25 February 2016
EMA/385492/2016
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Alendronic Acid/Colecalciferol Mylan

International non-proprietary name: alendronic acid / colecalciferol

Procedure No. EMEA/H/C/004172/0000

Note

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

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List of abbreviations

AE	adverse event
AP	Applicant's Part of ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ATC system	Anatomical Therapeutic Chemical system
AUC	Area Under the plasma Concentration
$AUC_{0-\infty}$	Area Under the plasma Concentration-time curve from time zero to infinity
AUC_{0-t}	Area Under the plasma Concentration-time curve from time zero to t hours
AV	Acceptance value
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BfArM	German National Competent Authority
BHA	Butylated Hydroxyanisole
BHT	ButhylHydroxyToluene
BLQ	Below limit of quantification
BMI	Body Mass Index
CEP	Certificate of suitability with the European Pharmacopoeia Monograph
CHMP	Committee for Human Medicine Products
CMA	Critical Material Attribute
C_{max}	maximum plasma concentration
CoA	Certificate of Analyses
CQA	Critical Quality Attribute
CRF	Case report form
CRO	Contract Research Organisation
CV	(1) Curriculum Vitae, (2) Coefficient of Variance
DMF	Drug Master File
DRL	Drug Reference list
DT	Disintegration Time
EC	European Commission
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines & HealthCare
EDTA	Ethylenediaminetetraacetic acid
EMA	European Madicines Agency
EP CRS	European Pharmacopoeia Chemical Reference Substance
EV code	EudraVigilance code
FBP Granulation	Fluid Bed Granulation
GC	Gas chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HDPE	High Density PolyEthylene
HPLC	High Pressure Liquid Chromatography
HQC	High quality control
ICMR	Indian council of medical research
ICH	International Conference of Hamrnization
IH	In house
IISR	Inconsistent internal standard response
INN	International Non-proprietary Name
IS	Internal standard
ISR	Incurred Sample Reanalysis
IU	International unit
λ_z	Individual estimate of the terminal elimination rate constant
LC-MS	Liquid chromatography - mass spectrometry
LDPE	Low density PolyEthylene
LLOQ	Lower Limit of Quantification
LMQC	Lower Medium Quality Control

LOA	Letter of Access
LOD	(1)Limit of Detection, (2) Loss of drying
LOQ	(1) Limit of Quantification, (2) List of Questions
LQC	Low quality control
LS means	Least squares means
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MedDRA PTs	MedDRA Preffered terms
MedDRA SMQ	Standardised MedDRA Queries
MF	Matrix Factor
MHRA	British National Competent Authority
MIA	Manufacturing and Importation Authorisation
MS	Mass Spectrometry
MQC	Medium Quality Control
ND	Not detected
NLT	Not less than
NMT	Not more than
OGYI	Hungarian National Competent Authority
OPA/Al/PVC//Al	oriented polyamide/aluminium/ polyvinyl chloride foil laminated on aluminium foil
Ph. Eur.	European Pharmacopoeia
PIL	Package Leaflet
PK	pharmacokinetic
PSD	Particle size distribution
PSMF	Pharmacovigilance Systém Master File
PT	Preferred Term
PVC/PE/PVDC	PolyVinyl chloride / Polyethylene / Polyvinylidene chloride
QA	Quality Assurance
QC	Quality Control (samples)
QbD	Quality by design
QP	Qualified Person
QPPV	Qualified Person for pharmacovigilance
QTPP	Quality Target Product Profile
RH	Relative Humidity
RI detector	Refractive Index detector
RMG Granulation	Rapid Mixer Granulation
RRT	Relative Retention Time
RS	Related substances
RSD	Relative standard deviation
Rt	Retention time
SLS	Sodium Lauryl Sulphate
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Querie
SOP	Standard Operating Procedure
STD	Standard Deviation
T/R	Test/Reference
TAMC	Total Aeerobic Microbial Count
TDI	Total Daily Intake
T_{max}	time for maximum concentration (* median, range)
TSE/BSE	Transmissible Spongiform Encephalopathy / Bovine Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
ULOQ	Upper limit of quantification
UOD	Uniformity of Dosage Units
USAN	United States Adopted Name
USP	United States Pharmacopoeia
UV detector	Ultra Violet detector
XRD	X-Ray Diffraction (PXRD – Powder X-Ray Diffraction)

Not all abbreviations may be used.

1. Recommendation

Based on the CHMP review of the data on quality, safety, clinical and risk management plan, the CHMP considers that the generic application for Alendronic Acid/Colecalciferol Mylan 70 mg/5,600 IU and Alendronic Acid/Colecalciferol Mylan 70 mg/2,800 IU in the treatment of postmenopausal osteoporosis in women at risk of vitamin D insufficiency and in reducing the risk of vertebral and hip fractures,

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 List of Questions.

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

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

1. Uncertainties relating to amendments of the approved protocol referred to in the documentation
2. Administration of a statistical analysis method that does not appear as pre-specified in the submitted protocol after the one requested by the approved protocol failed to demonstrate bioequivalence. Furthermore, performing the submitted statistical analysis with the data of subjects showing pre-dose concentration >5% of C_{max} when the submitted protocol specifies otherwise.
3. Similarity between the test product bio-batch and lower strength cannot be concluded as f2 similarity factors regarding the biowaiver were not properly calculated considering that the %RSD values were not within the acceptance criteria.

Questions to be posed to additional experts

Inspection issues

GMP inspection(s)

None required.

GCP inspection(s)

None required.

2. Executive summary

2.1. Problem statement

N/A (generic application)

2.2. About the product

This application for a marketing authorisation concerns a generic application of a Centrally Authorised Medicinal Product according to article 10(1) of Directive 2001/83/EC for Alendronic Acid/Colecalciferol Mylan 70 mg/5,600 IU tablets and Alendronic Acid/Colecalciferol Mylan 70 mg/2,800 IU tablets. The

reference product is Fosavance 70 mg/2,800 IU and 70 mg/5,600 IU tablets which has been authorised in the EU since 24/08/2005 through centralised procedure by Merck Sharp & Dohme Ltd., UK.

Alendronate sodium is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

Cholecalciferol (Vitamin D_3) is produced in the skin by conversion of 7-dehydrocholesterol to vitamin D_3 by ultraviolet light, which is then converted to 25-hydroxyvitamin D_3 in the liver, and stored until needed. Conversion to the active calcium-mobilizing hormone 1,25-dihydroxyvitamin D_3 (calcitriol) in the kidney is tightly regulated. The principal action of 1,25-dihydroxyvitamin D_3 is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption, which results in reducing the risks from abnormal bone formation.

Combination of alendronic acid and colecalciferol (bisphosphonate with vitamin D) is indicated for the treatment of postmenopausal osteoporosis in women at risk of vitamin D insufficiency. Besides, it reduces the risk of vertebral and hip fractures.

Bioequivalence study was conducted at the highest strength (70mg/5600 IU) which is recommended according to the Guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr**. For the lower tablet strength bioequivalence testing is waived with in vitro dissolution tests. However, f2 similarity factors regarding the biowaiver for lower strength were not properly calculated considering that the %RSD values were not within the acceptance criteria. Also, during the assessment of the presented bioequivalence study, major objections regarding GCP, biowaiver and statistics were observed. Therefore, bioequivalence has not been conclusively established with the submitted data.

2.3. The development programme/Compliance with CHMP Guidance/Scientific Advice

Alendronic Acid/Colecalciferol Mylan Tablets are immediate release tablets. The product is formulated to contain 70 mg of alendronic acid (as sodium alendronate) and 2,800 IU or 5,600 IU of cholecalciferol.

Alendronic Acid/Colecalciferol Mylan 70 mg/5,600 IU tablets and Alendronic Acid/Colecalciferol Mylan 70 mg/2,800 IU tablets were developed as generic to the reference product Fosavance 70 mg/2,800 IU tablets and 70 mg/5,600 IU tablets manufactured by Merck Sharp and Dohme Ltd. which has been authorised in the EU since 2005 through centralised procedure.

Bioequivalence study was conducted according to the *Guideline on the Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98 Rev.1/Corr**, at the highest strength (70mg/5600 IU) which is acceptable according to the Guideline. According to Applicant, a generic product Alendronic Acid/Colecalciferol Mylan tablet in comparison to the reference product has the same qualitative and quantitative composition in active substances, same pharmaceutical form as the reference medicinal product and similar qualitative composition. For more information on the quality of Alendronic acid/colecalciferol Mylan and essential similarity to the reference product see Rapporteur day 80 critical assessment report on Quality.

The applicant did not receive Scientific Advice from the CHMP.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Satisfactory evidence has been provided that all sites involved in the manufacture of the drug product comply with European guidelines on GMP.

No issues that would trigger a GMP inspection have been identified during the assessment of quality part of the dossier however an adequate GMP certificate for the EU microbiological testing site should be submitted before approval of the drug product.

GCP

Some study aspects do raise concerns regarding the GCP compliance. There are issues that need to be clarified concerning protocol changes mentioned in the documentation; (i) are the "*Changed in protocol (Version 05)* upgrade of the submitted *Protocol Version No. 05* and if so, (ii) was the updated version of the protocol in question approved by the Ethics Committee, (iii) was the study 692-10 performed according to the approved *Protocol Version No. 05* or according to a revised version of this protocol, *Changed in protocol (Version 05)* for which no approval is submitted, (iv) was the subject information sheet received by the study subjects *"Subject information sheet (Version 03)"* or *"Changed in Subject information sheet (Version 03)".*

As only the list of EU competent authority inspections conducted at the Clinical/Bioanalytical/PK and statistical study site Lambda Therapeutic Research Ltd., Gujarat, India, is provided, the Applicant is asked to provide a summary of the final outcomes of the performed inspections.

Besides, list of Inspection/s performed by the competent EU authority at the bioanalytical study site Warnex Bioanalytical Services and the summary of the final outcomes, should be provided as well. Moreover, in case of major or critical findings, a comment on their potential impact on the study 692-10 is to be provided.

Additionally, issue concerning the absence of the on-site monitoring is raised. As stated in the documentation, on-site monitoring was not performed and clinical update was sent from Lambda to the Sponsor.

2.5. Type of application and other comments on the submitted dossier

Type of application for Alendronic Acid/Colecalciferol Mylan 70 mg/5,600 IU tablets and Alendronic Acid/Colecalciferol Mylan 70 mg/2,800 IU tablets is a generic application made according to Article 3(3) of Regulation EC 726/2004 "Generic of a Centrally Authorised Medicinal Product" and Article 10(1) of Directive 2001/83/EC. The Applicant is Mylan S.A.S., France. The reference medicinal product is Fosavance 70 mg/2,800 IU tablets and 70 mg/5,600 IU tablets authorised in the EU since 2005 through centralised procedure, with Merck Sharp and Dohme Ltd., UK as a marketing authorisation holder.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product contains sodium alendronate trihydrate and cholecalciferol as active substances. Both active substances sources are the subject of certificates of suitability issued by the EDQM.

The chemical-pharmaceutical documentation in relation to Alendronic Acid/Colecalciferol Mylan is not of sufficient quality in view of the present European regulatory requirements.

3.1.2. Active Substance

General Information

The sources of both drug substances, sodium alendronate trihydrate and cholecalciferol, are the subject of certificates of suitability issued by the EDQM.

Manufacture, characterisation and process controls

Further data should be provided for sodium alendronate trihydrate including updated QP declaration, if applicable. For chlolecalciferol manufacturer, a new QP declaration is expected based on a re-audit.

Specification

The drug substance specifications for both drug substances applied by the finished product manufacturer reflect the requirements of the relevant Ph. Eur. monograph. Additional controls for residual solvents, XRD, particle size and microbial contamination for sodium alendronate trihydrate are listed. For cholecalciferol additional controls for identification by HPLC, loss on drying and microbial contamination are listed. However, complete drug product manufacturer specification for both APIs should be provided.

Stability

The re-test period of 5 years for alendronate sodium is acceptable. Since there is no data for retest period of cholecalciferol in the CEP and additional stability data in the dossier is not provided, it is not possible to conclude on re-test period of cholecalciferol. Additional data should be provided.

Comparability exercise for Active Substance

N/A

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The proposed drug product Alendronic Acid/Colecalciferol Mylan is an immediate release tablet available in two strengths considering cholecalciferol: 70 mg of alendronic acid (as sodium trihydrate) and 2,800 IU or 5,600 IU of cholecalciferol per tablet. Two package sizes (4 and 12 tablets in Alu/Alu blister) are proposed.

The development of Alendronate sodium/Colecalciferol tablets as generic product of Fosavance tablets manufactured by Merck Sharp and Dohme Ltd. was done using some elements of QbD concept. Quality Target Product Profile (QTPP) for the drug product has been defined based on characteristics of Fosavance tablets. Critical quality attributes (CQAs) for the drug product have been established with justification of criticality for each of the selected quality attributes. Critical material attributes (CMA) of both APIs and main excipients have also been identified and risk assessment on process steps and attributes of the drug product which required additional control has been done. However, disintegration of tablets should be included in the list of CQA since both formulation and process variables may affect

disintegration and a fast disintegration of tablets may impact safety of drug intake (GI related adverse events).

The bioequivalence study was carried out with higher strength tablets. Comparative dissolution profiles of the batches of the test and the reference product used in BE study confirm similarity for alendronate sodium in all media used while for cholecalciferol similarity is not confirmed in used physiological media, but is confirmed in chosen QC media. Difference in qualitative composition regarding excipients and manufacturing process of test and referent product (patent protected process) may be reason for different dissolution profiles. For the lower tablet strength bioequivalence testing is waived with in vitro dissolution testing since general biowaiver criteria according to the Guideline Investigation of bioequivalence are met. Although f2 values obtained for cholecalciferol are in line with Guideline, conditions for calculation are not fulfilled. Also 75 rpm rotation speed cannot be accepted for biowaiver until additional data are provided (for details see clinical AR). Consequently, proposed QC dissolution methods cannot be accepted at this moment and will be evaluated following submission of additional data requested in clinical AR.

Manufacture of the product and process controls

The manufacturing process and in process control testing have been described in sufficient details. Since the manufacturing process could be considered as a non-standard process regarding low-dose cholecalciferol substance, full validation data for pilot and commercial batches of both tablets strengths are presented including validation protocol. Several questions have been raised relating to additional primary packaging site / EU batch control testing site, batch formula, process control and detected different upper limit for hardness of tablets for last production batches which could potentially compromise dissolution results and affect bioavailability. Detailed justification and additional data are requested.

Excipients are in accordance with Ph. Eur. However, functionality-related characteristics of some excipients should be included in the drug product manufacturer specifications.

Product specification

Proposed drug product specifications are standard for the pharmaceutical form and include relevant tests. Since several questions are raised regarding proposed limits and since proposed dissolution methods should be assessed later following submission of additional data, specifications are not acceptable at this moment. Also several questions have been raised on characterisation of impurities, certificates of analysis, justification of specification and container closure system data provided.

Stability of the product

Although all available results of the stability studies are within proposed specification limits, considering that several objections about the drug product specifications and analytical methods have been raised and lack of stability data according to the Guideline has been detected, proposed shelf-life of 24 months and temperature storage condition (store below 30°C) cannot be accepted at this time point. Additionally, results of stability studies should be discussed by drug product manufacturer considering relationship between changes for different parameters.

Comparability exercise for Finished Medicinal Drug Product

N/A

Adventitious agents

The finished product contains the active substance cholecalciferol and the excipients gelatine and magnesium stearate, which are the only ingredients that may be of animal origin. Cholecalciferol obtained from sheep wool is used in the product. Valid TSE CEP from the supplier of cholecalciferol used in the manufacture is provided. Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the supplier of the gelatine used in the manufacture is provided. Magnesium stearate is of vegetable origin.

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

Both the drug substances are the subject of certificates of suitability issued by the EDQM. There are some other concerns related to additional data provided by applicant regarding drug product manufacturer specifications, manufacture of alendronate sodium, update of QP declaration and stability data for cholecalciferol.

The drug product is an immediate release tablet. Concerning the drug product, several other concerns have been raised regarding drug product development data, manufacture, control of excipients and control of drug product, container closure system and drug product stability data. The detailed information is given in the quality assessment report.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

There are no major objections raised on quality issues. However, a number of other concerns have been raised as outlined in the List of Questions. These should be resolved before recommendation to grant marketing authorisation.

3.2. Non clinical aspects

3.2.1. Pharmacology, Pharmacokinetics and Toxicology

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Although there are no objections to approval of Alendronic Acid/Colecalciferol Mylan from a non-clinical point of view, the CHMP considers that the non-clinical overview should be updated with one important safety aspect of long-term administration of alendronate (risk of atypical stress fractures).

3.2.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Alendronic Acid/Colecalciferol Mylan is considered unlikely to result in any significant increase in the combined sales volumes for all alendronate/vitamin D_3 containing products and in exposure of the environment to the active substances. Thus, the ERA is expected to be similar and not increased.

3.2.3. Conclusion on non-clinical aspects

There are no major objections to approval of Alendronic Acid/Colecalciferol Mylan from a non-clinical point of view. As stated above, there are some issues that need to be addressed (see LoQ).

3.3. Clinical aspects

Exemption

As MAH applied for a marketing authorisation for two strengths of Alendronic Acid/Colecalciferol Mylan (70 mg/5,600 IU and 70 mg/2,800 IU), a biowaiver has been requested for the lower strength which is found applicable considering that the general biowaiver criteria according to the *Guideline on Investigation of bioequivalence* are met.

Similarity between the test product bio-batch and lower strength cannot be concluded as f2 similarity factors regarding the biowaiver were not properly calculated considering that the %RSD values were not within the acceptance criteria. Proof of similarity between the two strengths as per Guideline or a discussion on this topic and an appropriate calculation if considered necessary, are to be provided by the Applicant.

- ***Tabular overview of clinical studies***

To support the application, the Applicant has submitted one bioequivalence study.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy subjects or Diagnosis of patients	Duration of Treatment	Study status; Type of Report
BA	Not Applicable								
E	Project No. 692-10	Clinical Study Report & PK Report and Adverse Event Listing 5.3.1.2 Bio-Analytical Report & Method validation Report 5.3.1.4 CRFs and Individual Subject Listings 5.3.1.2 Literature References 5.4	To characterise the pharmacokinetic profile of sponsor's test formulation (Alendronate Sodium *I* Cholecalciferol tablets 70 mg *I* 5600 IU) in comparison to the reference formulation (FOSAVANCE® 70 mg *I* 5600 IU Tablets, Marketing authorization holder: Merck Sharp & Dohme Ltd., Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, United Kingdom) after a single oral dose administration to healthy, adult, human subjects under fasting condition and to assess the bioequivalence. And To monitor adverse events and ensure the safety of the subjects.	Study Design: A single dose, open label, balanced, randomised, two-treatment, two-period, two-sequence, crossover, comparative oral bioequivalence study of two formulations of Alendronate Sodium / Cholecalciferol Tablets 70 mg *I* 5600 IU in healthy, adult human subjects under fasting conditions. **Type of Control:** No control groups	Reference Product-A FOSAVANCE® (Alendronate Sodium *I* Cholecalciferol Tablets 70 mg *I* 5600 IU) Dosage Regimen: Alendronate Sodium 70 mg and Cholecalciferol 5600 IU Test Product-B Alendronate Sodium *I* Cholecalciferol Tablets 70 mg *I* 5600 IU Dosage Regimen: Alendronate Sodium 70mg and Cholecalciferol 5600 IU **Route of administration:** Ora	Planned-110 Enrolled-116 (including four additional subjects viz. X-1, X-2, X-3 & X-4 and two extra subjects with ASN 30 & 119) Dosed-110 Completed-0 2 Analysed-110 (In which 08 withdrawn subjects were also analysed as per protocol requirement) Withdrawn/ Discontined-08	Healthy Subjects	Single dose	Complete; Abbreviated

The administrative structure of the study is as follows:

Contract Research Organization (CRO): Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380061, Gujarat, India.

Clinical study site: Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380061, Gujarat, India.

Bioanalytical Study Site:

- for alendronate: Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380061, Gujarat, India.
- for cholecalciferol: Warnex Bioanalytical services, 3885 Industriel Blvd., Laval (Québec), Canada, H7L 4S3.

Pharmacokinetic and Statistical Analysis site: Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380061, Gujarat, India.

The study protocol (project No. 692-10 Version No. 05,dated:13-SEP-2011) was approved by the Independent Ethics Committee - Adltya, ACEAS Clinical Research, India. The Ethics Committee approval letter and the list of Ethics Committee members are enclosed.

The clinical part of the study was conducted between 18-OCT-2011 and 15-NOV-2011. The dosing dates were 21-OCT-2011 for period 1 and 11-NOV-2011 for period 2.

The *Clinical study report* has been amended from Version No. 00 to Version No. 01 to follow the current eCTD report template requirements however, the Applicant is asked to submit the original *Version No. 00* , dated 28-FEB-2012.

3.3.1. Pharmacokinetics

Methods

Study design

The bioequivalence study was conducted with the 70 mg/5600 IU strength under fasting conditions. The use of the highest strength is acceptable and recommended in BE guideline as it is the most sensitive to detect potential differences between the products.

This study was an open label, balanced, randomized, two treatment, two sequence, two period, single dose crossover, oral bioequivalence study of the test product, Alendronate Sodium / Cholecalciferol Mylan Tablets 70 mg / 5600 IU and Fosavance Tablets 70 mg / 5600 IU (Alendronate Sodium / Cholecalciferol 70 mg / 5600 IU) of Merck Sharp & Dohme Ltd., Hertford Road, Hoddesdon, Hertfordshire EN11 9 BU, United Kingdom, in healthy adult human subjects under fasting conditions. Also, monitoring of adverse events and ensurance of the subjects safety was performed.

Study consisted of two periods (Period 1 and Period 2) separated with a 21 days of washout period. As showed in the literature, mean half-life of cholecalciferol in human plasma does not exceed 50 hours and plasma half-life of alendronate is 1.9 hours. Therefore, the wash-out period of 21 day was considered sufficient to minimise the carry-over effect.

Subjects were housed from minimum 60 hours prior to drug administration until 96 hours after drug administration in both periods. Blood sampling periods were 24 hours and 96 hours for alendronate and cholecalciferol, respectively.

In the morning of each period after an overnight fasting of at least 10 hours, a single dose of either test or reference Alendronic Acid/Colecalciferol 70 mg/5600 IU tablets, as per randomization schedule, were administered orally with 240 ml of water in sitting posture.

As per the protocol, a total of 38 blood samples were collected from each subject in each period. All samples were collected as in-house samples. In all, 8042 blood samples were collected during the study. Entire blood sampling was performed under sodium vapour lamp covered with red gelatin paper. Blood samples were collected through an indwelling intravenous cannula (Venflon) placed in a forearm

vein of the subjects. The blood samples were withdrawn using syringe and transferred into pre-labeled sample collection tubes containing K_3EDTA as anticoagulant for the analysis of cholecalciferol and K_2EDTA as anticoagulant for the analysis of alendronate. Sample collection tube was kept in a wet ice bath during sample collection activity.

For alendronate, the blood samples were centrifuged at 3000 rcf for 5 minutes at 8°C. The separated plasma was transferred to pre-labeled polypropylene tubes in two aliquots. The samples (4870 per aliquot) were stored upright in dry ice and in a freezer at a temperature -65 ± 10 °C for interim storage. During transfer, the samples were kept in a box containing adequate amount of dry ice. All the received samples were transferred to the freezer maintained at -65±10°C at the bioanalytical facility.

For cholecalciferol, the blood samples were centrifuged at 3000 rcf for 5 minutes below 10°C. The separated plasma was transferred to pre-labeled polypropylene tubes in three aliquots. The samples were stored upright in a box containing dry ice and a freezer at a temperature -65 ± 10°C for interim storage till transfer of the same to Warnex Bio-analytical Services, Canada. The inventory of samples was done by the clinical staff. Total of 10572 vials (two aliquots, 5286 vials per aliquot) containing plasma samples, were shipped to the analytical site packed in zip-lock bags, packed in airtight bio pouches which were packed in thermocol boxes filled with adequate dry ice. Each thermocol box was kept inside a carton box, which was then sealed completely for shipment. The first & duplicate lot of plasma samples was shipped to Warnex Bio-analytical Services, Canada, on 18-NOV-2011.

Entire sample separation activity was done under sodium vapour lamp covered with red gelatin paper.

Alendronic acid/colecalciferol is considered a light sensitive medicinal product. Therefore, the applicant is requested to confirm that, for the whole study, the dosing (dispensing), blood sampling (i.e. storage in amber coloured tubes), plasma separation and storage of samples was performed under appropriate conditions for a light-sensitive product, and to further explain these measures.

Safety was assessed from the screening period to the end of the study. Protocol deviations concern post-dose sampling, concomitant medication, pre-dose non-compliance (subject withdrawn), pre-dose sampling, posture restriction, housing, sample separation and vitals and are addressed appropriately.

Test and reference products

Considering that Fosavance 70 mg/5,600 IU tablets of Merck Sharp & Dohme Ltd are approved via centralised procedure (as a full application under Art 8(3) of Directive 2001/83/EC) on 24-th of August 2005, the choice of the reference product is acceptable. From the provided Certificates of analysis of the biobatches, difference in the assay not greater than 5%, between the two products can be concluded.

Product Characteristics	**Test product**	**Reference product**
Name	Alendronate Sodium / Cholecalciferol Tablets 70 mg / 5600 IU	FOSVANCE® (Alendronate Sodium / Cholecalciferol Tablets 70 mg / 5600 IU)
Strength	Alendronate Sodium 70 mg and Cholecalciferol 5600 IU	Alendronate Sodium 70 mg and Cholecalciferol 5600 IU
Dosage form	Tablet	Tablet
Marketing Authorisation Holder	-	Merck Sharp & Dohme Ltd., Hertford Road, Heddesdon, Hertfordshire EN11 9BU, United

		Kingdom
Batch number	EC11275	Y0325
Measured content(s) **(% of label claim)**	Alendronate Sodium 100.0% Cholecalciferol 99.3%	Alendronate Sodium 101.7% Cholecalciferol 99.7%
Expiry date (Retest date)	Manufacturing date: 08/2011	May 2012

Population(s) studied

A total of one hundred sixteen (116) subjects (age between 18 to 45 (both inclusive), BMI between 19.0 to 29.0 kg/m2 (both inclusive)), having no significant disease in medical history or clinically significant abnormal findings during screening and having given their written informed consent, were enrolled in the study. Study was open for both male and female volunteers but only males were available for the study.

Out of 116 enrolled, 110 Subjects were dosed in Period 1 and 102 subjects were included in the Pharmacokinetic and Statistical Analysis.

The population is according to the guideline. The inclusion and exclusion criteria are acceptable.

Randomization was generated using statistical software package SAS (SAS Institute Inc., USA, Version 9.2). Drop-out and withdrawal of subjects are fully documented.

Subjects were instructed not to consume any medication at any time within 14 days prior to dosing in Period 1 until completion of the study. However, one subject who completed the study and whose data were used in the PK and statistical analysis administered 500 mg of paracetamol. Pre-study validations confirmed no effect of paracetamol on the determination of both analytes.

Analytical methods

The bioanalytical method documented in a pre-study validation report MV-323-09 for alendronate and VAL294.R1 for cholecalciferol.

Out of 5060 of total sample number prescribed by the protocol, 4870 was analysed. A total of 53 samples (1.09% of total samples analysed) were reanalysed for alendronate. Incurred sample reanalysis was performed on 366 samples (7.5% of total samples analysed) and total of 99.45% were within the acceptance criteria. The established long term stability of alendronate in human plasma of 92 days at –65 ± 10°C is adequate since sample storage period for alendronate lasted for 48 days at -65 ± 10°C.

For cholecalciferol, 5498 were analysed (5286 samples received from the clinical facility for single lot + 212 pre-dose samples analyzed without the addition of internal standard). A total of 2.3% (129/5498) samples were repeated. Incurred sample reanalysis was performed on 670 samples (12.7% of total 5286 samples) and 95.37% were within the acceptance criteria.

Two samples (out of total 5498; 0.04%) were re-assayed and the reassay was performed due to a pharmacokinetic reason which is unacceptable as this may affect and bias the outcome of such a study.

Following the observed high batch rejection rate (out of 100 analysed batches, 20 were rejected and 14 found unacceptable) an investigation was initiated as per SOP and the issue was resolved.

The established long term stability of cholecalciferol in human plasma (284 days at -80±15°C) is not found adequate since it does not support the stability of the analyte under conditions it was subjected during the course of the study (at –65±10°C at the clinical site then at -80±15°C at the bioanalytical site).

Pharmacokinetic variables

The PK variables are adequate. Primary PK parameters (C_{max} and AUC_{0-t}) and secondary PK parameters ($AUC_{0-\infty}$, T_{max}, λ_z, $t_{1/2}$ and $AUC_{\_\%Extrap\_obs\ (\%)}$) were calculated for alendronate, baseline adjusted and unadjusted data for cholecalciferol by non-compartmental model using WinNonlin Professional Software Version 5.3 (Pharsight Corporation, USA).

Baseline adjustment of cholecalciferol was done by taking average of plasma concentration of baseline hours (-24, -18 -12, -6, -1 and 0 h) and this average was subtracted from the plasma concentration of each time point starting for each subject to yield the net effect of drug administration as per criteria set in protocol 692-10 Version 05.

Additional baseline adjustment method, not pre-specified in the *protocol* - AUC baseline adjustment, has been performed.

Bioequivalence criteria:

The 90% confidence intervals of the relative mean (Geometric mean) AUC_{0-t} and C_{max} of the test to reference formulation for Ln-transformed PK data should be within 80% to 125% for alendronate and cholecalciferol baseline adjusted data in order to establish bioequivalence.

Statistical methods

Descriptive statistics is reported for PK parameters for alendronate and for cholecalciferol baseline adjusted / unadjusted data. The un-transformed and ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were subjected to Analysis of Variance (ANOVA) for Alendronate and Cholecalciferol. ANOVA model included Sequence, Formulation, Subject (Sequence) and Period as fixed effects. An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha=0.05).

Results

Table 1 Pharmacokinetic parameters for alendronate (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	CV%	arithmetic mean	CV%
$AUC_{(0-t)}$ (ng.h/mL)	160.956	57.7	160.078	60.7
$AUC_{(0-\infty)}$ (ng.h/mL)	170.533	57.3	169.920	60.1
C_{max} (ng/mL)	53.724	62.9	51.551	60.6
T_{max}* (h)	1.000	(0.500-2.500)	1.000	(0.500-3.000)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours>			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 2 Pharmacokinetic parameters for cholecalciferol (non-transformed values) for baseline unadjusted data

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	CV%	arithmetic mean	CV%
$AUC_{(0-t)}$ (ng.h /mL)	434.753	33.0	446.096	31.8
$AUC_{(0-\infty)}$ (ng.h / mL)	523.320	48.8	535.744	43.9
C_{max} (ng / mL)	10.525	26.9	10.948	25.5
T_{max}* (h)	12.000	8.000- 16.000	12.000	8.000- 18.000
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 3 Pharmacokinetic parameters for cholecalciferol (non-transformed values) for baseline adjusted data

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	CV%	arithmetic mean	CV%
$AUC_{(0-t)}$ (ng.h /mL)	352.152	28.5	361.324	25.1
$AUC_{(0-\infty)}$ (ng.h / mL)	376.336	29.9	386.778	26.3
C_{max} (ng / mL)	9.660	26.9	10.065	24.6
T_{max}* (h)	11.961	(8.000- 6.000)	12.000	(8.000- 8.000)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 4 Pharmacokinetic parameters for cholecalciferol (non-transformed values) for AUC baseline adjusted data

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	CV%	arithmetic mean	CV%
$AUC_{(0-t)}$ (ng.h /mL)	349.778	29.1	359.952	25.4
$AUC_{(0-\infty)}$ (ng.h / mL)	438.345	40.0	449.600	33.8
C_{max} (ng / mL)	10.525	26.9	10.948	25.5
T_{max}* (h)	12.000	8.000- 16.000	12.000	8.000- 18.000
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 5 Statistical analysis for alendronate (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	97.4%	87.32 – 108.61	49.6
C_{max}	100.0%	89.67 – 111.63	49.8
* estimated from the Residual Mean Squares			

The results of two statistical analyses for cholecalciferol have been provided: for baseline adjusted data (Table 6) in which bioequivalence was not shown and for AUC baseline adjusted data (Table 7):

Table 6 Statistical analysis for cholecalciferol (ln-transformed values) for baseline adjusted data

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	90.7	78.65 – 104.59	67.5
C_{max}	92.0	83.57 – 101.29	43.2
* estimated from the Residual Mean Squares			

Table 7 Statistical analysis for cholecalciferol (ln-transformed values) for AUC baseline adjusted data

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	98.4	93.80 – 103.32	21.0
C_{max}	93.9	87.94 – 100.35	29.0
* estimated from the Residual Mean Squares			

For alendronate, the test to reference ratio of geometric LS-means and corresponding 90% confidence interval for the C_{max} and AUC_{0-t} are all within the acceptance range of 80.00 to 125.00%.

Concerning cholecalciferol, the results of the statistical analysis performed as per protocol did not demonstrate bioequivalence.

The AUC baseline adjustment method (Table 7) does not appear as pre-specified in the protocol 692-10 Version No. 05, and the results cannot be regarded as confirmatory.

Furthermore, the submitted statistical analysis, performed on 102 subjects, includes also the data of subjects showing, for cholecalciferol, pre-dose concentration >5% of C_{max} (e.g. subject 1058) even though, according to the Protocol 692-10 Version No. 05, for these subjects, all of their cholecalciferol data are to be excluded from the statistical analysis.

The applicant is requested to provide means of all pre-dose values for all subjects as well as the justification on their inclusion in the performed statistical analysis, considering that the Protocol Version No. 05 prescribes otherwise; present a detailed explanation on both methods of baseline adjustment for cholecalciferol and subsequent statistical analyses, clarify as to whether or not the AUC baseline adjustment was pre-specified in the protocol and if this was not the case; to submit a re-analysis as per protocol exactly i.e. excluding all subjects with too high pre-dose using the protocolled

baseline adjusted analysis, and a re-analysis excluding all subjects with too high pre-dose concentrations using the additional AUC baseline adjusted analysis.

With the data as presented so far, bioequivalence has not been conclusively established.

Safety data

Neither death nor serious adverse event (AE) occurred during the study. In total, 10 AE occurred in study (6 for the test and 4 for the reference product) and all were mild in nature expect for one AE which was moderate in nature (Subject 1100; toothache).

The Applicant explained that the AE that occurred in the study (except for gastroenteritis and toothache, judged as unlikely), are possibly related to the study products. These adverse events considered as the most common adverse events mentioned in the literature.

Two AE were reported as significant: gastroenteritis and toothache. Both subjects were withdrawn from the study on medical grounds. The causality assessment for both the significant AEs was judged as unlikely to the study products by the Applicant.

The medicines were generally safe and well tolerated by the subjects in the study. However, from the Quality AR, fast disintegration of tablets is observed for the test product. Considering the risk of oesophageal irritation and related adverse reactions often observed with the administration of alendronate/cholecalciferol tablets (highlighted in the reference product SmPC), discussion on the potential impact of differences regarding product performance (fast disintegration of tablets) on safety and tolerance of the long-term use of the proposed product, from a clinical point of view, should be provided.

3.3.2. Pharmacokinetic conclusion

Due to the raised major objections regarding GCP (questionable study conduct in accordance with the approved version of Protocol), Statistics (performed AUC baseline adjustment method appears not to be pre-specified in the protocol) and Dissolutions regarding the biowaiver as well as due to other concerns raised from the assessment of the presented bioequivalence study, Alendronic Acid/Colecalciferol Mylan 70 mg/5,600 IU, tablets are not considered bioequivalent with Fosavance 70 mg/5,600 IU tablets of Merck Sharp & Dohme Ltd, under fasting conditions. Therefore, final decision regarding the bioequivalence cannot be made at this time point. Refer to the List of Questions in Section 5.

The results of study 692-10 with 70 mg/5,600 IU formulation cannot be extrapolated to the other strength 70 mg/2,800 IU, according to conditions in the relevant Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1/Corr**).

3.3.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

3.3.4. Additional data

In vitro dissolution tests complementary to the bioequivalence study

Dissolution profiles were conducted in three dissolution media: pH 1.2 (0.1 N HCl), pH 4.5, pH 6.8 and in QC media (purified water for alendronate and 0.9% NaCl and 2% SLS in Purified water for

cholecalciferol), in 900 ml volume for alendronate and 500 ml for cholecalciferol, using apparatus 2 (paddles) at agitation speed 75 rpm, at 37ºC.

For alendronate, results of in vitro comparison of the bio-batches demonstrated for all dissolution media >85% drug dissolved in first 15 minutes for both test and reference medicinal product.

It has been noted that, on the comparative dissolution test, standard conditions have not been followed as per the *Guideline on the investigation of bioequivalence* (e.g. 75 rpm instead of 50 rpm). The applicant is requested to justify this choice of conditions. Additionally, for cholecalciferol, in QC media >85% of drug was dissolved for both test and reference product. However, results in 0.1 N HCl, pH 4.5 and pH 6.8 showed a slow dissolution rate of the test medicinal product and significant discrepancy between the two formulations. Possible reasons for this discrepancy and its potential clinical significance should be discussed.

3.3.5. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

3.3.6. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate. To support this application the Applicant has submitted one bioequivalence study that is supported with the statement from the Applicant that the study complies with GCP principles. After reviewing the study results, major concerns are raised regarding the GCP compliance (uncertainties regarding protocol changes and corresponding ethical approvals) and the performed statistical analysis.

The study was an open label, balanced, randomized, two treatment, two sequence, two period, single dose crossover, oral bioequivalence study of Alendronate Sodium / Cholecalciferol Mylan Tablets 70 mg / 5600 IU and Fosavance Tablets 70 mg / 5600 IU (Alendronate Sodium / Cholecalciferol 70 mg / 5600 IU) of Merck Sharp & Dohme Ltd., United Kingdom, in 110 healthy adult male volunteers under fasting conditions. Study consisted of two periods (Period 1 and Period 2) separated with a 21 days of washout period. Subjects were housed from minimum 60 hours prior to drug administration until 96 hours after drug administration in both periods. Blood sampling periods were 24 hours and 96 hours for alendronate and cholecalciferol, respectively. The blood samples were withdrawn using syringe and transferred into pre-labeled sample collection tubes containing K3EDTA as anticoagulant for the analysis of cholecalciferol and K2EDTA as anticoagulant for the analysis of alendronate. A total of 38 blood samples were collected from each subject in each period. Validated LC-MS/MS methods were used. Pharmacokinetic variables were adequate. Both the test and the reference medicine were generally safe and well tolerated by the subjects included in the study.

For alendronate, the test to reference ratio of geometric LS-means and corresponding 90% confidence interval for the C_{max} and AUC_{0-t} are all within the acceptance range of 80.00 to 125.00%.

For cholecalciferol the results of two statistical analyses have been provided: (1) for baseline adjusted data in which bioequivalence was not shown and (2) for AUC baseline adjusted data. This AUC baseline adjustment (2) does not appear as pre-specified in the protocol 692-10 Version No. 05 and the results cannot be regarded as confirmatory. Furthermore, the submitted statistical analysis, performed on 102 subjects, includes also the data of subjects showing pre-dose concentration >5% of C_{max} (e.g. subject 1058) even though protocol 692-10 prescribes exclusion of these data. With the data as presented so far, bioequivalence has not been conclusively established.

Dissolution profiles comparing both test and reference medicinal product and two strengths of test medicinal product were conducted at pH 1.2, pH 4.5, pH 6.8 and in QC media, using apparatus 2 (paddles) at agitation speed 75 rpm.

It has been noted that, on the comparative dissolution test, standard conditions have not been followed as per the *Guideline on the investigation of bioequivalence* (e.g. 75 rpm instead of 50 rpm). The applicant is requested to justify this choice of conditions. Additionally, for cholecalciferol, the in vitro comparison of the bio-batches demonstrated slow dissolution rate and significant discrepancy between the two formulations (except in QC media when SLS is used) which need to be addressed.

For the lower tablet strength bioequivalence testing is waived with in vitro dissolution testing since general biowaiver criteria according to the Guideline on Investigation of bioequivalence are met. However, similarity between the test product bio-batch and lower strength cannot be concluded as f2 similarity factors regarding the biowaiver were not properly calculated considering that the %RSD values were not within the acceptance criteria. Proof of similarity between the two strengths as per Guideline or a discussion on this topic and an appropriate calculation, if considered necessary, is requested. Additionally, the results of the study 692-10 for strength 70mg/5600 IU cannot be extrapolated to lower strength, considering the bioequivalence has not been indisputably demonstrated.

3.3.7. Conclusions on clinical aspects

Alendronic Acid/Colecalciferol Mylan is not approvable since "major objections" have been identified and thus the bioequivalence between Alendronate Sodium / Cholecalciferol Mylan Tablets 70 mg / 5600 IU and Fosavance Tablets 70 mg / 5600 IU (Alendronate Sodium / Cholecalciferol 70 mg / 5600 IU) of Merck Sharp & Dohme Ltd, UK, cannot be concluded.

From the assessment of the presented bioequivalence study major objections regarding GCP (questionable study conduct in accordance with the approved version of Protocol), Statistics (the performed baseline adjustment method appears not to be pre-specified in the protocol) and biowaiver conditions (f2 similarity factors were not properly calculated) were observed, among others concerns. All observations are presented in this report in detail.

For all major and minor questions raised during this assessment, refer to section 5.

3.4. Risk management plan

Safety concerns

The Applicant identifies the following safety concerns

Table 2: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Osteonecrosis of jaw (MedDRA SMQ: Osteonecrosis)
Important potential risks	Atypical femur fracture (MedDRA PTs: Atypical femur fracture, Femur fracture)
Missing information	Use in patients below 18 years of age

Having considered the data in the safety specification, the CHMP considers that the following issues should be addressed:

In line with the reference product, the CHMP considers that the following should also be a safety concern "Oesophageal adverse experiences" and should be included as important identified risk.

Also, "Use during pregnancy and lactation" and "Use in patients with severe renal insufficiency [GFR less than 35 mL/min]" should be included in section "Missing information".

The Applicant is advised not to include MedDRA terms into the section SVIII, Part II of the RMP.

Pharmacovigilance plan

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

However, in line with the comments above, the Applicant is requested to propose in a revised version of the RMP pharmacovigilance activities to monitor additional safety concerns identified in Part II.

Risk minimisation measures

Table 3: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Osteonecrosis of jaw (MedDRA SMQ: Osteonecrosis)	Section 4.4 and 4.8 of the SPC contain adequate information on this safety concern. Sections 2 and 4 of PL advise patients on this safety concern.	None
Atypical femur fracture (MedDRA PTs: Atypical femur fracture, Femur fracture)	Section 4.4 and 4.8 of the SPC contain adequate information on this safety concern. Sections 4 of PL advise patients on this safety concern	None
Use in patients below 18 years of age	Section 4.2 of the SPC contains information on the lack of experience in children under the age of 18 years. Section 2 of PIL addresses this lack of information in children under the age of 18 years.	None

The CHMP, having considered the data submitted, is of the opinion that:

In line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

However, in line with the comments above, the Applicant will have to propose in an updated version of the RMP with appropriate risk minimisation measures to manage any additional safety concern.

Conclusion

The RMP could be acceptable provided an updated RMP and satisfactory responses to the list of questions below is submitted.

3.5. Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

4. Benefit/risk assessment

4.1. Conclusions

The overall B/R of Alendronic Acid/Colecalciferol Mylan is currently negative.