



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 February 2012
EMA/253013/2012
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report for Megestrol Alkermes

International non-proprietary name: Megestrol

Procedure no. EMEA/H/C/2177

Applicant: Alkermes Pharma Ireland Ltd (formerly: Elan Pharma International Ltd)

This Withdrawal Public Assessment Report is based on the CHMP Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.
This should be read in conjunction with the "Question and Answer" document on withdrawal of the application.



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LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
AE	Adverse event
ASM	Active Substance Manufacturer
AUC	Area under the concentration-time curve
AUC ₀₋₂₄	Area under the concentration-time curve to 24 hours
AUC _{0-t}	Area under the concentration-time curve to time t
AUC _∞	Area under the concentration-time curve to infinity
BA	Bioavailability
BE	Bioequivalence
BMS	Bristol Myers Squibb
C _{avg}	Average plasma concentration
C _{max}	Maximum plasma concentration
C _{min}	Minimum plasma concentration
IL	Interleukin
ITT	Intention to treat
MA	Megestrol acetate
Megace (BMS)	Megace [®] Oral Suspension (Bristol Myers Squibb) 40mg/ml
PD	Pharmacodynamic
PK	Pharmacokinetic
PS	Performance status
QOL	Quality of Life
SAE	Serious adverse event
SOC	System organ class
SS	Steady state
SSA	Subjective sense of appetite
T _{max}	Time to maximum plasma concentration
TNF-α	Tumour Necrosis Factor-α

1 RECOMMENDATION

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the application for Megestrol Acetate, in the treatment of anorexia, cachexia, or an unexplained significant weight loss in AIDS and oncology patients, is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of outstanding issues (Section III).

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Quality

Comparable data from batches on microscopic imaging of particle morphology and particle size distribution should be provided to demonstrate the consistency of the proposed manufacturing process between the development and commercial manufacturing sites should be demonstrated.

Particle size is the parameter that controls the function of the product and should be adequately controlled, especially as it also substitutes the test for dissolution in the finished product specification. The particle size distribution should be controlled using D_{10} , D_{50} and D_{90} in addition to the D_{mean} in the manufacturing process and finished product. Proposed upper and lower limits should be based on batch and stability data from the development/clinical batches. Wider limits than those observed in the currently presented data should be justified based on further data.

Clinical: Efficacy and Safety

Given that the new formulation results in a higher bioavailability, the applicant tried to develop a strength that would lead to similar exposure to the 800 mg strength of the reference product. However, the exposure after the 625 mg did not meet the acceptance criteria normally used to establish bioequivalence. Hence, the applicant has failed to show comparable exposure following administration of their formulation and the reference.

Given the failure to establish similar exposure, efficacy in weight-losing AIDS and cancer patients has not been demonstrated with the applicant's 625mg dose formulation.

Questions to be posed to additional experts

N/A

Inspection issues

None

2 EXECUTIVE SUMMARY

2.1 Problem statement

Megestrol acetate is a well known and established progestogen dosed in humans for over 20 years as either a tablet or an oral suspension. It was introduced in the EU as a palliative agent in oncology, typically in endometrial and breast cancer in strengths of 40 mg and 160 mg tablets with recommended doses ranging from 40 mg to 320 mg in divided doses.

The drug substance was subsequently introduced in various territories (mid 1990s) in suspension form (40mg/mL) for the treatment of anorexia and/or cachexia disorders, usually associated with AIDS and oncology patients. The product is available in a number of territories including Ireland and Spain as a viscous oily suspension requiring doses of 800 mg (20 mL/day). In either tablet or oily suspension form, the high doses of reference product place a considerable treatment burden on the patient, additional to all the other pharmaceutical therapies they are likely to be receiving given the advanced state of their oncology or AIDS illness, and bearing in mind that the patient is already anorectic and/or cachectic.

2.2 About the product

The Applicant has developed an oral suspension dosage form in which the particle size of the active substance megestrol acetate has been substantially reduced. This causes increased surface area per unit mass of the particles which increases water solubility, rate of in vivo absorption and overall bioavailability. The particle size reduction is also meant to reduce the variability in absorption between fed and fasted states. The resultant formulation, compared with reference product Megace from Bristol-Myers Squibb, affords a reduced quantity of drug substance (625 mg versus 800 mg) at a reduced volume (5 ml versus 20 ml) without the requirement to co-administer with food to obtain optimal beneficial effects.

The product under review has been marketed in the USA since 2005 under the trade name Megace ES.

The product is intended for the treatment of anorexia, cachexia, or an unexplained significant weight loss in AIDS and oncology patients at a recommended adult daily dose of 625 mg (5 ml) once daily. The product is not recommended for use in children.

2.3 The development programme/compliance with CHMP guidance/scientific advice

No CHMP scientific advice has been sought for the development of this product.

The clinical development programme conducted to GCP for Megestrol Alkermes

- Literature as the basis for efficacy/safety data and development of risk/benefit argument, supplemented by
- Ten PK studies (single-dose, multiple doses, fasted/fed) including:
 - Five studies conducted as part of the formulation selection process.
 - Two pivotal BE studies conducted (single dose and food effect study) comparing Megestrol Alkermes with Megace 40mg/mL (BMS) confirming BE at a lower total daily dose and the absence of a food effect.
 - Two studies (single dose fasted and fed) were conducted by Elan Drug Technologies (prior to the merger with Alkermes) to demonstrate the bioequivalence of the EU and US reference products (MA-BMS 40mg/mL oral suspensions).
 - One fasted/fed study comparing Megestrol Alkermes with that of Megace (BMS-EU market).
- Two in vitro studies examining the effect of Megestrol Alkermes on cytochrome P450 induction or inhibition.
- One drug interaction study with Indinavir (reduction in indinavir exposure).

- One clinical efficacy study (including PK evaluation) in AIDS wasting cachexia patients.

The clinical development programme relies largely on the historic demonstration of safety and efficacy of megestrol acetate, and does not replicate previous clinical efficacy evaluations, consistent with its filing as a hybrid application.

2.4 General comments on compliance with GMP, GLP, GCP

GLP: Since a literature review has been presented for a large proportion of the non-clinical aspects, it cannot be verified whether the studies cited were in compliance with the GLP regulations; however, it is assumed that the studies conducted by the originator would have been conducted in compliance with the standards prevailing at the time.

GCP: The CHMP has been assured that all clinical studies were performed to acceptable standards of GCP and agreed ethical principles.

GMP: The CHMP has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the CHMP has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

2.5 Type of application and other comments on the submitted dossier

- Legal basis

The legal basis for this application is Article 10(3) of Directive 2001/83/EC; i.e. a hybrid application.

The reference product that has been authorised in the EEA for > 10 years is MEGACE 40 mg/ml Oral Suspension, licensed to Bristol-Myers Squibb Holdings Ltd by the Irish medicines Board on 10.12.1998 (PA 48/27/3). The Spanish product is named as European reference product: Maygace Altas Dosis, MA number 60.783, Bristol-Myers Squibb, 1.7.1996. Reference product from Ireland has been used in the BE study. The reference product is currently authorised in 8 EU member states (Czech Republic, Hungary, Ireland, Lithuania, Portugal, Poland, Slovenia and Spain).

3 SCIENTIFIC OVERVIEW AND DISCUSSION

3.1 Quality aspects

Drug substance

The active substance megestrol acetate was sourced from two ASMs during development. Only one API ASM will be used in commercial product and the other ASM was deleted from the license application at Day 121. The API is described in the PhEur. A CEP for micronised material is provided for API and the FPM controls the active substance in line with the PhEur & CEP requirements for megestrol acetate. The analytical methods are mostly compendial or those annexed to the CEP. Acceptable batch and stability data are provided and the API has a re-test period of 5 years.

Drug product

The finished product is an oral suspension containing 125 mg/ml of megestrol acetate and packaged in HDPE bottles with PP closures available in three different pack sizes. The 5 ml pack size is a single dose unit while the 25 ml and 150 ml are multiple unit dose configurations.

The physico-chemical properties of the finished product and information on particle size distribution (d10, d50 and d90) have been provided. However, the provided response with regards to routine control of particle size during manufacture and in the finished product is not considered to be acceptable and the major objection raised at D120 remains.

The manufacturing process was transferred from co-operation sites. While data on the particle size and shape has been provided for the commercial site, these results should be compared to the batches manufactured at the development site; the major objection raised at D120 remains therefore. Data for batches manufactured at both sites are provided throughout section 3.2.P; assurance regarding the control of the manufacturing process has been provided. The manufacturing process is validated on commercial scale on 3 bulk batches and filled into the 3 different bottle sizes 150 ml, 5 ml and 25 ml.

The excipients are all compendial apart from the flavouring agents.

The finished product specification limits are identical at release and during shelf-life for active substance assay and related substances indicating low/no degradation for the active substance. The specification has been updated with regards to particle size control, impurities and sodium benzoate shelf-life limits. Particle size control limits should be tightened further. Batch data are provided and are acceptable.

The HDPE bottle with polypropylene closure proposed for the market has been properly described. The materials comply with directive 2002/72/EC.

Stability data are provided covering the proposed shelf-life of the product (36 months), bulk suspension, in-use testing (30 days) and photostability. The submitted stability data support the proposed shelf-life/storage condition: "3 years /no special precautions for storage" when the product is stored in the container proposed for the market.

Conclusions on the chemical, pharmaceutical and biological aspects

The data are generally well presented. Some points for clarification remain and the questions related to particle size distribution are still considered to be major objections. It is expected that the applicant will be able to resolve these points.

3.2 Non clinical aspects

Megestrol acetate is a widely used, well-known active substance and the non-clinical overview was therefore primarily based upon a literature review, which is appropriate. The applicant has also summarised data from a pharmacokinetic study (dog) and a 3-month repeated-dose study (rat) to demonstrate how the absorption and toxicity profiles for the proposed formulation (125 mg/mL) compare with those currently marketed within the EU (40 mg/mL). In addition, the applicant has presented data from studies which investigated the CYP inhibition/induction potential of megestrol acetate.

The non-clinical overview has been written by an adequately qualified consultant. The report (dated November 2009) refers to 49 publications up to the year 2007. The pharmacology, pharmacokinetics and toxicology aspects of this report were considered adequate. Although, a number of deficiencies were noted, as megestrol acetate is a marketed drug with an established pharmacological, pharmacokinetic and toxicological profile, updates to correct these deficiencies are not considered to be essential. The applicant has elaborated upon the genotoxicity data available for megestrol acetate; however the SmPC should be updated to reflect these findings.

With the exception of Natural and Artificial Lemon flavouring and Artificial Lime flavouring, which are controlled to in-house specifications, all remaining excipients are of pharmacopoeial grade and there are no issues in respect of their inclusion in the proposed product.

Based on a maximum dose of 625 mg per day, the proposed limit for Impurity A within the drug substance exceeds the limit of 0.15% as specified by ICH Q3A(R2). However, the active substance is compendial; hence, the proposed level of the impurity is considered qualified from a toxicological point of view. The proposed limits for the residual solvents within the drug substance comply with the limits outlined in ICH Q3C(R5). In addition, the impurities within the drug product are in line with the limits outlined in ICH Q3B(R2).

The proposed container closure system consists of a high-density polyethylene (HDPE), round, white bottle and polypropylene cap which both comply with the Commission Directive 2002/72/EC, as amended. The components of the closed container system meet Ph Eur requirements and/or the 2002/72/EC Directive.

The applicant has conducted phase I of the environmental risk assessment. The applicant has provided a calculation for the predicted environmental concentration based on the proposed clinical dose of 625 mg per day and has refined the F_{pen}. Refinement of the F_{pen} on the basis of forecast data is not acceptable. The calculations provided suggest that the predicted environmental concentration is below the threshold of 0.01 µg/L. However, the drug substance is a hormone and is therefore likely to act as an endocrine disruptor. Hence, the absence of an environmental risk assessment is not justified; a full environmental risk assessment is required.

3.3 Clinical aspects

Pharmacokinetics

As a hybrid application a number of bioequivalence/bioavailability studies have been provided by the applicant. Most have been conducted with a US sourced comparator, Megace.

Study 02097 examined the bioequivalence of 3 doses of the test formulation (150, 250 and 450mg/day versus 800mg of Megace in fasted patients. This showed that both formulations were poorly absorbed in fasted patients and that none of the 3 test doses were bioequivalent to Megace.

Study 02098 examined the same doses but in fed patients. This showed greatly increased absorption of megestrol, especially for the Megace formulation. Again, none of the test doses were bioequivalent and all fell under the results for Megace.

Study 30146 examined the bioequivalence of a 375mg/day test formulation versus 800mg of Megace in fasted patients. This dose was chosen from study 02098, although it is not quite clear why as the 450mg/day dose ranked under the 800mg dose of Megace. This study showed, as expected, that the two formulations were not bioequivalent and that a significant fasting effect was seen again.

Study 30147 examined the same doses but in fed patients. Again, as expected, bioequivalence was not shown and exposure appeared to be under half that of Megace.

Study 30421 examined the bioequivalence of 3 doses of the test formulation (575, 625 and 675mg/day versus 800mg of Megace in fed patients. This study demonstrated that the two higher doses (625 and 675mg/day) were bioequivalent to the 800mg dose of Megace.

Study 30422 looked at the differences in bioavailability in fed and fasting subjects given 675mg dose of the test formulation. It showed significantly lower absorption in fasted patients, 40% in AUC and 50% in C_{max}.

Study 100.1.C.003 looked at the differences in bioavailability in fed and fasting subjects given 625mg dose of the test formulation. It showed significantly lower absorption in fasted patients, 35% in AUC and 47% in Cmax.

Study 90278 looked at the bioequivalence between US and EU sourced Megace in fasted subjects, in an attempt to bridge the US comparator data for the EU application. This showed bioequivalence, however the EU SPC states that Megace must be taken with food.

Study 90279 looked at the bioequivalence between US and EU sourced Megace in fed subjects, in an attempt to bridge the US comparator data for the EU application. This showed bioequivalence.

Study 100121 examined the bioequivalence of a 625mg/day dose of the test formulation versus EU reference Megace in fed and fasted individuals- the only trial to do so. As expected a large food effect was seen and bioequivalence was not shown in fasted patients. In fed patients bioequivalence was also not shown, as the lower 90% CI for AUC₀₋₇₂ fell just below the 80% threshold.

Of note all of these studies show results of a similar pattern, with a high Cmax for the applicant's formulation, often above 100% of that of Megace and then a much lower AUC result. This suggests that, although at its peak the applicant's formulation causes higher amounts of absorption, that over the total absorption time, less is actually absorbed.

The applicant collected PK data in patients with AIDS related wasting in a separate study, study 002 but did not analyse the data formally. It did show that trough concentrations of the lower test dose used (575mg/day) were very similar to those of Megace.

Possible interactions have been well covered, with an in vitro experiment (272-1052-01) to determine the effects of megestrol on CYP450 isoforms, in which little of concern was seen. An in vivo study (1053-02) looking at the suspected interaction between megestrol and indinavir. This effect was confirmed in the experiment. There was also comprehensive discussion of the literature data on possible interactions.

Pharmacodynamics

Whilst its exact mode of action is not understood; the efficacy of megestrol in AIDS and cancer related wasting is proven and it has been in clinical use for some time. The possible mechanisms given (as an anticytokine, appetite promoter and causing metabolic alterations) are biologically plausible. The majority of its adverse events are related to the fact that it is a steroid and therefore these are well understood and characterised. However, the difficulty in showing bioequivalence in the studies above, as well as the AUC and Cmax differences and the efficacy results of study 002 do raise significant concerns that the applicant's formulation has not just altered the pharmacokinetics but also the pharmacodynamics.

Conclusions on clinical pharmacology

The applicant has not established bioequivalence for its formulation when compared to Megace from an EU source. However, given the differences in the formulation this may be expected and it may be the case that a bioequivalence approach may not be correct for this type of formulation. The critical question is whether these differences in pharmacokinetics reflect to differences in the safety and efficacy profile compared to the reference. The data from studies with a US comparator that show bioequivalence, whilst supportive do not provide direct data for the EU application. There are also indications that although Cmax is high, the overall absorption of a single dose is actually lower than the reference and this will need to be addressed. Whilst the applicant has explained the food

differences between their formulation and the reference, their assertion that they have a minimal food effect is not accepted.

Whilst the mechanism of action is not fully understood, the efficacy of megestrol is well established. However, there are enough pharmacokinetic and efficacy differences from the studies presented using the applicant's formulation that a more in depth discussion of the pharmacodynamics of their formulation is required.

Clinical Efficacy

AIDS

Two placebo-controlled randomized studies from the U.S. have been enclosed to argue for efficacy on weight and well-being by supplementation with MA in AIDS patients with the anorexia-cachexia syndrome. Both studies demonstrated superior efficacy of MA, 800 mg/day compared with PL on weight. A weight increase, mainly driven by body fat accumulation, is supported by within-group results from 2 active-controlled trials and one small open pilot study that compared Megestrol Alkermes with Megace. Weight increases has differed somewhat between studies, however have been in the range 2.5-5 kg over 2-3 months therapy.

A moderate weight increase may not in itself be beneficial to the patient, unless it is associated with other beneficial effects, such as appetite improvement, better survival, improved tolerance to treatment or an increased quality of life. Both placebo-controlled studies also demonstrated that MA to some extent may benefit general well-being and appetite; however non-validated questionnaires were used to measure these variables. Better survival and improved tolerance to treatment with MA have not been examined adequately. Although the studies scored relatively high on the JADAD-scale, both have several methodological weaknesses, apart from the inherent one with this patient population of large drop-out rates. Lastly, the Cochrane systematic review finds that there are too few studies to determine if MA compared to placebo has an influence on weight, appetite or quality of life. The indication is very limited after the introduction of Highly Active Anti-Retroviral Therapy (HAART) for HIV infection and it is not likely that more recent clinical data will become available.

The pilot efficacy study (study 002) was performed by the applicant. However, it has a number of issues. It enrolled 63 patients with the objective of exploring weight gain in adult HIV-positive subjects who have weight loss associated with AIDS-related wasting (anorexia/cachexia) in the first 12 weeks of treatment with either megestrol acetate oral suspension (575mg/day) or Megace (800mg/day). The study showed that for weight gain and body mass that the 575mg/day dose of the applicant's formulation was statistically significantly better than Megace. This raises a significant concern as this was not the dose studied in the PK programme and chosen for development. It is not clear why the sponsor chose a different dose for the clinical study than the one identified from the pharmacokinetic programme as most similar to the reference. Furthermore, the only limited conclusions can be made on the comparative efficacy and safety of the proposed product to the reference due to the small sample size and lack of blinding.

Cancer

Six placebo-controlled randomized studies have been presented on the efficacy of MA in the treatment of the anorexia-cachexia syndrome in cancer, 4 studies including non-hormone-pendent cancers, 1 study gastro-intestinal cancers and 1 study head-and-neck cancer patients. The daily dosage of MA varied between 160 mg and 1600 mg, and treatment duration varied from 2 weeks to 12 months. In 3 studies a benefit on weight with MA compared to placebo was demonstrated, while no effect on weight was observed in the 3 remaining studies. Many of the controlled studies (and 1 open study) also

included anthropometric variables, and they suggest that the increase in weight with MA is mainly caused by an increased fat mass. A minor to moderate but clinically relevant appetite stimulation was observed in 5 studies (1 study did not examine for appetite). Few studies have examined quality of life using validated instruments and in none of these studies has quality of life improved with MA. Food intake has been insufficiently examined in the presented studies. Survival was not improved in MA-treated patients. Further, a dose-finding randomized open study has been presented that demonstrated that maximum benefit on weight seemed to occur at a daily dosage of MA of 800 mg. JADAD-scores were 3-4, however studies had several methodological deficiencies.

The evidence for an improvement in weight and appetite in cancer patients treated with MA from the presented controlled studies is vague, however a well-conducted systematic Cochrane review and meta-analysis including all randomised, controlled trials (n=26), demonstrated an effect of MA compared to PL on weight gain and improved appetite in patients with cancer anorexia-cachexia.

The applicant did not perform any clinical dose ranging or efficacy studies on the strength and formulation of megestrol in this application.

The literature data provided covered the efficacy of megestrol in both AIDS and cancer related wasting, using both placebo and active control. One major meta-analysis of treatment in both cancer and AIDS related wasting included 32 trials with mixed results. It was felt that although there was evidence of efficacy in AIDS related wasting, that there was not enough to fully support it. However, efficacy in cancer related wasting was proven, in studies against both active and placebo comparators. The studies in AIDS related wasting all showed significant improvements in weight, appetite, caloric intake and lean body mass. In studies in cancer related wasting, similar results were found, with higher doses being more effective than lower doses in most cases.

Clinical Conclusion

The literature data confirms the general efficacy of megestrol in cancer related wasting. The evidence is less compelling in AIDS related wasting. However, there are significant concerns raised by their pilot study in AIDS wasting, although this is significantly flawed methodologically. The superior efficacy levels shown by 575mg/day of the applicant's formulation when compared to Megace raise the question whether the pharmacokinetics of the applicant's formulation relate to the efficacy in the same way it does for the reference product.

The applicant will therefore have to discuss the clinical implications of the pharmacokinetic differences seen between the test and reference formulations and more specifically how their dose chosen relates to the efficacy and safety of their reference product.

Statistical Conclusion

Study 100121 has failed to demonstrate formally that the new test product is bioequivalent to Megace in either the fed or fasted state. However the relevance of this finding depends on the availability of relevant clinical data providing evidence of efficacy and safety.

It is accepted that Study 002 was originally planned as a pilot study and therefore no formal statistical methods were pre-specified and no attempt was made to choose a sample size which would provide sufficient power for statistical analyses. However presentation of p-values from the Wilcoxon Rank Sum test in the synoptic report cannot be accepted as there is no justification why a nonparametric test was appropriate in place of ANCOVA which would usually be used for this type of continuous variable. Therefore the data should be reanalysed using an appropriate ANCOVA model. Further statistical details including a full description of patient disposition and the handling of missing data would be necessary before any assessment of the robustness of the results of any statistical analysis can be made.

Conclusions on clinical efficacy

AIDS

There is not sufficient evidence to support an indication for the applicant's formulation for an increase in weight and appetite in patients with AIDS-related cancer anorexia-cachexia. There is also insufficient documentation for an effect on survival, improved tolerance to treatment or quality of life.

Cancer

MA in daily dosages of 800 mg administered for 3 months may increase (fat) weight and appetite in patients with cancer-related anorexia-cachexia. Megestrol Alkermes has not shown bioequivalence to MEGACE.

Clinical Safety

Megestrol has been used clinically in this indication for some time and shows good safety and tolerability, as shown in the literature data. However, as bioequivalence is not demonstrated, the applicant will have to discuss how this data relates to their formulation.

The clinical study program exposed a total of 327 healthy subjects and patients to varying strengths of the applicant's formulation, as would be expected for a hybrid application. A total of 61 healthy volunteers were exposed to the 625mg/day dose that has been applied for in this application. Most of this exposure was single dose in the bioavailability studies, with study 30054 exposing for a maximum of 14 days and study 002 for a maximum of 12 weeks. Neither used the 625mg/day dose.

The adverse event profile in the bioavailability studies was relatively modest, with few events. These were only presented as summaries. The events were evenly spread across the active treatments, with the applicant's formulation not showing any significantly higher levels of adverse events when compared to Megestrol. Most events were non-serious and only 10 patients discontinued due to adverse events. There were no deaths. Most of the adverse events were either due to procedures for the study (venipuncture etc) or gastrointestinal in nature.

In the single efficacy study in patients with AIDS related wasting more adverse events were recorded, but again the rates were not of concern. Almost all patients suffered an adverse event, most of which were said to be related to study drug. However, most were non-serious in nature and only 5 patients discontinued due to adverse events. The adverse events were split evenly between the applicant's formulation and Megace, with no untoward events seen. Three patients died who had participated in the study were all from the Megace arm. One died during the study of unknown causes and 2 over 60 days after the study, one of an infection and the other of progression of their AIDS.

The laboratory changes seen in all studies were mainly mild and transient and equally spread amongst the active treatments. Changes in cortisol were seen, as expected with long term steroid treatment but these stopped on withdrawal of treatment. Transient changes in blood counts were also seen, mainly with very mild and clinically insignificant anaemias.

The applicant presented post marketing experience with their formulation, as it is licensed in the US. From July 2005 to July 2008, 265 adverse events were reported. General disorders were most common (eg ineffective drug and pharmaceutical product complaint), then vascular disorders (deep vein thrombosis- a well known side effect of megestrol), then gastrointestinal complaints (distension, diarrhoea, constipation and flatulence) and finally nervous system (dysgeusia). These events are in line with what is expected with megestrol and the conditions which it treats.

The literature safety data from the studies discussed in the efficacy section show a similar adverse event profile to the post marketing experience and the studies performed by the applicant. Patients

were exposed to varying doses, from 160mg to 1600mg a day and the adverse events recorded were mainly transient and within what are expected of megestrol.

Probable drug-induced AEs that are related to its hormonal effects are oedema, impotence (in men), thrombo-embolism (including deep venous thrombosis), hypertension, hyperglycaemia and hypocorticism. Calculations from the included studies suggest the following frequencies in the total patient population exposed to MA and the population exposed to the proposed dosage range, respectively; thrombo-embolism: 2% and 4%; impotence: 11% and 12%; and oedema: 9% and 10%. Although these frequencies are high, it is recognized that weight-losing cancer and AIDS patients have a higher risk of these conditions irrespective of treatment with MA. MA suppresses cortisol levels and may in few cases induce Cushing disease. An effect on glucose metabolism and blood pressure has not been adequately studied. There does not seem to make any difference in deaths between MA treated and PL treated patients and MA treatment does not seem to influence survival.

In the Cochrane review Impotence in men, oedema of the lower limbs, deep vein thrombosis and gastro-intestinal intolerance were the most frequently reported AE. None of the differences between treatment and PL groups were found to be statistically significant, except for the occurrence of oedema, which occurred with greater frequency in patients receiving MA.

Discussion on clinical safety

The safety profile of megestrol is well known, and the data presented here supports that the applicant's formulation is likely to have the same profile. However, without showing bioequivalence, it is difficult to bridge this data across to the EU application and the applicant will therefore have to discuss this. The adverse event profile is as expected for a steroid, used at such doses and for such lengths of time in a patient set who are prone to adverse events, some of which may be serious.

The differences in efficacy of the applicant's formulation in study 002, when compared to the reference, raise concerns about the relation of the pharmacokinetics of their formulation with its pharmacodynamic effects. The applicant will therefore have to discuss the clinical implications of the pharmacokinetic differences seen between the test and reference formulations and more specifically how their dose chosen relates to the efficacy and safety of their reference product.

Conclusions on clinical safety

Most AEs have been mild or moderate. However, based on the enclosed clinical studies, there is a high occurrence of thrombo-embolism, including deep venous thrombosis ($\approx 4\%$), oedema ($\approx 10\%$) and impotence ($\approx 12\%$) in patients treated with high dose MA (>800 mg/day). Although these AEs may be explained by the hormonal effects of MA, it must also be recognized that the neoplastic disease in patients with the anorexia-cachexia syndrome by itself increases the risk of such events. Low cortisol levels and adrenal insufficiency are other AEs from treatment with MA, however its clinical significance is not fully known.

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system as described by the Applicant has the deficiencies as detailed in the list of questions.

Provided that the deficiencies are rectified prior to the Applicant placing the medicinal product on the market, the CHMP may consider that the pharmacovigilance system will fulfil the requirements. The Applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

Risk management plan

The Applicant has updated the RMP in accordance with some of the previous requests, however the RMP has not been updated consistently and requires further amendment before approval. The following specific points should be addressed by the Applicant:

- The Applicant was requested to include a summary of postmarketing ADRs that have been observed to date with the preparation available in the US, however a full list of individual ADRs has been provided in the RMP, and the Applicant is requested to summarise this information as originally requested.
- The Applicant is again requested to consider whether any of the serious recognised adverse events in the US product information warrant inclusion in the RMP as important identified risks.
- Further discussion (and consideration as to inclusion in the RMP as an important identified or potential risk) is requested in relation to the risk of cardiac events (in particular cardiac failure); furthermore, lack of information on use in patients with cardiac impairment should be considered important missing information and described in the RMP as such.
- 'Tumour flare' is also requested to be included as an important identified risk throughout the RMP.
- The Applicant should remove all references to risks of sucrose intolerance/hypersensitivity from the RMP.
- The Applicant should consider whether a) clinical study in renal impairment, and b) an exposure registry for patients, should be performed as additional pharmacovigilance measures to attempt to address the important missing information. If considered that they are not warranted, a discussion should be provided to justify why.

The list of important potential and identified risks and missing information is not consistent throughout the document. The Applicant must ensure that all sections of the RMP are consistent with regard to important identified and potential risks and important missing information; these should be clearly differentiated in the RMP. Furthermore, section 2.3 (detailed action plan for specific safety concerns) at present refers to labelling in the SmPC/PIL and provision of a measuring spoon, however, these are not Pharmacovigilance measures. This section should be revised to focus on what Pharmacovigilance measures the Applicant proposes to monitor/collect further data on these risks, and to remove references to routine Risk Minimisation Measures such as labelling and additional Risk Minimisation measures such as provision of a measuring spoon.

In addition, the Applicant is requested to make an estimate, if possible, of the magnitude of off-label use both in adults and in children. It is not endorsed to have the sales force educate prescribers of the age restriction without presenting any material intended to be used as educational material for assessment first. Pending the magnitude of off-label use, the Applicant is asked to consider if off-label use is to be considered a safety concern.

4 ORPHAN MEDICINAL PRODUCTS

N/A

5 BENEFIT RISK ASSESSMENT

Benefits

Megestrol has been shown, through the bibliographic data presented to increase body weight in patients with cancer related wasting. Although this effect may not be large it is clinically significant. However, limited data is presented on the effects on quality of life outcomes and the data is unconvincing on AIDS related wasting.

Beneficial effects

A good body of clinical data has been presented for the efficacy in Cancer related wasting that shows that an increase in weight, appetite, caloric intake and lean body mass is achieved. This has been found in studies mainly using a dose of 800mg a day. The weight increase is not caused by increased retention of water as previously had been expected.

Uncertainty in the knowledge about the beneficial effects

The lack of bioequivalence shown in study 100121 means that we cannot bridge across to the efficacy and safety profile of the reference medicine and also the bibliographic data presented for it. Therefore we currently do not know what level of efficacy would be seen for the applicant's formulation. Little was presented on the effects of megestrol on the quality of life for the patients treated and the results seen in study 002 also raise significant questions over the efficacy of the applicant's formulation and also the dose chosen, as the lower dose used (575mg vs 625mg) would seem to have greater efficacy in AIDS related wasting than the reference. However, such a small, flawed pilot trial is difficult to draw conclusions from.

The body of evidence in AIDS related wasting is smaller, with few studies and small patient populations. The applicant's own efficacy study in AIDS related wasting (using a different dose of megestrol) did show efficacy with regards weight gain but as a small, pilot study its usefulness is limited.

Risks

Megestrol is known to increase the risk of thromboembolic events, adrenal insufficiency, oedema and can cause male impotence. These are explained by the hormonal effects of megestrol (which is also used to treat certain hormone sensitive tumours) but can also be due to the patient's underlying disease. There are also concerns that limited or no data has been presented in renal and hepatic impairment.

Unfavourable effects

The most common side effects that are clinically significant were thromboembolic events (mainly DVT), oedema and male impotence. There were also cases of adrenal insufficiency recorded. However, no unexpected adverse events were seen and the profile did fit in with what would be expected for such a medicine.

Uncertainty in the knowledge about the unfavourable effects

The lack of bioequivalence shown in study 100121 means that we cannot bridge across to the efficacy and safety profile of the reference medicine and also the bibliographic data presented for it. Therefore

we currently do not know what safety profile would be seen for the applicant's formulation. In view of this the body of data collected in the studies presented is not enough to characterise the overall safety profile of this formulation.

Balance

The efficacy profile in the bibliographic data shows efficacy in cancer related wasting. The data in AIDS related wasting is unconvincing. It also confirms the expected safety profile for megestrol. However, the lack of bioequivalence to the reference product means that the efficacy and safety of the applicant's formulation is currently unknown.

Importance of favourable and unfavourable effects

Despite the favourable efficacy profile for cancer related wasting in the bibliographic data and the expected adverse event profile from the data presented, the uncertainty of how this relates to the applicant's formulation meant that currently the favourable and unfavourable effects are not understood.

Benefit-risk balance

The benefit risk balance is still negative for this application as because of the lack of bioequivalence the efficacy and safety profile for this formulation is not understood. It would seem from the data presented that the formulation does not have the level of systemic exposure expected by the applicant.

5.1 Conclusions

The overall Benefit-Risk for the application for Megestrol Alkermes is still considered negative due to the lack of bioequivalence. It is therefore not clear how this is reflected in the efficacy and safety profile of the product compared to the reference.