European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT
FOR
orBec

International Nonproprietary Name:
Beclomethasone dipropionate

Procedure No. EMEA/H/C/803

Applicant: DOR BIOPHARMA UK Ltd.[1]

Day 180 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 the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

[1] The Marketing Authorisation Application for orBec was initially made by Voisin Consulting S.A.R.L. The applicant was changed to DOR BIOPHARMA UK Ltd. during the procedure.

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LIST OF ABBREVIATIONS

BAL	Broncho-Alveolar Fluid
BDP	Beclomethasone dipropionate
17-BMP	Beclomethasone 17-monopropionate (active metabolite)
21-BMP	Beclomethasone 21-monopropionate (inactive metabolite)
BOH	Beclomethasone
CTD	Common Technical Document
EC	Enteric coated
ED_{50}	Dose causing 50% of maximal effect
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practices
GvHD	Graft versus Host Disease
HED	Human Equivalent Dose
IC_{50}	Concentration causing 50% inhibition
IL	Interleukin
i.p.	Intraperitoneal
IR	Immediate release
i.v.	Intravenous
LAR	Late Asthmatic Response
Ph. Eur.	European Pharmacopoeia
s.c.	Subcutaneous

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for orBec, an orphan medicinal product in the treatment of gastrointestinal Graft-versus-Host Disease (GvHD), in conjunction with a brief course of prednisone

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the list of outstanding issues (Section VI).

Proposal for Questions to be posed to additional Experts
NA

Inspection issues
NA

II. EXECUTIVE SUMMARY

II.1 Problem statement

GvHD is a serious and potentially fatal condition that results when T-cells from a usually allogeneic tissue or organ transplant, particularly from a bone marrow transplant, react immunologically against the recipient's antigens resulting in cell and tissue damage, especially to the skin, gastrointestinal tract, and liver, and associated with symptoms that include skin rash, fever, diarrhoea, liver dysfunction, abdominal pain, and anorexia.

Gastrointestinal involvement represents a prominent feature of GvHD. Treatment for gastrointestinal GvHD is usually managed by using immunosuppressive agents. Unfortunately such agents, including corticosteroids, have serious adverse effects when administered systemically.

The medical rationale for orBec is to maintain a high local glucocorticoid concentration in the intestine, whilst achieving a lower systemic exposure.

II.2 About the product

orBec is supplied as two separate drug products: a 1 mg immediate release (IR) tablet and a 1 mg enteric coated (EC) gastro-resistant tablet, administered in combination. Hence the pharmaceutical forms are tablet and gastro-resistant tablet.

The commercial primary container is a high-density polyethylene bottle containing 200 tablets of either the IR or the EC tablets. The total daily dose, 8 mg/day, is equally divided between the two forms. The rationale for using both dosage forms is to deliver BDP to both the proximal and distal portions of the gastrointestinal tract, with the objective of maximizing the efficacy in treating GvHD. orBec is to be administered during 50 days, after a brief course of prednisone, a systemic corticosteroid.

orBec is intended to be supplied under medical prescription and administered by medical practitioners in hospital facilities.

The recommended dosage regimen for orBec is 2 mg (1 mg IR tablet + 1 mg EC tablet) *per os quarter in die*. The treatment should be preceded by a 1 mg/kg/day prednisone treatment for 10 days.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

No formal scientific advice was sought from the CHMP; national scientific advice was given by Germany, France and UK in November 2005.

II.4 General comments on compliance with GMP, GLP, GCP

The majority of publications cited by the Applicant do not state whether the studies were conducted in compliance with GLP and many of these studies were made prior to 1979, i.e. before GLP regulations came into force. Thus, most studies are considered non-compliant. On the other hand, there is a considerable clinical experience in dermatological (eczema, psoriasis) and inhalatory (asthma) applications, rendering the lack of formal GLP compliance less important.

The clinical development program performed by DOR Biopharma has been carried out outside the European Union. The applicant certifies that all the clinical studies have been conducted in accordance with the Declaration of Helsinki, the ICH recommendations about Good Clinical Practice (ICH E6) and Directive 2001/20/EC.

II.5 Type of application and other comments on the submitted dossier

This application is made under Article 8.3 of Directive 2001/83/EC, as amended. That is a complete and independent application for an EU marketing authorisation through the centralised procedure with Dr Ljungberg acting as Rapporteur and Dr Yerro as Co-Rapporteur. The dossier is formatted according to the CTD standard.

Beclomethasone 17, 21-dipropionate (oral use) was granted orphan designation in the EU in March 2002 for the orphan indication "Treatment of intestinal graft-versus-host disease" (EU/3/02/093).

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Active substance
Beclomethasone dipropionate is a corticosteroid included in the Ph. Eur. A Certificate of Suitability of Monograph is submitted. Beclomethasone dipropionate is practically insoluble in water and essentially stable. The applicant adheres to the Ph. Eur. monograph plus the specifications of this CoS, residual solvents and particle size.

A 5 year re-test period is acceptable for the drug substance.

Medicinal Product
The drug product comprises immediate release (IR) 1 mg tablets and 1 mg enteric-coated (EC) tablets aiming at extending the duration of exposure to the drug substance. The two tablet types are packed in separate HDPE containers fitted with a child resistant polypropylene cap with a continuous screwthread and an induction seal liner that are co-packed in a cardboard box. The commercial drug product will be distributed as a unit of use package containing one bottle of 200 IR tablets and one bottle of 200 EC tablets.

The tablets have the same core composition and are identical except for the shape. No information has been provided regarding the choice of the coating systems and their effect on the local distribution over the intestine for this drug that is stated to have local action.

Dissolution data generated in 0.1 N hydrochloric acid and in pH 6.8 phosphate buffer containing 0.5% sodium lauryl sulphate (SLS) is provided for the EC tablets; and in 0.1 N hydrochloric acid (no information is provided regarding presence of SLS) and in the same phosphate buffer system as for the EC tablet is provided for the IR tablet. Thus, *in vitro* release data indicating at which pH the EC coated tablet starts to release the drug substance is missing, please refer also to the pharmacokinetic and clinical assessment.

The excipients chosen including those used for the gastro-resistant coating are well known and commonly used in this kind of tablets.

The drug substance is dissolved during the manufacture in order to ensure content uniformity. The drug substance is dissolved in the granulation fluid, thus particle size and polymorphic form is not critical. The manufacturing process of the drug product is a standard process where the key steps in manufacture are granulation, compression and film-coating (for the EC tablet). No validation data for the manufacturing process is planned post-approval.

The specification for the finished product includes tests for physical properties, identity, purity, dissolution, assay, uniformity of dosage units and microbiological purity. All analytical methods are described in a detailed manner and acceptable validated except for some details.

The description and choice of container is acceptable. Data from stability studies demonstrate adequate protection of the product.

In general the tablets are very stable. The stability studies have been carried out on clinical and registration batches in accordance to ICH Guidelines.

Although the documentation has been satisfactorily elaborated and justified in accordance with relevant guidelines, there are some issues requiring to be resolved.

III.2 Non clinical aspects

Pharmacology

The cited publications adequately demonstrate that BDP and its main metabolite (17-BMP) bind to the glucocorticoid receptor and have pronounced anti-inflammatory effects. The studies are mainly concerned with inflammatory response in the airways but there is no reason to suspect that the results should not be applicable to other locales, such as the gastro-intestinal tract.

The lack of studies in animal GvHD models and gastro-intestinal inflammation is a weakness. With the Day 120 LoQ the Applicant was requested to justify the lack of studies. In the Applicant responses to the Day 120 LoQ, the rationale to not perform studies on animal models of GvHD has been presented. The rationale presented by the Applicant is mainly that clinical evidence exists for the clinical potential of BDP in the treatment of inflammatory disorders of the gastrointestinal tract and that only the GVHD model in primates resembles human disease. The use of this model has several difficulties, like ethical and financial constraints and also technical difficulties. The explanation is accepted.

It must be stressed that there is no supportive non-clinical evidence for the proposed indication. Consequently, the indication must depend solely on clinical efficacy data and no mechanistic claims can be accepted in section 5.1 of the SPC.

BDP treatment suppressed endogenous cortisol production in dogs and horses, which is unsurprising. Besides the usual caveat that the patients should be monitored for signs of temporary adrenal hypofunction after treatment, the findings do not raise any special concerns.

The safety pharmacology package is not compliant with GLP and current guidelines. However, these deficiencies are largely offset by the clinical experience with BDP. For this reason no further studies are deemed necessary.

Pharmacokinetics

Published ADME studies in the rat and, to a lesser extent, the dog are referred to by the applicant.

In the rat, the major metabolite (17-BMP) dominated in plasma, while BDP either was undetectable (after oral administration) or was rapidly degraded (after i.v. administration). Beclomethasone, which could be regarded as the result of further hydrolysis, and the inactive metabolite 21-BMP were present but at considerably lower concentrations. As 17-BMP has a comparatively long half-life in plasma ($t_{½}$ about 1.5 h vs. 3-4 min for BDP) and is a more potent glucocorticoid than either BDP or beclomethasone, it is clearly the major contributor to the systemic pharmacological effect.

The dog study is less informative as only total radioactivity was determined; presumably most of this radioactivity corresponds to 17-BMP. The absolute bioavailability after oral dosing of 4 mg/kg was estimated to 35.6%.

In a distribution study using daily oral doses in the rat for up to 24 days, the increase in tissue radioactivity was substantial, reflecting an accumulation of BDP and/or metabolites. The proportion of pharmacologically active metabolites, particularly 17-BMP, is unknown. There were only minor differences in organ distribution between oral and subcutaneous rat studies. Interestingly, high concentrations were found in the intestine also after subcutaneous administration.

In the rat, the metabolism of BDP is simple and dependent on esterases; conversion of BDP to 17-BMP seems to be very rapid and occurs to a large extent already in the intestinal lumen. The human *ex vivo* studies suggest that human metabolism is similar. No metabolism data were presented for the dog but there is no reason to suspect that the metabolism should be markedly different in this species; given the importance of esterases for the metabolism.

The excretion of BDP was studied following oral and parenteral administration of ^{3}H-BDP to rats and dogs. With both oral and parenteral administration, the major route of excretion in dogs and rats was the feces. There are no data about secretion of BDP or its metabolites in milk.

Toxicology

The applicant did not conduct any new studies but refers to published studies in mice, rats, dogs and rabbits. Most of these studies were made in the 1970s and their GLP-status is unknown. Only a minor part of the studies used the oral route of administration.

Single dose studies in mice, rats, rabbits, and dogs indicate that the acute toxicity of BDP is low, when administered orally, subcutaneously, intraperitoneally or by inhalation. Thus, oral doses ≤ 3 g/kg caused no mortality in mice or rats. In the dog, two inhalations of up to 100 mg/kg caused no mortality.

Repeat dose toxicity studies were mainly conducted in rats and dogs. In both species, the findings were consistent with well-known, exaggerated pharmacological effects of steroids, including immuno-suppression, adrenal effects, liver enlargement and effects on reproductive organs, particularly the uterus and oestrus cycle. Following a 5 week recovery period in the 3-month study, evidence for reversibility was obtained for all findings. Dogs appear to be more sensitive than rats with a NOAEL < 0.5 mg/kg/day. There were no findings, indicating that there is any toxicity of BDP that would be unrelated to the pharmacological effect.

The dog studies, using various combinations of inhalation and oral administration, are not optimal. One would wish for a ‘pure’ oral study of sufficient length in the dog. On the other hand, GvHD is routinely treated with high doses of systemic steroids and the purpose of orBec concept is to reduce the total systemic steroid exposure and still achieve sufficient efficacy. Consequently, it seems unreasonable to require such a study in the dog.

Unfortunately, toxicokinetic data are very limited and of insufficient quality to calculate exposure margins for oral administration. In lieu of such data, the applicant employed the human equivalent dose (HED)

method to calculate dose margins. Using the most sensitive species (dog), it can be concluded that such margins are virtually nonexistent (< 2).

In the reproductive and developmental toxicity studies, the findings were consistent with known effects of corticosteroids. However, very few fertile females with GvHD are supposed to be able to become pregnant, which lessens the risk.

Two epoxy metabolites, D2 (9β,11β-epoxy-16β-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione and D3 (the corresponding 21-propanoate to D2 y D3) found in human plasma in vitro have not been identified in animals. With the Day 120 LoQ, the Applicant was requested to clarify the in vivo relevance and the toxicological profile of these two metabolites. However, the Applicant has not presented clear evidence of these metabolites to be formed in animals. In order to discard any toxic effect of these two metabolites and in order to affirm that these metabolites have been intrinsically tested in toxicology studies, we need the evidence that D2 and D3 have been formed in animals and not only the assumption. Therefore, the Applicant should demonstrate the formation of these two metabolites in animals.

Moreover, the epoxy-BDP (9,11-epoxy beclomethasone dipropionate) has been identified as a degradation product that appears in the BDP tablets during storage and it is over the level defined in ICH guidance Q 3 B (R). With the Day 120 LoQ, the Applicant was requested to provide information about the toxicological profile of this product. However, only the draft study reports have been presented. Moreover, it is not clear which test article has been used to perform the genotoxicity studies. The Applicant is requested to present the complete final AR and to clarify which test article has been used, in order to allow the assessment.

The applicant supplied an ERA that contained formal errors. Nevertheless, it was concluded that a correctly calculated $PEC_{surface\text{-}water}$ would still be much below the threshold, and no Phase II assessment is required.

III.3 Clinical aspects

Pharmacokinetics

The pharmacokinetics of BDP has been sparsely documented. The analytical methods used in the pharmacokinetic studies have limitations and interference is observed. The rationale for combining an IR and EC formulation is to extend the duration of local exposure to BDP. However, no *in vivo* studies have been performed showing where in the GI tract the dissolution of the tablets and local exposure takes place. After oral administration, no BDP is detected in the circulation. Two metabolites 17-BMP and BOH are formed, presumably by esterase catalysed hydrolysis and/or CYP3A catalysed metabolism and are detected in the circulation. These two metabolites, and in particular the 17-BMP metabolite (due to markedly higher activity as well as concentrations) significantly contribute to the pharmacological effect of BDP. It is unknown how much of the clinical effect on GvHD stems from local BDP (and metabolite) concentrations and how much can be derived from systemic metabolite levels. However, accounting for differences in GR affinity and protein binding and exposure the systemic activity is estimated to be comparable to 2 mg dexamethasone i.v or to 2.5 mg of prednisolone administered p.o. six times daily. The exposure of 17-BMP is comparable to the exposure obtained after oral inhalation treatment.

The applicant has performed two pharmacokinetic studies (with a 6 mg dose) showing that similar AUC of metabolites is obtained with suspension, IR tablets and EC tablets as well as that similar AUCs are obtained after administration of the IR-EC combination as with EC or IR tablets alone. High-fat food did not affect the metabolite exposure of the IR-EC combination. Nothing is known regarding a possible effect on local exposure. The recommendation to take the drug with food as recommended in the clinical studies is adequate. The applicant included blood sampling in one of the pivotal clinical studies showing that there is an approximate 60% accumulation at multiple-dose conditions of 17-BMP. The variability was quite high in the few patients included in the pk part of this study and the study was small (n=4). The high variability may be due to the variability in intestinal motility seen in this patient population. There are no dose-proportionality studies. The applicant has not performed a mass-balance study. There are no studies in special populations, including children. Patients with impaired renal of hepatic function could

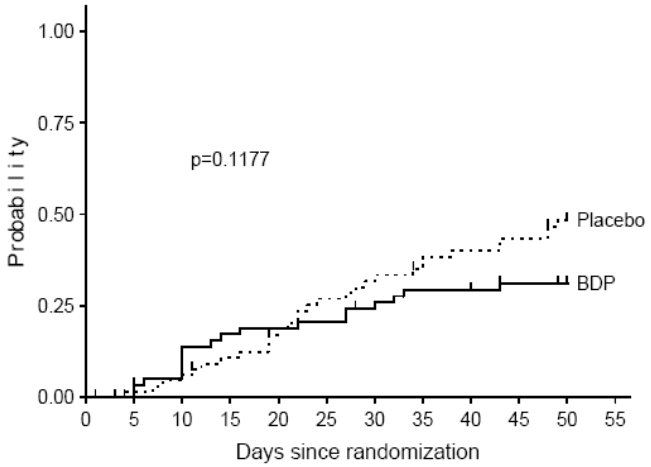
obtain higher systemic metabolite exposure. There are no in vitro or in vivo interaction studies. The applicant should perform in vitro interaction studies on the effect of BDP and 17-BMP on intestinal CYP3A4 and cytochrome P450 enzymes, respectively. There is no information on population characteristics or interactions leading to differences in local BDP and metabolite exposure. This should be discussed by the applicant.

Pharmacodynamics
BDP belongs to the class of corticosteroids, with well known effects on the HPA axis and well known side effects. After cessation of treatment, especially when treatment is abruptly terminated, signs of adrenal hypofunction can occur.

The exact role of BDP in the gastrointestinal mucosa, the drug levels at the site of action and the drug's efficacy on GI manifestations have not been satisfactorily demonstrated by the Applicant. Supportive information from clinical and/or experimental data on mucosal exposure to the drug need to be provided. No clinical dose finding study has been conducted in support of the claimed dosing.

Clinical efficacy
Dose-response studies and main clinical studies
No real dose response studies were performed for this application.
The pivotal study ENT 00-02 was a phase III randomised placebo-controlled multicentre study of the safety, efficacy and pharmacokinetics of BDP in conjunction with ten days of high dose prednisone therapy in the treatment of patients with grade II GVHD with gastrointestinal symptoms. 129 patients who had signed informed consent were randomised to one of the two treatment groups:
a) 8 mg oral BDP daily, administered as one 1 mg IR tablet and one 1 mg EC tablet four times daily
b) oral placebo tablets, 2 tablets four times daily.
On study day 10, patients who were considered to have their GVHD controlled had their prednisone tapered rapidly over 7 days.
It would have been of value to confirm the local steroid effect in the intestinal mucosa, e g by biopsies. Otherwise, endpoints are relevant. The comparison period chosen for the primary endpoint was short (50 days). 46% of the total study population was enrolled at one centre. The dominance of one centre in the study questions the external validity of the results. This even more critical since this is the same centre that had performed all pre-pivotal studies. Mean age in the placebo group was 44.9 years vs 45.9 years in the BDP group. This difference is not considered to be of importance. The frequency of multiple myeloma was 10 % in the BDP group and just 1 % in the placebo group. 22 % in the placebo group were patients with acute myelogenous myeloma in first remission while only 15 % of patients in the BDP group had this diagnosis. These differences could possibly have influenced the results. When patients were subdivided into one of the two categories (according to their primary diagnosis) higher or lower risk of relapse post-transplant, 43 % of placebo patients and 65 % of BDP patients were classed as being at higher risk of relapse.
This difference could have influenced the outcome in favour of the placebo group. 78 % of patients in the placebo group received myeloablative conditioning regimen while only 58 % of patients in the BDP group received this type of conditioning regimen. A myeloablative conditioning regimen could possibly have increased the risk for fatal outcome during the first months after transplantation. Patients in the BDP group had a longer period between transplant and randomisation for recipients of non-myeloablative conditioning regimens, 57.3±41.89 days for the BDP group vs 50.3±31.30 days for the placebo group which could be expected to possibly have a negative impact on the outcome. The mean compliance rate in the BDP and placebo groups was very high, 97%.
Primary endpoint: The primary endpoint of time to treatment failure in the first 50 days failed to reach statistical significance. More of treatment failures occurred in the BDP group than in the placebo group during the first 10 days of treatment, when prednisone dose was still high. An analysis, not pre-planned, was performed with censoring for treatment failure during the first 10 days of the study. This analysis showed a significantly reduced risk of treatment failure for the BDP arm relative to placebo.

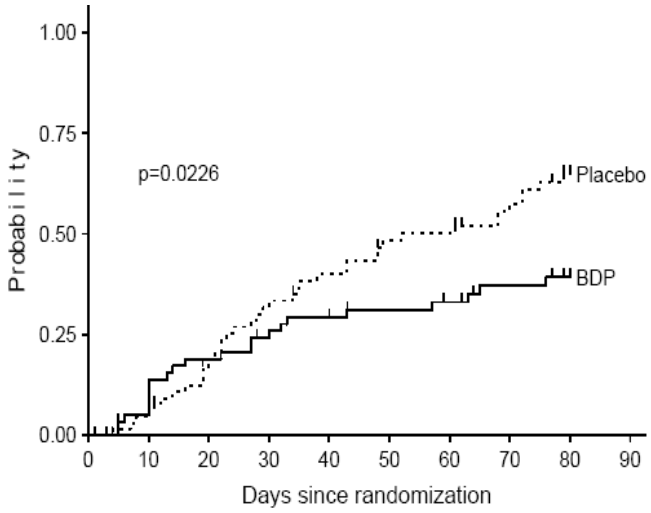
Fig 1. Time to treatment failure through study day 50, Kaplan-Meier curve.



The analysis censoring for treatment failure during the first 10 days is not considered justified since it was a retrospective analysis performed on a not longer randomised material. The sensitivity analyses gave results that were not essentially different from the primary results with respect to magnitude of effects.

Secondary endpoints:
On day 80 the overall cumulative treatment failure rate by study day 80 was 0.39 for the BDP group versus 0.65 for the placebo group (p=0.0005). For the entire 80 day study period, the risk of treatment failure was significantly reduced by 44 % for patients in the BDP group relative to the placebo group (adjusted hazard ration 0.56; 95 % CI: 0.33, 0.94; p = 0.0226, Fig.2).

Fig 2. Time to treatment failure through study day 80, Kaplan-Meier curve.



Survival in the first 200 days post transplant was significantly better in BDP- than in placebo- patients (odds ratio 0.29, 95 % CI 0.10, 0.82, p = 0.0139). In sensitivity analyses where drop-outs were counted as treatment failures, the day 80 time to treatment failure analysis and the survival analysis were no longer statistically significant.

The univariate and multivariate analyses showed that patients whose donor was not an HLA-matched sibling had a greater survival advantage; no other contributing factors for survival were seen. Relapse of GVHD (10 %) and multiorgan failure (9 %) was contributing cause of death in some of the placebo group deaths but did not contribute to death in any patient in the BDP group.
In addition to a better survival in the BDP group for patients who got their graft from other source than an 2 HLA-type identical sibling, a centre effect was seen in the overall survival data, in favour of patients included at the biggest centre.
The overall dose of corticosteroids during the study period did not significantly differ between the BDP group and the placebo group. In contrast, there was a significant difference in total steroid dose between patients with and without recurrence of GVHD. Two methods for analysing HPA axis abnormality indicated a higher incidence of abnormal HPA axis function in the BDP treated patients. This is compatible with a considerable intestinal absorption of BDP. The treatment-by-centre interaction was not statistically significant. However, this might very well be due to lack of power in the interaction test and relevant interaction cannot be ruled out.

The Applicant presented, in response to the Day 120 LoQ, complementary sensitivity analyses for the time to GvHD treatment failure during the first 80 days but these analyses are not considered to change the principal major objection, the failure of the primary efficacy endpoint.

Supportive studies
Results from study 875 (60 patients) are claimed by the applicant to support study results from the pivotal study ENT 00-02. However, the retrospective analysis performed on mortality data from study 875 is difficult to evaluate since the numbers are small and 5/7 subjects lost to follow-up were from the BDP group.
Study 615 (40 patients) was an uncontrolled study on BDP in GVHD-patients who did not respond well to systemic steroids.
Study 1500 (16 patients) was an uncontrolled study with a different drug administration schedule than this application concerns (no EC capsules). It is suggested that using only an IR formulation may give a lower distribution of drug to the late parts of the ileum so that the administration form used in study 1500 is not directly comparable to the one used in the pivotal study which makes it difficult to draw efficacy conclusions concerning orBec from this study.
Studies 615, 875 and 1500 were performed with the IR (study 1500) or IR plus EC capsules (studies 615 and 875) while the other studies were performed with tablets. There is no bioequivalence study comparing these formulations with the formulations intended for marketing. Even if the AUCs of 17-BMP and BOH obtained are expected to be similar to those after administration of the IR and EC tablets, the local exposure of the IR and the EC tablets may be different.

Clinical studies in special populations
No studies have been performed in children or in elderly patients. No children under the age of 6 were included in the clinical studies.

Sixteen children and adolescents between 6 and 18 years of age were included in clinical studies. Two children under the age of 18 were included in the pivotal study and three in study 1500. Efficacy data from the eight children in study 875 were analysed separately in the 875 study report. Patients with hepatic or renal impairment were not included in the clinical studies.

Analysis performed across trials (pooled analyses AND meta-analysis)
A pooled analysis of safety data for children was performed in response to the Day 120 LoQ.
In response to the Day 120 LoQ, the Applicant has provided supportive data from the treatment of inflammatory bowel disease with other locally acting corticosteroids plus data from treatment of asthma with BDP spray. However, specific data in support of the claimed local mechanism of action for orBec in the treatment of gastrointestinal GvHD is still lacking and should be provided since the presented data are not considered to be able to be fully relevant for the present application.

Clinical safety

Patient exposure

The drug has not been marketed. A total of 269 patients participated in clinical trials: 24 were included in phase I studies and 245 were patients with GVHD (150 of them received beclomethasone dipropionate, BDP) in phase II and phase III clinical studies. The number of patients exposed to the drug in the present application is small. However, considering that the drug has been licensed for many years for inhalation, exposure data are considered to be sufficient.

Safety data from studies 615, 875 and 1500 are difficult to evaluate adequately as AEs and laboratory abnormalities were only reported if considered to be unexpected and/or possibly or probably related to treatment.

Adverse events

AEs were reported by essentially all patients in study ENT 00-02. In total, AEs were reported more frequently in the placebo group than in the BDP group. Other AEs occurring more than 1.5 times more frequently in the BDP than in the placebo group were dehydration and chest pain. There was no difference in cardiac events between groups. The number of subjects with at least one TEAE was significantly higher in the placebo arm than in the BDP arm in study ENT 00-02. Pooled study data on TEAEs generally shows fewer events in BDP treated patients and no major differences between groups.

Serious adverse events and deaths

SAEs were common in these severely ill patients and endocrine disorders were more common in the BDP group while infections were more common in the placebo group.

Safety in special populations

The Applicant provided, in response to the Day 120 LoQ, satisfactory accounts for pooled safety data in children, and also of the infectious complications in study ENT 00-02.

Safety related to drug-drug interactions and other interactions

Multi-drug treatment was administered to all patients in the clinical studies. No interactions were described.

After the Applicant's response to the Day 120 LoQ, there still remains uncertainty about the systemic exposure of corticosteroids from orBec. The Applicant has presented somewhat conflicting calculations on the absorbed systemic steroid dose resulting from administration of orBec in the dose of 8 mg daily. This should be clarified.

Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

Risk Management plan

The RMP for orBec is not prepared according to the EU guideline. However, the content provided is acceptable. No new safety issues were identified apart from already known ADRs attributable to other oral corticosteroids. The applicant has specified infections as an identified risk, and clinical adrenal insufficiency, allergic reactions, incorrect dosing, overdose and off-label use as a potential risk. Information on drug use in pregnancy and in paediatric patients is missing. These safety issues are adequately addressed in the SPC and PL.

Overall, it is considered that the updated version of the RMP fulfils nearly all the requirements but at present there is still room for improvement**.** The Applicant should further elaborate their RMP including a description and discussion of the potential interactions with other medicines, their intention to perform additional pharmacovigilance studies, the actions intended to ascertain the absence of any cardiovascular damage and/or the measures to clarify the chest pain incidence.

Safety Specification
The updated version of the RMP includes the description of the Safety Specifications including the Non-clinical and Clinical sections. Importantly for the former the missing non-pharmacology information is detailed. For the latter the limitations of the human safety database and a description of the populations not studied in the pre-authorisation phase (children, elderly, pregnant or lactating women, hepatic and renal impairment, patients with disease severity different from the studied in clinical trials and patients of different ethnic origins...) are included. Notably, the laboratory evidence of suppression of the hypothalamic-pituitary-adrenal axis is included as an identified risk. Potential risks are described including errors in dosage and off-label use.

Evaluation of the need for a Risk Minimisation plan
Taking into account currently available treatment of gastrointestinal GVHD which includes high doses of oral corticosteroids in combination with other immunosuppressants and the safety profile of orBec, the CHMP agrees that risk minimisation activities are not warranted at the moment.

IV. ORPHAN MEDICINAL PRODUCTS

Beclomethasone 17, 21-dipropionate (oral use) was granted orphan designation in the EU in March 2002 for the orphan indication “Treatment of intestinal graft-versus-host disease” (EU/3/02/093).

According to the conclusion of the COMP (Opinion dated 23 January 2003) the prevalence of intestinal GvHD is approximately between 0.1 and 0.2 in 10,000 persons in the Community at the time the application for orphan designation was made.

V. BENEFIT RISK ASSESSMENT

V.1 Clinical context

GvHD is a serious and potentially fatal condition that results when T-cells from a usually allogeneic tissue or organ transplant, particularly from a bone marrow transplant, react immunologically against the recipient's antigens resulting in cell and tissue damage, especially to the skin, gastrointestinal tract and liver, and associated with symptoms that include skin rash, fever, diarrhoea, liver dysfunction, abdominal pain and anorexia. Gastrointestinal involvement represents a prominent feature of GvHD. Gastrointestinal GvHD is usually managed by using immunosuppressive agents. Unfortunately such agents, including corticosteroids, have serious adverse effects when administered systemically.

The medical rationale for orBec is to maintain a high local glucocorticoid concentration in the intestine, whilst achieving a lower systemic exposure. The concept of reducing systemic steroid exposure by administering a steroid with mainly local effect on the intestine in GVHD may appear attractive. If the extensive and intense inflammatory reactions in the bowel wall tissues associated with GVHD could be controlled by local steroid treatment that reaches large parts of the bowel, such treatment could be more effective than that of steroids that predominantly exert systemic effects. Furthermore, in theory, a reduction of systemic steroid exposure could be achieved.

V.2 Benefits

This application is essentially based on one pivotal study. Unfortunately, the efficacy results from this study appear non-convincing. The BDP treatment arm showed a trend towards better results than the placebo arm but was not significantly better than the placebo arm for the primary efficacy parameter, time to treatment failure in the first 50 days. A retrospectively performed analysis with censoring of treatment failure during the first 10 days of the study demonstrated a significantly longer time to treatment failure in the BPD group. However, such a comparison between no longer randomised study groups cannot be considered to provide substantial support for the claimed efficacy of BDP. Among the secondary endpoints, the risk of treatment failure during the entire 80 day study period was significantly reduced. Furthermore, survival in the first 200 days post transplant was significantly better in BDP- than in placebo patients. In sensitivity analyses, where drop-outs were counted as treatment failures, the day 80 time to treatment failure analysis was no longer statistically significant. Furthermore the results were heavily driven by the results from one single center. Another uncertainty in the trial design is the rather rapid tapering of systemic steroid treatment which may have disfavoured the placebo group. The difficulties to design clinical studies convincingly demonstrating superior efficacy within this area is acknowledged. However, in a study where the experimental treatment is added to "standard treatment" in the actively treated arm, as was done in the pivotal study, a demonstration of superior efficacy must be required.

The results of a survey performed by the Applicant, which involves different European transplant centres, to know the best clinical practice for treatment of GVHD, show that there is no consensus among the 21 centres questioned. Although there is a wide variability in the regimens used, a high percentage of centres reported higher doses and/or longer total duration of immunosuppressive therapy compared to those used in ENT-002 (prednisone 1 mg/kg/day during 10 days, tapering 7 days) making a possible extrapolation of the results difficult.

Data from the supportive studies are considered weak as the studies were performed with other administration forms than the pivotal study. These administration forms could theoretically have different local effects on the intestinal mucosa. Notwithstanding these differences, the results from the mostly small supportive studies fail to provide substantial evidence for efficacy.

The presumed local effect of BDP on the intestinal mucosa has not been satisfactorily shown. To some extent external preclinical or clinical evidence supporting the concept that a local anti-inflammatory bowel effect is beneficial in GVHD could contribute to a positive benefit risk evaluation. However, the Applicant has not provided such evidence.

There is no information in the dossier at which pH the EC coating is dissolved and no in vivo data on where local exposure of BDP and 17-BMP is obtained with the formulations applied for. There is no systemic exposure of BDP but the concentrations of 17-BMP reached could contribute to the potential clinical effects. Clinically relevant systemic steroid effects in the BDP treated patients most probably were at hand since HPA axis abnormalities were significantly more common in the BPD group than in the placebo group (treatment failures excluded).

Taken together, efficacy has not been sufficiently shown.

V.3 Risks

- Demonstrated risks

Side effects seen in clinical studies are those of corticosteroids. Side effects are no worse in patients treated with BDP than in the control group. The overall dose of corticosteroids during the study period did not significantly differ between the BDP group and the placebo group. Safety data in the supportive studies were not reported in the same way as in the pivotal study which makes comparison difficult.

- Potential risks

Even if the systemic steroid absorption of orBec is less than with conventional steroid treatment, the exact amount of systemic exposure remains unclear and seems not to be negligible.

V.4 Balance

In summary, the safety profile of the product is comparable to that of other corticosteroids but since efficacy for the actual indication is poorly demonstrated, the risk/benefit balance is currently considered to be negative.

V.5 Conclusions

The overall B/R of orBec for the applied indication is negative.