EMA/CHMP/547710/2010

Human Medicines Development and Evaluation

Assessment Report

Alli

International Nonproprietary Name: orlistat

Procedure No. EMEA/H/C/000854/X/10

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

1.1. Submission of the dossier

The applicant Glaxo Group Ltd submitted on 28 August 2009 an extension application for Marketing Authorisation to the European Medicines Agency (EMA) for alli 27mg, chewable tablet, through the centralised procedure falling within the Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II (point 2, intend iii and iv). In addition, the applicant proposed the classification for supply of alli 27 mg chewable tablet to "medicinal product not subject to medical prescription".
Glaxo Group Ltd. is already the Marketing Authorisation Holder for alli 60 mg, capsule hard (EU/1/07/401/007-011).

Licensing status:

The initial product, XENICAL, had been granted a centralised Marketing Authorisation on 29 July 1998. alli was submitted as an informed consent application in accordance with Article 10 (c) of Directive 2001/83/EC. Therefore, consent from the MAH of the XENICAL application, which had been submitted as a full application under Article 8(3) of Directive 2001/83/EC, has been given allowing access to Module 2 to Module 5 of the initial dossier of this authorised product and any subsequent post-marketing procedures submitted, assessed and approved. The Marketing Authorisation for alli was granted in the EU on 23 July 2007.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Rafe Suvarna**

1.2. Steps taken for the assessment of the product

- The application was received by the EMA on 28 August 2009.
- The procedure started on 23 September 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 December 2009 (Annex 4.1).
- During the meeting on 18-20 January 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 January 2010 (Annex 4.2).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 July 2010
- The Rapporteur circulated the Day 150 Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 03 September 2010 (Annex 4.3).

2. Scientific discussion

2.1. 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].

Orlistat is a potent, specific and long-acting inhibitor of gastrointestinal lipases. It 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.

alli (orlistat) is approved as a non-prescription medicine for weight loss in adults who are overweight (body mass index, BMI, ≥28 kg/m2) and should be taken in conjunction with a mildly hypocaloric, lower-fat diet.

The currently approved formulation for alli is presented as 60 mg hard capsules.

This is an application for an extension to the Marketing Authorisation for alli (orlistat) to include a new strength and a new pharmaceutical form (alli 27 mg chewable tablets) made pursuant to the Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II (point 2, intend iii and iv). The goal of the MAH was to provide a new strength and pharmaceutical form of orlistat that is less than half the strength of the alli 60 mg capsule, which improves mixing efficiency of active substance with dietary fat.

The proposed indication for alli 27 mg chewable tablets as a non-prescription medicine is the same as currently registered for alli 60 mg hard capsules, namely weight loss in adults who are overweight

(body mass index, BMI, ≥28 kg/m2) and should be taken in conjunction with a mildly hypocaloric, lower-fat diet.

In order to support its application the MAH has provided quality and clinical information that were evaluated.

No specific issues were identified in relation to a pre-approval inspection of the drug product manufacturing sites.

The QRD review of the alli 27 mg chewable tablets product information were also implemented to the alli 60 mg hard capsules, where applicable.

2.2. Quality aspects

2.2.1. Introduction

alli is currently presented as 60 hard capsules in HDPE bottles of 42, 60, 84, 90 and 120 capsules. The aim of this line extension is the addition a new strength and new pharmaceutical form. The new strength (27 mg) is presented as chewable tablets containing 27 mg of orlistat as active substance. The other ingredients are mannitol, lactose, xylitol, sodium starch glycolate, microcrystalline cellulose, povidone, sucrose monopalmitate, glyceryl dibehenate, sodium stearyl fumarate, macrogol stearate and water. The new strength of 27 mg chewable tablets will be packaged in high-density polyethylene (HDPE) bottle with a foil induction seal cap liner with polyprophylene child resistant caps containing 42, 60, 84 or 90 tablets.

2.2.2. Drug Substance

The applicant confirmed that no further changes were made in the documentation already submitted for the active substance (orlistat). The applicant has taken into account the quality information of active substance which has been assessed and updated by means of approved variations. The active substance used in this line extension, is identical to that used in the manufacture of the approved alli 60 mg capsule.

2.2.3. Drug Product

Pharmaceutical Development

The primary aim of the applicant was to develop a new pharmaceutical form alli 27 mg chaweble tablets, in order to improve mixing efficiency of active substance with dietary fat.
The objective of this pharmaceutical development was to obtain an immediate release dosage form, a new pharmaceutical form with acceptable organoleptic properties, improve disintegration, solubilisation and dispersion of the active substance, equivalence to alli 60 mg capsule and stable pharmaceutical form.

The chewable tablets contain excipients that enhance tablet disintegration and improve the aqueous solubility and dispersion of the lower dose of the active substance, which is needed to achieve equivalence with alli 60 mg capsules.
The pharmaceutical development took into account the appropriate size suitable for chewing, which would disintegrate rapidly and ensure dispersion of the active substance in the stomach.
The organoleptic properties of the new pharmaceutical form were improved by the slection of some excipients.

The new strength was chosen on the basis of multiple clinical studies running across a range of tablet strengths (40 mg, 30 mg, 27 mg and 24 mg of orlistat). The 27 mg dosage strength was found to be equivalent to alli 60 mg capsules. Dissolution profiles of the proposed 27 mg tablets and 60 mg capsules demonstrated orlistat release from chewable tablets is quicker and greater compared with capsules, which indicates the tablet formulation solubilises the active substance more efficiently.

Adventitious Agents

Among excipients used in the finished product only lactose present is of animal origin. Declarations from lactose supplier was provided stating that milk used for production of lactose is sourced from healthy animals under the same conditions as milk collected for human consumption.

Manufacture of the Product

The manufacturing process used for alli 27 mg chewable tablets is well described and standard process for this pharmaceutical form involves standard technology using standard manufacturing processes such as wet granulation, screening, fluid bed drying, blending, milling, compression and packaging. The manufacturing process will be validated at the proposed sites on the three commercial batches. The critical steps of the manufacturing process have been identified and adequately studied. Appropriate in-process controls of the critical steps have been established. The batch analysis data show that this s new pharmaceutical form can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of the tablets.

Product Specification

It was noted that 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 based on the specification of the approved alli 60 mg capsules. The specifications include the following tests for appearance, assay, identification (HPLC; IR), impurities (HPLC), uniformity of dosage units, dissolution (Ph.Eur.) and microbial limit (Ph.Eur.)
All analytical procedures that were used for testing the finished product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines. Batch analyses results have been provided for three batches of the new pharmaceutical form (alli 27 mg chewable tablets) and showed the conformity with specifications. Therefore, it can be concluded 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. Three batches (two pilot scale batches and one full scale batch) of product stored in the proposed type of marketing containers for periods up to 18 months at 25°C/60%RH, 30°C /75%RH. Samples were not stored at 40°C as orlistat has poor chemical stability at 40°C due to a low melting range (42 - 44°C) of the active substance.
Supporting data has been submitted for four batches of 24 mg tablets (up to 18 months) and three batches of 30 mg tablets (up to 24 months).
Based on the available stability data, the proposed shelf life as stated in the SPC is acceptable.

2.2.4. Discussion on chemical, pharmaceutical aspects

The active substances manufacture and control is essentially the same as that reviewed for the already authorised pharmaceutical form (alli 60 mg capsule).
The development of the formulation and manufacturing process for the new pharmaceutical formulation (alli 27 mg capsule) has been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product.

2.3. Non-clinical aspects

2.3.1. Ecotoxicity/environmental risk assessment

At the time of the submission of this extension application there were still outstanding pre-clinical issues involving the reference product, alli 60mg capsules. The MAH agreed to perform the following studies:

OECD 211. Daphnia magna reproduction test.
OECD 210. Early life stage test on fish.
OECD 218/219. Sediment water chironomid test.
OECD 307. Aerobic and anaerobic transformation in soil.
OECD 208. Terrestrial plants growth test.
ISO 11267. Collembola, reproduction test.

The MAH has submitted the requested studies to investigate the risk to aquatic and terrestrial environments for orlistat. An updated ERA has also been submitted incorporating the updated data and Phase I and Phase II analysis provided. The revised ERA indicates that orlistat is a highly lipophilic compound and the MAH has provided evidence to suggest the terrestrial compartment to be the target of orlistat exposure.

The exposure to the aquatic compartment is expected to be low as shown by the low surface water PEC/PNEC **<** 1 value. Orlistat is toxic to aquatic species following chronic but not acute exposures and whilst not inherently biodegradable it is expected to sorb to sewage sludge solids and sediment where it will undergo mineralisation, thus reducing even further the amounts present in surface water and exposure to the aquatic species.

As orlistat is highly lipophilic it is expected to sorb and bioconcentrate in the fatty tissue of fish (particularly oily fish) and the lipid surfaces of other aquatic species if exposure is achieved. However exposure in the aquatic compartment is not expected to be high. As the physiochemical properties of orlistat indicate that orlistat will bioaccumulate in fish (should exposure be achieved) it is not considered necessary to conduct a fish bioconcentration study (OECD 305).

Orlistat is not toxic to most representative organisms of the terrestrial compartment tested although there was some evidence of toxicity in one soil dwelling organism. It was not toxic to plants but it was absorbed by the roots and shots of the agricultural plants tested. No information was provided on how long the orlistat residues remained present in the plant tissue, however this finding was observed at the only concentration tested (1000 mg/kg) which is considered to be an unrealistic soil concentration. The soil metabolism study indicated rapid mineralisation of orlistat residues that bind to soil following land spreading of sewage sludge containing orlistat. Mineralisation is also expected to occur at the STP and when bound to sewage sludge solids although the rate in real life conditions is unknown.

The studies submitted have enabled an assessment of the potential effects of orlistat in both the aquatic and terrestrial compartment of the environment. It is considered that no further studies are required as the data generated is sufficient to predict effects in the environment. It can be concluded that orlistat yields no increased risk to the aquatic or terrestrial environment and the updated ERA acceptable.

2.4. Clinical aspects

2.4.1. Introduction

The MAH claims in this extension application that Orlistat 27 mg chewable tablet is pharmacodynamically equivalent to the reference product: alli 60 mg capsule (demonstrated using the faecal fat excretion (FFE) model). The MAH has submitted seven comparative pharmacodynamic studies in support of this application, all of which provide data on the pharmacodynamic endpoint, FFE. The MAH did not seek EMA or Regulatory Authority Scientific Advice regarding this application. The applicant's rationale for use of the faecal fat excretion model to establish pharmacodynamic equivalence is derived from the fact that orlistat's therapeutic activity is based on local activity within the stomach and small intestine. The current EMA advice states that for a product for local use

intended to act without systemic absorption, pharmacodynamic or comparative clinical studies are in principle required (CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence. 2001. CPMP/EWP/QWP/1401/98; CHMP Draft Guideline on the Investigation of Bioequivalence. 2008. CPMP/EWP/QWP/1401/98 Rev. 1).

No clinical trials have been performed in support of this application. European guidance on the clinical investigation of drugs used in weight control does not provide any information on alternative pharmacodynamic endpoints that could be used to demonstrate bioequivalence (CHMP Note for guidance on clinical investigation of drugs used in weight control. CPMP/EWP/281/96 Rev.1 2006).

Tabular overview of clinical studies

Seven pharmacodynamic studies are included in this application. Four studies were performed by GSK and three supportive studies were conducted by Roche.

All were randomised and, apart from the Roche weight-loss study (BM16757), were primarily designed to evaluate the effect of orlistat on FFE. The four GSK studies were conducted in subjects aged 18 - 60 in good general health and with a body mass index (BMI) of 25 - 33 kg/m2. The pivotal study has compared 27 mg chewable tablet with the 60 mg capsule is Study W3680604.

The three supportive Roche studies provide background for the development of the chewable form, and information on clinical safety at a range of doses. These studies are summarised in the tables 1 & 2 below.

Table 1 Overview of GSK studies with orlistat chewable tablets (N = 161)

Study No. (Location)	Type of study	Role in application (No. randomised)	Duration of test	No. subjects treated* (dose t.i.d.)
W2650370 (UK)	Dose ranging. Incomplete block crossover in-patient. Near-infrared absorptiometry (NIRA) assay for faecal fat.	Pharmacodynamics, pharmacokinetics and safety (N=36)	4 day run-in: baseline 5 day test 3 day washout	18 (20 mg chewable) 36 (40 mg chewable) 17 (80 mg chewable) 17 (120 mg chewable) 18 (160 mg chewable) 35 (60 mg capsule) **Total (chewable): 36**
W2660371 (UK)	Equivalence 30 mg chewable. Crossover in-patient. Titrimetric assay for faecal fat.	Pharmacodynamics and safety (N=30)	6 day run-in: baseline 9 day test 2 day washout	29 (30 mg chewable) 28 (60 mg capsule) 28 (120 mg capsule) **Total (chewable): 29**
W3230488 (UK)	Equivalence 24 mg chewable. Crossover in-patient. Titrimetric assay for faecal fat.	Pharmacodynamics and safety (N=48)	6 day run-in/ baseline 9 day test 2 day washout	48 (24 mg chewable) 45 (60 mg capsule) 46 (120 mg capsule) **Total (chewable): 48**
W3680604 (UK)	Pivotal equivalence 27 mg chewable. Crossover in-patient. Titrimetric assay for faecal fat.	Pharmacodynamics and safety (N=48)	6 day run-in/ baseline 9 day test 2 day washout	48 (27 mg chewable) 46 (60 mg capsule) 48 (120 mg capsule) **Total (chewable): 48**

Table 2 Overview of Roche studies with orlistat chewable tablets (N = 391)

Study No. (Location)	Type of study	Role in application (No. randomised)	Duration of test	No. subjects treated* (dose t.i.d.)
BP16562 (France)	Dose ranging. Parallel group, in-patient.	Supportive. Pharmacodynamics and safety (N=36)	5 day run-in 9 day test 4.5 day washout	9 (60 mg chewable) 9 (90 mg chewable) 9 (120 mg chewable) 9 (120 mg capsule) **Total (chewable): 27**
BP16882 (France)	Dose ranging. Parallel group, in-patient.	Supportive Pharmacodynamics and safety (N=40)	4 day run-in 10 day test 2 day washout	10 (20 mg chewable) 10 (40 mg chewable) 10 (60 mg chewable) 10 (120 mg capsule) **Total (chewable): 30**
BM16757 (Europe, Canada, Australia, Brazil, Mexico)	Dose ranging. Parallel out-patient, placebo-controlled. Faecal fat data for ~40% of subjects; pharmacokinetic data for ~50% of subjects	Supportive Efficacy, pharmacodynamics, pharmacokinetics and safety (N=551)	4 week lead-in 12 week test	. 114 (50 mg chewable) 110 (90 mg chewable) 110 (120 mg chewable) 105 (placebo) 112 (120 mg capsule) **Total (chewable): 334**

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.

2.4.2. Pharmacokinetics

In the current application, plasma concentrations of orlistat were measured in some of the studies, two of which are summarised below.

Study W2650370 was a single site, in-patient, incomplete block crossover, dose-ranging study in 36 subjects. It was conducted in subjects aged 18 - 60 in good general health and with a body mass index (BMI) of 25-33 kg/m2. Five doses of chewable orlistat (20, 40, 80, 120 and 160 mg) were compared with orlistat 60 mg capsules. All doses were administered orally with meals, three times daily. Each subject was randomised to receive both the 60 mg capsule and 40 mg chewable tablet plus two additional doses of the chewable tablet (20, 80, 120 or 160 mg) during a 35 day confinement at the study centre. Subjects first completed a 4 day baseline period, followed by four treatment periods each of 5 days. During each treatment period, subjects received orlistat at each meal for 5 days. There was a 3-day washout between the dosing periods.

Blood samples were collected from volunteers before and after (2 and 4 h) study medication was taken on day 1 (morning dose) and day 5 (evening dose) for each treatment period. The mean plasma concentrations are presented in the table 3 below.

Table 3 Mean orlistat plasma concentrations: Study W2650370

Time (Day of test; time post-dosing)		**Orlistat t.i.d. Capsule 60 mg N=35**	**Chewable Tablet 20 mg N=18**	**40 mg N=36**	**80 mg N=17**	**120 mg N=17**	**160 mg N=18**
		Mean orlistat concentration (ng/ml)* (Number of subjects with quantifiable plasma levels of orlistat)					
Day 1	2 hour	0.04	0.03	0.19	0.62	1.21	1.61
		(3)	(2)	(14)	(14)	(15)	(17)
Day 1	4 hour	0.01	0.01	0.17	0.82	1.19	1.39
		(3)	(1)	(17)	(17)	(17)	(18)
Day 5	0 hour	0.13	0.02	0.17	0.43	0.88	0.94
		(12)	(3)	(23)	(17)	(17)	(18)
Day 5	2 hour	0.05	0.01	0.09	0.41	0.88	1.43
		(10)	(1)	(14)	(17)	(17)	(18)
Day 5	4 hour	0.26	0.01	0.12	0.36	0.82	1.10
		(25)	(2)	(20)	(15)	(17)	(18)

* Mean for all subjects. For subjects with levels <LOQ, a value of 0 was assigned.

There is evidence of increasing absorption of orlistat with increasing dose of the orlistat chewable tablet, but the concentrations remain very low. The number of subjects with detectable levels of orlistat and the mean plasma concentrations seen with the 60 mg capsules are generally in the range observed for the 20 - 40 mg chewable tablets.

The maximum observed plasma concentrations of orlistat for the 20 mg and 40 mg chewable were 0.44 and 1.32 ng/ml, respectively; while the maximum concentration observed for the 60 mg capsule was 1.51 ng/ml. No plasma concentration exceeded 7 ng/ml in this study even at the highest dose evaluated (160 mg, over 5-fold higher than the dose proposed for marketing).

The second PK Study BP16757 perhaps has the most relevant data from the three Roche studies since it provides pharmacokinetic data for over 200 subjects after 57 days of treatment with the orlistat, and the formulation tested is claimed to be similar (although not identical) to the one developed by GSK.

In this 12 week weight loss study, most subjects in all of the orlistat treatment groups had measurable plasma levels of orlistat, and almost all of the subjects had measurable plasma levels of metabolite - M1. The data are summarised in Table 4 below.

Table 4 Plasma concentrations of orlistat and metabolite, M1 (day 57): Study BM16757

Treatment Analyte	N/Total	Mean (ng/ml)	Range (ng/ml)	SD (ng/ml)	%CV
Orlistat 120 mg capsule					
Orlistat	30/54	1.09	0.23 – 5.07	1.05	96.2
M1	54/54	20.47	0.78 – 73.00	14.36	70.2
Orlistat 50 mg chewable tablet					
Orlistat	36/53	0.98	0.23 – 3.14	0.86	87.9
M1	52/53	24.81	1.60 – 54.00	12.61	50.8
Orlistat 90 mg chewable tablet					
Orlistat	40/50	1.48	0.23 – 5.92	1.25	84.1
M1	49/50	37.19	3.60 – 120.00	26.10	70.2
Orlistat 120 mg chewable tablet					
Orlistat	48/52	2.05	0.27 – 12.10	2.09	101.9
M1	52/52	50.36	0.66 –150.00	31.60	62.8

N/Total: number of samples with measurable concentration / total number of samples Data are for samples with measurable concentrations: LOQ was 0.2 ng/ml for orlistat 0.32 ng/ml for M1

Systemic absorption of orlistat from the chewable tablets remained low (plasma concentrations of orlistat on day 57 ≤12.1 ng/ml; although most subjects in all of the orlistat groups had measurable levels of orlistat. Orlistat 90 and 120 mg chewable tablets consistently produced higher mean plasma concentrations of orlistat and M1 than the orlistat 120 mg capsule, the highest dose of the chewable tablet producing levels of orlistat and M1 were about two-fold higher than for the 120 mg capsule. Data for the 50 mg chewable tablet are particularly relevant as they appear comparable to data for the 120 mg capsule.

The maximum individual orlistat plasma concentrations observed were 3.14, 5.92, and 12.1 ng/ml for the chewable 50, 90 and 120 mg doses, respectively, compared to 5.07 ng/ml for the Xenical 120 mg capsule. The maximum individual M1 plasma concentrations observed were 54.0, 120.0, and 150.0 ng/ml for the chewable 50, 90 and 120 mg doses, respectively, compared to 73.0 ng/ml for the 120 mg capsule.

The results show that when equal doses are compared, there is increased absorption of orlistat from the chewable dosage formulation compared with the capsule formulation. There was wide variability in the individual plasma concentrations both for orlistat and M1. The proportion of the study population with detectable levels of orlistat increased with increasing dose of the chewable tablet.

2.4.3. Pharmacodynamics

- ***Mechanism of action***

Orlistat is a potent, specific and long-acting inhibitor of gastrointestinal lipases. It 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. From clinical studies, it has been estimated that orlistat 60 mg taken three times daily blocks the absorption of approximately 25% of dietary fat.

The onset of action of orlistat on faecal fat excretion is relatively rapid. Faecal fat values gradually increase during the first 1 to 2 days of treatment reaching a plateau within 3 days that is then maintained, with some variability, as treatment continues. The effect is reversible with the excretion of faecal fat reducing to baseline values, usually within 2 to 3 days of stopping treatment.

These data demonstrate that the maximum effect of orlistat on dietary fat is achieved in the first three days of treatment and remains constant thereafter. The effect is quickly reversible on cessation of treatment.

- ***Relationship between dose and effect***

A retrospective, population-based meta-analysis was undertaken to evaluate the relationship between orlistat dose and the degree of inhibition of dietary fat absorption. Data were collected from 19 Phase I studies involving a total of 308 evaluable subjects who received placebo or orlistat 30 mg to 1,200 mg for 5 to 15 days according to a t.i.d regimen. The studies were double-blind, placebo-controlled, randomised and parallel group in design. This analysis was an extension of an earlier publication [Zhi, 1994]. The results of the daily mean faecal fat excretion percentage, relative to ingested fat, were correlated to the orlistat daily dose. A simple E_{max} model including a basal value was used in fitting the above dose-response relationship for all evaluable subjects. The dose-response curve exhibits an initial steep portion with a subsequent plateau at approximately 35% inhibition of dietary fat absorption for doses greater than 400 mg/day (Figure 1) below.

Figure 1

Dose-response curve for faecal fat excretion

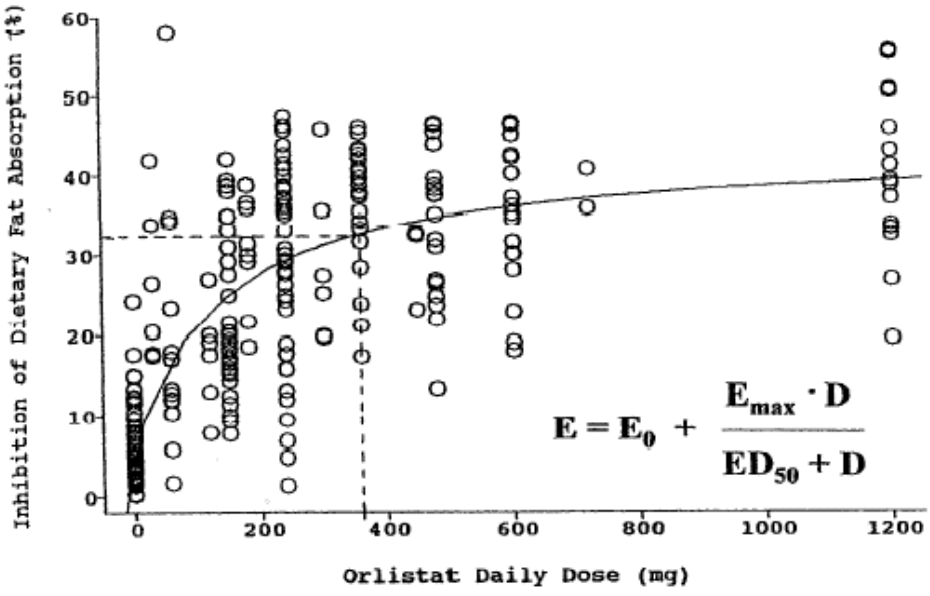

Fig 2. Dose-response relationship for orlistat in human volunteers. The effect is the percentage of ingested fat excreted, referred to as fecal fat excretion percentage. Both individual data (*open circles*) and the curve predicted for the population with the maximum-effect (E_{max}) model (*continuous line*) are shown.

Based on these data, it is estimated that treatment with orlistat 60 mg tid blocks the digestion of 25% of dietary fat. The equivalent figure for 120 mg tid is 30% of dietary fat, thus the 60 mg dose achieves approximately 80% of the effect seen with the prescription dose of 120 mg.

The plateau effect is appropriate and desirable from a therapeutic perspective since some fat is required in the diet and this still allows for the absorption of fat-soluble essential nutrients.

From these data, 60 mg orlistat tid has almost as much effect on dietary fats as 120mg tid, which theoretically should translate into similar efficacy as regards weight loss. However, no such estimations are available for the 27mg dose of orlistat.

The MAH has chosen to demonstrate therapeutic equivalence using faecal fat excretion as a surrogate for the efficacy of orlistat. The dose response relationship of orlistat for the amount of faecal fat excreted is shown in the graph above. If a study is conducted at too high a dose of orlistat these studies would probably lack sensitivity as it would be looking at effects at the top of the dose response curve. If a dose of 60mg is compared to the new formulation such a study should have the ability to detect differences between formulations if a difference exists.

- ***Primary and Secondary pharmacology***

<u>Studies W2650370, W2660371, W3230488 and W3680604</u>

The reference product in these studies was the orlistat 60 mg capsule. All of these four studies were crossover in design. The primary pharmacodynamic parameter was faecal fat excretion, expressed as percentage of the protocol specified dietary intake. This was referred to as percent faecal fat excretion (FFE).

Statistical analysis

The primary statistical analyses were based on the per protocol (PP) population in all three equivalence studies (W2650370, W2660371 and W3680604). The PP population was defined as subjects who were randomised and took at least one dose of medication, completed the treatment period and had no major protocol violation.
There were some minor differences between the three pharmacodynamic equivalence studies in the criteria used to define this population. In Studies W3230488, W3680604, subjects with chronic constipation and/or vomiting as determined by medical review (prior to unblinding) were excluded from the PP but this was not the case in the preceding study, W2660371. In Study W3680604, the final, pivotal study, subjects who failed to complete a meal or who were defined as a fat malabsorber (has ≥7% faecal fat at baseline) were excluded from the PP population. Further details of the definitions of the criteria applied to define the PP population are provided in the individual CSRs. An intention to treat (ITT) population was also described in all four studies and the key statistical analyses were repeated for this population.

• TOST [Schuirman, 1987] This method is based on the 90% CI of the ratio of geometric means of percent faecal fat. Analysis of variance was used to calculate the adjusted means for the test and reference products. Log-transformed percent faecal fat was the dependent variable. Equivalence was concluded if the 90% CI for the ratio of geometric means is included within the specified limits.

• Dose scale [Gillespie, 1997] The dose scale method is described in the Clinical Study Reports for Studies W2660371, W3230488 and W3680604. It was developed for drugs that act locally. The method allows for the assessment of bioequivalence using a combination of pharmacodynamic measurements and mathematical modelling of the dose-response relationship established for the reference product. The relative bioavailability (f) of the test product is estimated on the dose scale and a 90% CI is calculated. Bioequivalence is concluded if the 90% CI is contained within the pre-specified acceptance range.

Results
Pharmacological effect was assessed by daily measurement of total faecal fat as a surrogate for efficacy. This covers all assessments made during the baseline and treatment periods. Three related parameters were used in Study W2650370: percent of fat inhibited (per 24 hour); percent fat excreted (per 24 hour), and fat 24 hour mean change. In the three equivalence studies, the primary endpoint was faecal fat excretion expressed as percentage of the protocol specified dietary intake (referred to as "percent faecal fat.

Study W2650370, dose ranging, pharmacodynamics and pharmacokinetics
This was essentially a dose ranging study. It was a single site, in-patient, incomplete block crossover, dose-ranging study in 36 subjects. The selection of doses and study design was guided by review of three clinical research studies conducted by Roche. It was conducted in subjects aged 18 - 60 in good general health and with a body mass index (BMI) of 25-33 kg/m2. Five doses of chewable orlistat (20, 40, 80, 120 and 160 mg) were compared with orlistat 60 mg capsules. All doses were administered orally with meals, three times daily. Each subject was randomised to receive both the 60 mg capsule and 40 mg chewable tablet plus two additional doses of the chewable tablet (20, 80, 120 or 160 mg) during a 35 day confinement at the study centre. Subjects first completed a 4 day baseline period, followed by four treatment periods each of 5 days. During each treatment period, subjects received orlistat at each meal for 5 days. There was a 3-day washout between the dosing periods.

Percent fat inhibited – this is the change from baseline in mean 24 h fat divided by 60 g (fat content of meals) x 100. This represents the primary pharmacodynamic analysis variable, and corresponds to the inhibition evaluation used by Roche in their Phase I pharmacodynamic studies. Percent fat excreted – this is the 24 h mean fat divided by 60 g (fat content of meals) x 100.

The adjusted mean (least squares mean, LSM) for percent faecal fat (described as percent faecal fat excreted in the CSR) increased with increasing dose of the chewable tablet although the increase for doses ≥80 mg was relatively small, as shown in table 5 below. The value for the orlistat 60 mg capsule (12.2%) was intermediate between the value for the 20 mg (10.5%) and 40 mg (14.5%).

Table 5 Effect of orlistat dose on percent faecal fat: Study W2650370

Orlistat t.i.d.					
Capsule	Chewable tablet				
60 mg (N=35)	20 mg (N=18)	40 mg (N=36)	80 mg (N=17)	120 mg (N=17)	160 mg (N=18)

Percent faecal fat						
Adjusted mean*	12.2	10.5	14.5	19.0	19.4	20.6
(95% CI)	(10.1, 14.2)	(7.8, 13.2)	(12.4, 16.5)	(16.2, 21.7)	(16.7, 22.2)	(18.0, 23.3)

PP population
*LSM

Post hoc analyses of the faecal fat data from Study W2650370 suggested that doses of the chewable tablet of between 27 and 35 mg would potentially be bioequivalent to the 60 mg capsule [GSK, data on file]. Accordingly, the 30 mg dose of the chewable tablet was taken forward for further evaluation.

Study W2660371, pharmacodynamic equivalence (30 mg)
Study W2660371 was designed to establish equivalence between the orlistat 30 mg chewable tablet and 60 mg orlistat capsule.

The adjusted mean (LSM) for percent faecal fat was higher for the 30 mg chewable tablet (22.7%) than the reference 60 mg capsule (19.4%) but lower than that for the 120 mg capsule dose (24.8%) as shown in table 6 below. The 30 mg tablet was not bioequivalent to the 60 mg capsule using the dose scale method since the 90% CI was not contained within the specified acceptance interval (0.80, 1.25).

Table 6 Effect of orlistat dose on percent faecal fat: Study W2660371

	Orlistat t.i.d.		
	Chewable	**Capsule**	
	30mg	60 mg	2 x 60 mg
Percent faecal fat			
N	27	27	27
Mean (SD)	22.7 (7.4)	19.3 (8.3)	25.0(8.7)
% CV	32.6	43.4	34.7
Median	24.4	20.2	26.8
Range	9.2 – 33.3	4.2 – 39.5	4.3 – 39.5
Adjusted mean	22.7	19.4	24.8
95%CI	19.8, 25.6	16.5, 22.2	22.0, 27.7

A post hoc analysis was done using an average bioequivalence approach (TOST) but equivalence was not reached with this method. The ratio of geometric means for percent faecal fat (30 mg/60 mg) was 1.25 and the 90% CI (1.10, 1.41) [GSK, data on file]. The difference between the adjusted mean for percent faecal fat for the orlistat 30 mg chewable tablet and the 60 mg capsule was 3.3% compared with 5.4% for the difference between the 60 mg and 120 mg capsule dose.

The changes that were made to the study design and analytical method for the faecal fat assay in this study (and the subsequent studies) resulted in values for percent faecal fat that were comparable with those seen in the Roche studies. Consequently, comparisons could be made more readily across the Roche and GSK studies.

This study shows that the 30mg chewable tablet is superior to the 60mg capsule and therefore is not an appropriate dose to be considered therapeutically equivalent to the 60mg capsule

Study W2660488, pharmacodynamic equivalence (24 mg)
Study W3230488 was designed to establish equivalence between the orlistat 24 mg chewable tablet and 60 mg orlistat capsule.

The adjusted mean percent faecal fat was lower for the 24 mg chewable tablet (16.5%) than the reference 60 mg capsule (19.8%). The ratio of geometric means was 0.84. The 24 mg tablet was judged to be equivalent to the 60 mg capsule since the 90% CI (0.76, 0.93) was contained within the pre-specified acceptance limits of 0.70 and 1.43. Had the standard bioequivalence acceptance limits (0.80, 1.25) been applied, equivalence would not have been concluded (table7).

The 24 mg tablet was not equivalent to the 60 mg capsule using the dose scale method since the 90% CI was not contained within the specified acceptance limits (0.70, 1.43).

Table 7 Effect of orlistat dose on percent faecal fat: Study W2660488

	Orlistat t.i.d.		
	Chewable	Capsule	
	24 mg	60 mg	2 x 60 mg
Percent faecal fat			
N	41	39	42
Mean (SD)	16.4 (6.8)	20.3 (7.6)	25.1 (10.8)
% CV	41.5	37.3	43.1
Median	16.8	20.5	25.7
Range	3.6 – 30.0	3.8 – 33.3	3.0-43.1
Adjusted mean	16.5	19.8	25.1
95%CI	13.9, 19.0	17.2, 22.3	22.6, 27.7

This study shows that the 24mg chewable tablet is inferior to the 60mg capsule and therefore is not an appropriate dose to be considered therapeutically equivalent to the 60mg capsule.

Study W3680604, pivotal pharmacodynamic equivalence (27 mg)
The final equivalence study, W3680604, was an open label, single centre, randomised, three period, three treatment crossover study in 48 subjects.

The two previous equivalence studies, W2660371 and W3230488, investigated the pharmacodynamics of the 30 mg and 24 mg orlistat chewable tablet, respectively. These results showed that the 30 mg dose had a greater effect on faecal fat excretion than the 60 mg capsule whereas the 24 mg dose was less effective. A regression model based on data from these studies showed that the 27 mg dose should have a similar effect on faecal fat as the 60 mg reference product.

The primary analysis for establishing equivalence in this pivotal study was based on the 90% CI of the ratio of geometric means of the primary pharmacodynamic variable, percent faecal fat. Equivalence was to be concluded if the 90% CI of the ratio of geometric means was included in the standard bioequivalence acceptance interval (0.80, 1.25). Data for mean percent fat excreted are presented in Table 8 below

Table 8 Effect of orlistat formulation and dose on percent faecal fat: Study W3680604

		Orlistat t.i.d.		
		Chewable	Capsule	
	Baseline	27 mg	60 mg	2 x 60 mg
		Percent faecal fat		
Per protocol population				
N	46	44	42	46
Mean (SD)	2.5 (1.3)	19.8 (6.7)	19.8 (6.1)	23.7 (8.5)
% CV	53	34	31	36
Median	2.4	19.0	20.6	22.8
Range	0.1 – 6.6	9.0 – 36.6	4.7 – 34.7	6.9 – 46.0

Adjusted mean*		19.4	20.2	23.8
95%CI		17.3, 21.6	18.0, 22.4	21.7, 25.9
Intention to treat population				
N	48	48	45	48
Mean (SD)	2.4 (1.3)	18.7 (7.5)	19.5 (6.4)	23.3 (8.8)
% CV	54	40	33	38
Median	2.4	18.7	20.3	23.0
Range	0.1 – 6.6	1.9 - 36.6	4.7 – 34.7	4.3 – 46.0
Adjusted mean		18.7	19.6	23.3
95%CI		16.5, 21.0	17.3, 21.8	21.1, 25.5

* LSM

The mean percent faecal fat was almost identical for 27 mg chewable tablets and 60 mg capsules (19.8% and 20.2%, respectively; PP population). However, for the ITT population, the mean percent FFE for 27 mg chewable tablets and 60 mg capsules were 18.7% and 19.6% respectively; the figures for adjusted means were 18.7% and 19.6% respectively.

90% CI of the ratio for mean percent faecal fat: Study W3680604

Method / data	Orlistat t.i.d.	
	27 mg chewable tablet	60 mg capsule
N	44	42
TOST (log-transformed)		
Ratio of geometric means	0.96	
90% CI	(0.87, 1.06)	
Fieller's 90% CI		
Mean ratio	0.96	
90% CI	(0.87, 1.06)	
PP population		

This study shows that to the extent that FFE represents the mechanism of action, Orlistat 27mg Chewable Tablet generally appears to be comparable to 60mg capsule.

Studies BP16562, BP16882 and BM16757

Although the formulations of the Roche and GSK chewable tablets are not identical, they are quite similar. In particular, they both contain sucrose monopalmitate and sodium starch glycolate in the active granulation, which are considered key ingredients for the improved disintegration and dispersion observed with the chewable formulation. The comparator in Roche studies was the 120 mg capsule and the studies were all parallel group.

Studies BP16562 and BP16882 were pharmacodynamic studies measuring FFE. Faecal fat was evaluated as total fat excretion (g/24 h, baseline corrected), combining data for faecal fat excreted, oily spotting and free fat in faeces. Study BM16757 was a 12 week - parallel design outpatient study where the primary outcome measure was total weight loss. Faecal fat was measured on three occasions in this study in a subset of subjects. Plasma levels of orlistat and of the metabolite, M1, were measured in this study. BM16757 also provides some safety data for the chewable tablet (N=334).

The results of BP16562 and BP16882 are summarised in the table 9 below.

Table 9 Summary of total fat excretion by orlistat treatment group: Studies BP16562 and BP16882

Study	Form	Dose	Collection period during treatment period	N	Mean (SD) total fat excretion (g/24 h)
BP16562	Chewable	60 mg	Days 6 – 19	9	13.93 (2.44)
		90 mg		9	15.86 (2.16)
		120 mg		9	18.17 (3.86)
	Capsule	120 mg		9	10.73 (2.20)
BP16882	Chewable	20 mg	Days 4 – 12	10	9.70 (2.39)
		40 mg		10	18.37 (5.22)
		60 mg		10	22.84 (5.65)
	Capsule	120 mg		10	20.35 (4.06)

In Study BP16562, mean total fat excretion was greater than in the three groups receiving the chewable tablets than in the orlistat 120 mg capsule group. The percentage increase in mean total fat excretion relative to orlistat 120 mg capsules was 29% for 60 mg, 48% for 90 mg and 69% with 120 mg chewable tablets. In Study BP16882, fat excretion was lowest with the 20 mg chewable tablet and greater with the 60 mg chewable tablet than with the 120 mg capsule.

A dose response was apparent in both studies. Total fat excretions levels may have been lower in BP16562 because the period when stools were collected during treatment was extended by 5 days into the washout period. Another factor to be borne in mind is that the number of subjects in each of the treatment groups in these studies was low (N=9 or 10) and that this was a parallel group study; the GSK studies were crossovers involving many more (30 or 48) subjects.

Study BP16757, efficacy and pharmacodynamics

This was a multi-centre, placebo-controlled, randomised, parallel design study consisting of two periods during which the subjects were provided with a hypocaloric diet and received counselling from a dietician: a 4 week, single-blind, placebo lead-in period followed by 12 week double-blind treatment t.i.d. with placebo, orlistat 120 mg capsules or orlistat chewable tablets, 50, 90 or 120 mg. This was a multinational study conducted in adults who were overweight or obese (BMI 27 – 43 kg/m2), similar to the population that would potentially be eligible for treatment with Orlistat 27 mg Chewable Tablets.

The study objectives were to determine the weight loss effects and tolerability of the chewable tablets, orlistat 120 mg capsules and placebo over the 12 week treatment period. Criteria for evaluation included change in body weight, faecal fat excretion (about 40% of subjects), concentrations of orlistat and M1 in plasma at day 57 in about half of the subjects, adverse events (AEs), laboratory parameters and vitamin levels.

Efficacy

Placebo-corrected weight loss was dose-related, similar to the fat excretion data in all of the studies with chewable tablets, but it was not significantly different for any of the tested doses of the chewable tablet compared to the reference 120 mg orlistat capsule as shown in the table 10 below.

Table 10 Effect of orlistat chewable tablets on body weight: Study BM16757

Treatment	N	Mean* change from baseline to day 85	Mean* difference from placebo (delta)	Ratio of change in chewable group/change in capsule group	95% CI for ratio
Placebo	101	-1.64 kg			
120 mg capsule	112	-3.96 kg	-2.32 kg		

50 mg chewable	113	-3.53 kg	-1.89 kg	0.81	(0.53, 1.17)
90 mg chewable	110	-4.19 kg	-2.54 kg	1.10	(0.80, 1.54)
120 mg chewable	109	-4.31 kg	-2.67 kg	1.15	(0.84, 1.61)

LOCF data, ITT population
•Least squares mean
Results are intent-to-treat population, last observation carried forward

Throughout the double-blind treatment period, weight loss was consistently greater in all orlistat treatment groups than in the placebo group. Mean total weight loss was approximately 15% greater with the 120 mg chewable tablet than the 120 mg capsule. However, the difference between the 120 mg tablet and the 120 mg capsule was not statistically significant. The results suggest that a chewable tablet containing between 50 and 90 mg would be therapeutically equivalent to the 120 mg capsule.

Pharmacodynamics
Faecal fat was assessed at day –14, 29 and day 85. The fat excretion data generally paralleled the weight loss results with mean faecal fat excretion being slightly less with the 50 mg chewable tablet and greater with the 90 mg dose compared with the 120 mg capsule as shown in the table 11 below.

Table 11 Average total fat excretion by orlistat treatment group: Study BM16757

Study	Form	Dose	Study day	N	Mean (SD) total fat excretion (g/24 h)
BM16757	Chewable	50 mg	Day –14	44	2.3 (2.8)
			Day 29	36	25.2 (16.5)
			Day 85	37	24.1 (14.6)
		90 mg	Day –14	37	3.2 (3.8)
			Day 29	35	32.3 (20.1)
			Day 85	29	32.7 (21.9)
		120 mg	Day –14	29	2.7 (2.9)
			Day 29	28	32.3 (18.1)
			Day 85	10	19.0 (15.6)
	Capsule	120 mg	Day –14	44	2.7 (3.5)
			Day 29	36	28.3 (13.7)
			Day 85	34	26.6 (15.5)

In this study, the subjects were not in-patients, in which case, sample collection may have adversely affected the quality of the data. Nonetheless, fat excretion data generally paralleled the weight loss results, with higher faecal fat levels seen with higher doses, although the mean values seen for the two highest doses of chewable were similar. As with the weight loss data, the results suggest that for the orlistat chewable tablet the pharmacodynamically equivalent dose relative to the reference 120 mg capsule would lie somewhere between 50 mg and 90 mg.

2.4.4. Discussion on clinical pharmacology

The concept of measurement of the amount of faecal fat excreted after administration of orlistat is a relevant endpoint for the evaluation of efficacy. The question is whether this could suffice as the sole method of evaluation of efficacy in this particular case.

The major weakness of the submitted studies appears to be the considerable variability in fat excretion under similar treatments or even using the same treatment. This therefore raises the issue of reliability of the results regarding the demonstration of bioequivalence. As these are not pharmacokinetic bioequivalence studies, using 90% confidence intervals with limits of 0.80-1.25, which is the standard in bioequivalence trials, is not appropriate. In this case 95% confidence intervals for the analysis of the results should be used because this is the standard approach in pharmacodynamic

and therapeutic equivalence trials. The CHMP requested the MAH to justify the choice of equivalence margin.

The MAH justified that the FFE model, as developed originally by Roche and more recently by GSK, has been shown to be robust and sensitive, and the measurement of faecal fat excretion after administration of orlistat is a valid surrogate for weight loss. A margin of clinical equivalence expressed in terms of 24 h faecal fat (g) was calculated to permit the assessment of therapeutic equivalence for the three equivalence studies. This margin, 2.5 g faecal fat excreted over 24 h, is conservative and was derived from weight loss data since weight loss and faecal fat excretion are related.

From the data presented, therapeutic equivalence has been concluded between orlistat 27 mg chewable tablets and orlistat 60 mg capsules since the two-sided 95% CI for the treatment difference between the test and reference product was contained within the margin of clinical equivalence.

The other aspect of the bioequivalence approach is the requirement that the test and reference product formulations are essentially similar in both efficacy and safety. This normally requires firstly, that the two formulations are the same and secondly, that the reference product formulation to have been in clinical use for at least 10 years. This is not the case here. Although, the 60mg capsule was only licensed in 2007 the 120mg capsule has been licensed since 1998. The latter may therefore be considered not a major concern.

2.4.5. Conclusions on clinical pharmacology

The concept of measurement of the amount of faecal fat excreted after administration of orlistat is a relevant endpoint for the evaluation of efficacy. From the data presented, the FFE appear to indicate that orlistat 27mg chewable tablet is equivalent to the 60mg capsule.

The CHMP concluded that sufficient evidence of equivalence between the 27mg chewable tablet and the 60mg capsule has been provided.

2.5. Clinical efficacy

No new clinical trials have been performed with GSK Orlistat 27mg chewable tablet.

2.6. Clinical safety

The safety profile for orlistat has been well characterised in extensive clinical trials and over 10 years of marketing as a prescription medicine. Orlistat 120 mg (Xenical) has been evaluated in over 100 clinical trials in approximately 30,000 subjects; including a 4 year controlled clinical trial in non-diabetic obese subjects (the XENDOS study). Orlistat 120 mg is currently approved in over 145 countries including eight where this product is available without a prescription.

Patient exposure
Overall, 552 subjects have received orlistat chewable tablets containing various doses of orlistat. Most of these subjects were involved in the pharmacodynamic studies of duration ranging from 2-10 days; the exception being the 12 weeks of study BM16757 involving 334 subjects.

In the GSK studies, a total of 161 subjects were exposed to orlistat chewable tablets at doses from 20 to 160 mg t.i.d. for periods of up to 9 days of continuous treatment. 48 subjects received orlistat 27 mg chewable tablets for 9 days (Study W3680604). In addition, 113 subjects received orlistat chewable tablets in the other GSK studies at dosages from 20 to 160 mg t.i.d. for 5 to 9 days.

The chewable tablets formulated by Roche and used in the studies included in this application were similar to the one developed by GSK. In these supportive studies, a total of 391 subjects have been exposed to orlistat chewable tablets at doses from 20 to 120 mg t.i.d. for periods of up to 12 weeks. 334 subjects were exposed to orlistat chewable tablets at doses of 50, 90 or 120 mg t.i.d. for up to 12 weeks. In the two dose ranging studies, 57 subjects received orlistat chewable tablets at doses of 20, 40, 60, 90 or 120 mg t.i.d. for 9-10 days.

Although the safety profile for orlistat has been well characterised in extensive clinical trials and over 10 years of marketing as a prescription medicine, the number of patients exposed to orlistat chewable tablet is small and the duration of exposure is limited.

Adverse events
The overall incidence and intensity of AEs during treatment with orlistat chewable tablets in the GSK studies were largely comparable with the 60 mg capsule. In all four studies, subjects were in-patients and were confined to the study site.

As would be expected from the pharmacodynamic action of orlistat, most of the adverse events are related to the gastrointestinal (GI) system. Of those subjects with GI AEs, most experienced single episodes of these AEs, and almost all of these AEs were mild; there were very few reports where the events were considered moderate in intensity and no subjects reported severe events. Although the majority of AEs seen were GI, the most common single AE reported overall was headache. This was also true for the 60 mg capsule. In the four GSK studies, 27 to 69% of the subjects taking chewable tablets reported at least one AE, while 36 to 71% of the subjects taking orlistat 60 mg capsules reported one AE.

The data for the supportive Roche studies also showed that chewable orlistat had a similar AE profile to orlistat capsules.

The largest body of safety data on orlistat chewable tables is found in the 3 month Study BM16757. In this study, most of the subjects in all treatment groups had at least one AE during the double-blind treatment period. Fifty-six (56%) of subjects in the placebo group and 72 to 88% of subjects in the orlistat groups had GI AEs. Overall, there was a trend towards a higher incidence of GI AEs at the higher doses of the chewable tablet. All of the AEs reported apart from three (these three were serious adverse events, SAEs) were mild to moderate in intensity.

Table 12 Summary of most frequent adverse events (occurring in ≥5%) of subjects in a treatment group by body system and treatment (safety population): Roche Study BM16757

Body system / Adverse event	Placebo* (N=105) n (%)	Orlistat* capsule 120 mg (N=112) n (%)	Chewable orlistat* tablet 50 mg (N=114) n (%)	90 mg (N=110) n (%)	120 mg (N=110) n (%)
All body systems					
Subjects with ≥ 1 AE	80 (76)	96 (86)	95 (83)	102 (93)	101 (92)
Total number of AEs	217	359	340	382	354
Gastrointestinal disorders					
Subjects with ≥ 1 AE	59 (56)	81 (72)	82 (72)	97 (88)	92 (84)
Fatty / oily stool	7 (7)	31 (28)	39 (34)	43 (39)	41 (37)
Oily spotting	0	32 (29)	18 (16)	36 (33)	41 (37)
Stool soft	13 (12)	21 (19)	18 (16)	27 (25)	24 (22)
Faecal urgency	2 (2)	25 (22)	19 (17)	25 (23)	18 (16)
Flatus with discharge	2 (2)	21 (19)	16 (14)	22 (20)	23 (21)
Increased defaecation	5 (5)	15 (13)	20 (18)	16 (15)	22 (20)
Flatulence	16 (15)	13 (12)	15 (13)	12 (11)	13 (12)
Liquid stools	8 (8)	18 (16)	9 (8)	10 (9)	16 (15)
Oily evacuation	1 (<1)	11 (10)	8 (7)	18 (16)	18 (16)
Faecal incontinence	1 (<1)	13 (12)	10 (9)	14 (13)	13 (12)
Decreased defaecation	15 (14)	7 (6)	15 (13)	5 (5)	7 (6)
Abdominal pain NOS	5 (5)	10 (9)	7 (6)	13 (12)	9 (8)
Nausea	9 (9)	6 (5)	7 (6)	4 (4)	1 (<1)
Abdominal pain upper	5 (5)	3 (3)	3 (3)	3 (3)	2 (2)

Infections and infestations					
Subjects with ≥ 1 AE	29 (28)	27 (24)	30 (26)	32 (29)	23 (21)
Nasopharyngitis	7 (7)	13 (12)	14 (12)	16 (15)	9 (8)
Influenza	6 (6)	3 (3)	7 (6)	2 (2)	6 (5)
Gastroenteritis NOS	3 (3)	0	4 (4)	5 (5)	3 (3)
Nervous system disorders					
Subjects with ≥ 1 AE	22 (21)	17 (15)	24 (21)	21 (19)	13 (12)
Headache	17 (16)	14 (13)	17 (15)	17 (15)	11 (10)
Dizziness (excl. vertigo)	2 (2)	3 (3)	6 (5)	4 (4)	2 (2)
Musculoskeletal, connective tissue and bone disorders					
Subjects with ≥ 1 AE	9 (9)	19 (17)	12 (11)	17 (15)	9(8)
Back pain	4 (4)	6 (5)	5 (4)	5 (5)	1 (<1)

*Treatment administered t.i.d.

Overall, the four orlistat treatments in BM16757 had similar safety profiles but there was a trend towards a higher incidence of GI AEs at the higher doses of the chewable tablet. For the reference 120 mg capsule, the relevant comparison is with the 50 mg chewable tablet. Seventy-two (72%) of subjects in each treatment group reported GI AEs, and the overall pattern and incidence of all of the AEs were quite similar between these two groups.

Orlistat 27mg chewable tablet, as a lower dose would be expected to give rise to fewer adverse events than the currently licensed 120mg capsule. However, the fact that this is a new formulation and has higher bioavailability, raises the possibility that it may behave differently when administered over a period of time.

Deaths, Serious adverse events (SAEs) and Discontinuations
There were no deaths in any of the seven studies with orlistat chewable tablets.

There was one SAE in the four GSK studies, diverticulitis, which was considered unlikely to be related to study treatment. Eleven (11) subjects withdrew from the GSK studies. In five cases, this was due to AEs, but only two (rash and vomiting, respectively) were considered possibly or probably related to treatment.

There were no SAEs and no withdrawals in the two short-term Roche studies (BP16562, BP16882).

There were eight serious adverse events (SAEs) in Study BM16757, the 12 week weight loss study, but two, diverticulitis and Henoch-Schonlein purpura, were considered possibly or probably related to treatment (120 mg chewable tablet in both instances). The investigator considered the intensity of these events to be severe and moderate, respectively. About 10% of subjects withdrew from BM16757 in each of the groups. A higher percentage of subjects in the 120 mg chewable tablet group, the highest dose tested, withdrew because of AEs (5% compared with 0% to 2% in the other groups).

Laboratory findings
For the GSK studies, there were no notable findings in the laboratory test results.

For the Roche studies, there were several transient laboratory abnormalities noted, mostly involving haematuria or elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT) or serum phosphate. However, few of these were clinically significant and resulted in non-serious AE reports.

Vitamin levels
Vitamin levels were also measured in Study BM16757 (vitamins A, D, E, beta-carotene, K1 and prothrombin time (PTT) to monitor for malabsorption of vitamin K) at baseline and at day 85. Subjects were not allowed to take vitamin supplements during this study. At day 85, there was a very small decrease in mean vitamin A levels in the orlistat 120 mg capsule and orlistat 120 mg chewable tablet

group. Mean levels of vitamin D increased in all treatment groups with no apparent pattern. Mean levels of vitamin E increased in the placebo group but decreased in all orlistat groups. Mean beta-carotene and also vitamin K1 levels decreased to a greater extent in the orlistat groups than the placebo group. Mean changes in PTT were small in all treatment groups with no apparent pattern. For vitamin E and beta-carotene, there was evidence of a progressive decline in mean levels with increasing dose of the chewable tablet, perhaps indicative of the greater efficiency of this formulation.

Comparisons of the mean change from baseline were made with the orlistat 120 mg capsule group. The orlistat 120 mg chewable tablet produced statistically significant decreases in vitamin E and beta-carotene relative to the 120 mg capsule. None of the other comparisons was significant. These data appear to show that higher doses of orlistat can affect vitamin levels, particularly Vitamins A and D and Beta carotene. It is unlikely that the smaller doses such as orlistat 27 mg chewable tablet would cause vitamin deficiencies as is the case with the 120mg.

Safety in special populations
No new data are provided or required.

Immunological events
N/A

Safety related to drug-drug interactions and other interactions
There were no new findings from the studies included in this application. The data for orlistat 60 mg capsules are likely to be applicable to Orlistat 27 mg chewable tablets.

Post marketing experience/Risk management
No post-marketing data are available for the Orlistat 27 mg Chewable Tablets.

However, there is some experience of use with alli 60 mg capsules as a non-prescription medicine. There is also a very large body of post-marketing safety data for orlistat 120 mg capsules (generally only available on prescription).

Orlistat 120 mg was first approved for marketing in the EU in 1998. It is currently approved in over 100 countries and it is estimated that approximately 33 million have been treated with the product (to July 2008).

Orlistat 60 mg capsules was granted a licence for use as a non-prescription medicine in the EU in January 2009 and has been launched in 25 markets to date. To the end of May 2009, the estimated exposure to orlistat 60 mg capsules as a non-prescription product is approximately 6 million persons, with most of the usage in the US. Calculations are based on a median duration of treatment of 77.5 days and an estimated daily dose of 2.44 capsules per day.

2.6.1. Conclusions on the clinical safety

Adverse events reported with orlistat and considered to be causally related to orlistat are mainly gastrointestinal and relate to the pharmacodynamic effect of orlistat on fat absorption. This leads to diarrhoea, flatulence and oily/fatty stools, which correlate with the fat content of the diet.

A secondary effect of the action of orlistat is to affect the absorption of lipid soluble drugs and vitamins. This may lead to a loss of effect of the former and a deficiency in the latter. From the post-marketing database there do not appear to be reports of adverse events attributable to such interactions or deficiencies so they remain a theoretical possibility.

Regarding the current application, the safety of Orlistat 27mg chewable tablet has largely not been investigated as no clinical studies have been performed. This is further compounded by the recent FDA communication (24 August 2009) regarding 32 reports of serious liver injury including 6 cases of liver failure associated with orlistat treatment. This would suggest that systemic bioavailability of orlistat may not be insignificant, particularly in this case as the blood levels of the chewable tablet have been shown to higher compared with the capsule formulation for a given dose. However as a lower dose, Orlistat 27mg chewable tablet would be expected to give rise to fewer adverse events than the currently licensed doses.

2.7. Pharmacovigilance

Pharmacovigilance system
In the application, the MAH referred to the Detailed Description of the Pharmacovigilance System (version dated May 2009) as updated in the variation EMEA/H/C/000854/IA/0020 submitted to the Agency on 22 April 2010, which received a positive notification on 18 May 2010.
The CHMP considered that the Pharmacovigilance system as described by the applicant (version 1) fulfils the legislative requirements.

Risk Management Plan
The MAH did not submit an update to the risk management plan (RMP) in this extension application for the addition of new strength and pharmaceutical form (alli 27 mg chewable tablets). Despite this is a new formulation, it was not considered as a significant change in the presentation. Furthermore, there is no change to the already approved indication or posology, frequency or duration of use. The safety profile is not different from the current formulation. The differences in formulation and dosage were not considered to alter the pharmacokinetics and pharmacodynamics of the reference product. In this context, The MAH did not consider these were significant changes to the marketing authorization and therefore no update of the currently agreed EU-RMP (version 5.0) was necessary.

However, in view of the possible higher blood levels observed with this new formulation, and the possible higher rate of off label use, the CHMP has requested the MAH that an updated Risk Management Plan should be agreed before the launch of this new presentation.

User consultation
The justification for not performing another consultation with target a patient was accepted by the CHMP.

2.8. Benefit Risk Balance

Benefits
Orlistat taken with a hypocaloric diet has been shown to be effective in reducing weight.

The majority of patients taking orlistat are able to adhere to the low-calorie, low-fat diet and a third of patients increased the amount of exercise taken. In such patients orlistat may help obese patients to adopt and adhere to a healthier life-style.

The quality of this new strength and pharmaceutical form 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.

Risks
The safety profile of orlistat is well documented as orlistat 120 mg has been on the market since 1998. The safety profile of Orlistat 60 mg is largely similar to that of 120 mg and the most common side effects, which are dose related, involve the gastrointestinal tract. There are theoretical pharmacodynamic interactions with other fat-soluble drugs and these are addressed in the product information.

There is limited safety data for the new 27 mg chewable tablet presentation. However as a lower dose, it would be expected to give rise to fewer adverse events than the currently licensed doses.

In view of the emerging safety issues which may be associated with the change in formulation in particular the higher blood levels observed with the chewable tablet, and the possible higher rate of off label use, the CHMP has requested the MAH that an updated Risk Management Plan should be submitted and agreed before the launch of this new presentation.

Balance
Orlistat 27mg chewable tablet can aid to weight reduction and encouragement to a healthier life-style. Sufficient clinical information has been submitted to demonstrate that Orlistat 27mg chewable tablet is equivalent to (or interchangeable with) Orlistat 60mg capsule.

Conclusions
The overall B/R of Orlistat 27mg chewable tablet is positive.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of the new strength and pharmaceutical form (alli 27 mg chewable tablets) 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 was favourable and therefore recommended the granting of the marketing authorisation.