the safety of orlistat 60 mg, due to the design of the studies. The Applicant committed to conduct two surveys to assess demographic and clinical characteristics of alli users in the EU (first survey) and also the usage patterns in the EU (second survey). These measures will provide further data on how orlistat 60 mg will be used in the EU in order to ensure its appropriate safe and effective use in a non-prescription setting;

- The original clinical data available at the time of the initial marketing authorisation for the product confirmed that the reduced strength retains the efficacy (BM14149 and NM14161) with fewer and less severe undesirable effects observed. The data that have become available (from clinical trials and post-marketing experience of orlistat 120 mg and 60 mg in the US) on the safety and use of the product since its marketing authorisation also provided further reassurance of the overall safety profile. The CHMP therefore considered that there is no need to generate new safety/efficacy data to support the classification of alli 60 mg hard capsules as 'medicinal product not subject to medical prescription'.;

The CHMP concluded that studies NM17247 and NM17285 submitted by the Applicant for which the claim for one year data exclusivity is sought, were not relevant and necessary to the classification of alli 60 mg hard capsules as 'medicinal product not subject to medical prescription'.

8. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there is one minor unresolved quality issue, which does not have any impact on the benefit/risk ratio of the medicinal product. This will be addressed as part of the follow-up measures to be addressed post-authorisation.

Non-clinical pharmacology and toxicology

Since orlistat 60 mg and orlistat 120 mg capsules are dose proportional, the available pharmacodynamic, pharmacokinetic and toxicological data with orlistat 120 mg capsules (Xenical) are supportive of the lower strength, orlistat 60 mg. On the basis of this information, the CHMP considered acceptable that no additional non-clinical testing has been undertaken with orlistat 60 mg.

With respect to the ERA, the CHMP considered that it has been adequately addressed. A number of studies (OECD 218/219, OECD 307 and OECD 210) are expected to be submitted as part of a follow–up-measure.

Efficacy

The clinical data provided by the applicant are considered clinically relevant and sufficient to support the extension of the marketing authorisation to add the new lower strength, orlistat 60 mg in the following indication: *'alli 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.'*

Safety

The safety profile of orlistat 60 mg, new lower strength, is better than that of the currently approved strength, orlistat 120 mg. The dose of 60mg of orlistat causes milder gastrointestinal adverse effects than 120mg and this resulted in many fewer withdrawals due to adverse events in the pivotal studies conducted on orlistat 60mg and 120mg.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 5 adequately addressed these.

- User consultation

The results of the readability test of the package leaflet were considered acceptable by CHMP.

Risk-benefit assessment

The risk-benefit remains favourable under the proposed conditions of use of the medicinal product.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of alli 60 mg 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.'*, as a medicinal product not subject to medical prescription, was favourable and therefore recommended the extension of the marketing authorisation.

Furthermore, the CHMP reviewed the clinical data (studies NM17247 and NM17285, EU and US surveys) submitted by the applicant taking into account the provisions of Article 74a of Directive 2001/83/EC, as amended, and did not consider that the data submitted in support of the classification of the medicinal product, alli for the new lower strength 60 mg were significant.