28 January 2016
EMA/CHMP/182030/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Amlodipine/Valsartan Mylan

International non-proprietary name: amlodipine / valsartan

Procedure No. EMEA/H/C/004037/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
API:	Active Pharmaceutical Ingredient
AS(s)	Active substance(s)
AUC ratio	The ratio of AUC_{0-t} to $AUC_{0-\infty}$ expressed in (%) percentage
AUC_{0-72}	The area under the plasma concentration versus time curve from time 0 to 72 hours
$AUC_{0-\infty}$	The area under the plasma concentration versus time curve from time 0 to infinity
AUC_{0-t}	The area under Plasma concentration versus time curve from time 0 to t, where t = time of last measurable concentration
BMI	Body Mass Index
CC	Calibration curve
CEP	Certificate of Suitability
CFU	Colony-forming unit
C_{max}	Maximum measured plasma concentration over the time span specified
CoA	Certificate of analysis
CRC	Clinical Research Centre
CV%	Percentage Coefficient of Variation
CV	Captured volume
EC	Ethics Committee
EDQM	European Directorate for the Quality of Medicines and HealthCare
EEA	European Economic Area
ER	Environmental Risk
ERA	Environmental Risk Assessment
EU	European Union
f2	The similarity factor
GC	Gas chromatography
GCP	Good Clinical Practice
GLM	General Linear Models
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCl	Hydrochloric Acid
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation
ICMR	Indian Council of Medical Research
ID	Identification
IPC	In-process controls
IR	Infra-Red Spectroscopy
ISR	Incurred Sample Reanalysis
K_2EDTA	Di Potassium Ethylene Diamine Tetra Acetic Acid
K_{el}	Apparent first – order terminal elimination rate constant
KF	Karl Fischer
Kg/m^2	Kilogram per square meter
LOQ	Limit of quantitation
LQCT	Last measurable blood sampling point
LSM	Least Square Mean
MAH	Marketing Authorisation Holder
Mg	Milligram
min	Minute
Ml	Milliliter
N	Number of subjects

ng	Nanogram
NKEL	Number of points used in calculation of terminal elimination rate constant
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
No	Number
ºC	Degree Celsius
OOS	Out of specification
PCTFE	Polychlorotrifluoroethylene
Ph.Eur.	European Pharmacopoeia
PVC	Poly vinyl chloride
QCs	Quality Control Sample
QP	Qualified Person
RH	Relative Humidity
rpm	Revolutions per minute
SAS	Statistical Analysis Software
SmPC, SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TAMC	Total Aerobic Microbial Count
TYMC	Total Combined Yeasts/Moulds Count
$t_{1/2}$	Apparent first-order terminal elimination half-life calculated as $0.693/K_{el}$
TLIN	Time point at which log linear elimination begins
T_{max}	Time of the maximum measured plasma concentration
UPLC	Ultra-Performance Liquid Chromatography
USP	United States Pharmacopoeia
USNF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet light

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MYLAN S.A.S. submitted on 20 January 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Amlodipine/Valsartan Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26/06/2014.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Treatment of essential hypertension. Amlodipine/Valsartan Mylan is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and two bioequivalence studies with the reference medicinal product Exforge instead of non-clinical and clinical data.

Information on paediatric requirements

Not applicable.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
  - Product name, strength, pharmaceutical form: Exforge 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets
  - Marketing authorisation holder: Novartis Europharm Limited
  - Date of authorisation: (17-01-2007)
  - Marketing authorisation granted by:
    - Community
  - Marketing authorisation number:
    - 5 mg/80 mg: EU/1/06/370/001-008; EU/1/06/370/025-027; EU/1/06/370/034; EU/1/06/370/037
    - 5 mg/160 mg: EU/1/06/370/009-016; EU/1/06/370/028-030; EU/1/06/370/035; EU/1/06/370/038
    - 10 mg/160 mg: EU/1/06/370/017-024; EU/1/06/370/031-033; EU/1/06/370/036; EU/1/06/370/039
- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Exforge 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: (17-01-2007)
- Marketing authorisation granted by:
  - Community
- Marketing authorisation number:
  - 5 mg/80 mg: EU/1/06/370/001-008; EU/1/06/370/025-027; EU/1/06/370/034; EU/1/06/370/037
  - 5 mg/160 mg: EU/1/06/370/009-016; EU/1/06/370/028-030; EU/1/06/370/035; EU/1/06/370/038
  - 10 mg/160 mg: EU/1/06/370/017-024; EU/1/06/370/031-033; EU/1/06/370/036; EU/1/06/370/039

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Exforge 5 mg/160 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: (17-01-2007)
- Marketing authorisation granted by:
  - Community
  - Marketing authorisation number(s): EU/1/06/370/011
- Bioavailability study number(s): 3064/13

- Product name, strength, pharmaceutical form: Exforge 10 mg/160 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: (17-01-2007)
- Marketing authorisation granted by:
  - Community
  - Marketing authorisation number(s): EU/1/06/370/019
- Bioavailability study number(s): 3065/13

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

An application was filed in the following countries: USA and Japan.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Piotr Fiedor Co-Rapporteur: N/A

- The application was received by the EMA on 20 January 2015.

- The procedure started on 25 February 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 11 June 2015.
- During the meeting on 25 June 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 September 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 October 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 6 November 2015
- During the CHMP meeting on 19 November 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 December 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 January 2016.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 14 January 2016.
- During the meeting on 28 January 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Amlodipine/Valsartan Mylan.

2. Scientific discussion

2.1. Introduction

The present application is made under Article 10(1) generic application, i.e. Amlodipine/Valsartan Mylan 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets is a generic version of the already approved reference product Exforge 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets by Novartis Europharm Limited, which has been marketed in the UE for more than 6 years.

2.2. Quality aspects

2.2.1. Introduction

Amlodipine/Valsartan Mylan is presented as film-coated tablets containing 5 mg /80 mg, 5 mg /160 mg or 10 mg /160 mg of amlodipine (as besilate) and valsartan as active substances in a fixed dose combination.

Other ingredients in the tablet core are: cellulose microcrystalline, crospovidone, magnesium stearate, silica colloidal anhydrous and iron oxide yellow (only in 5 mg/160 mg strength);

ingredients in the coating of the 5 mg /80 mg and the 5 mg /160 mg are: hypromellose, titanium dioxide (E171), macrogol 8000, talc, iron oxide yellow (E172);

ingredients in the coating of the 10 mg /160 mg are: hypromellose, titanium dioxide (E171), macrogol 8000, talc, iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172), as described in section 6.1 of the SmPC.

The finished product is available in HDPE bottles or PVC/ PCTFE blister, as described in section 6.5 of the SmPC.

2.2.2. Active substance

Amlodipine besilate

General information

Amlodipine besilate is a well-known active substance often formulated in combination with other substances for the treatment of hypertension. The INN name of the active substance is amlodipine and the chemical name is 3-Ethyl-5-methyl (4RS)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine- 3,5-dicarboxylate benzenesulfonate. Its molecular formula and weight are $C_{26}H_{31}ClN_2O_8S$ and 567.05 g/mol, respectively, and its structure is shown below:

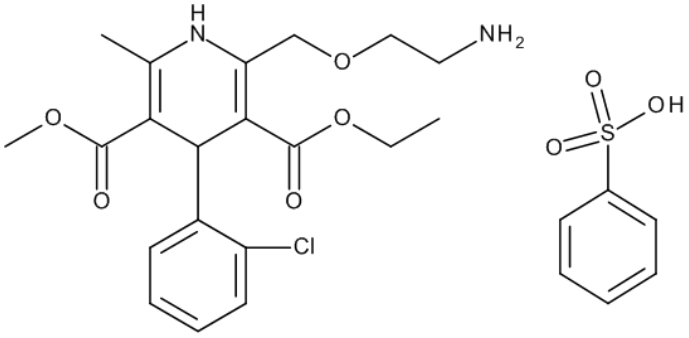

Figure 1: Amlodipine besilate structure.

Amlodipine besilate is a white or almost white powder. It is slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol.

As there is a monograph of amlodipine besilate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The description of manufacturing process steps and in-process controls, characterisation, control of materials and of critical steps and intermediates, process validation and manufacturing process development are all

covered by the CEP. The active substance is manufactured at one manufacturing site. it has been shown that the anhydrous form of amlodipine besilate is consistently manufactured by the proposed supplier.

Specification

The control tests comply with the specifications and test methods of the Ph. Eur. monograph, as confirmed by the CEP. The CEP includes an additional control for residual solvents used in the manufacturer's synthetic route. In addition a limit for an impurity and particle size distribution has been included in the active substance specification from the applicant. The proposed particle size limit was based on the particle size of the active substance batches used in the manufacturing of the finished product batches used for the bio-equivalence study.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standards has been provided.

Batch analyses data for two batches used for stability and/or process validation were provided. The results are consistent from batch to batch and comply with the specification in all cases.

Stability

The proposed re-test period and packaging material for amlodipine are covered by the CEP.

Valsartan

General information

Valsartan is a well-known active substance often formulated in combination with other substances for the treatment of hypertension. The chemical name of the active substance is (2*S*)-3-Methyl-2- [pentanoyl [[2' -(1H-tetrazol-5 -yl) biphenyl-4-yl methyl] amino] butanoic acid. Its molecular formula and weight are $C_{24}H_{29}N_5O_3$ and 435.5 g/mol, respectively, and its structure is shown below:

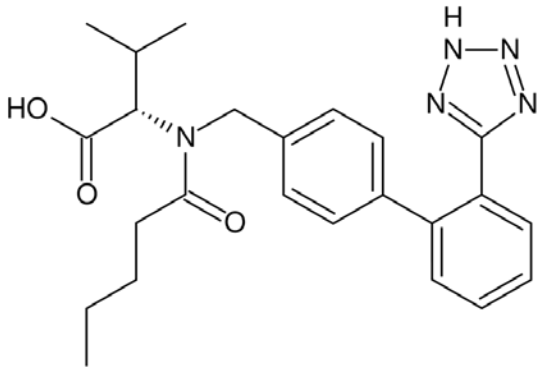

Figure 2: Valsartan besilate structure.

Valsartan is a white or almost white, hygroscopic powder. It is practically insoluble in water, freely soluble in anhydrous ethanol, sparingly soluble in methylene chloride.

As there is a monograph of valsartan in the European Pharmacopoeia, the manufacturer of the active substance has been granted a CEP which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The description of manufacturing process steps and in-process controls, characterisation, control of materials and of critical steps and intermediates, process validation and manufacturing process development are all covered by the CEP. The active substance is manufactured at two manufacturing sites of the same CEP holder. It has been shown that valsartan is consistently produced in its amorphous form.

Specification

The control tests comply with the specifications and test methods of the Ph. Eur. monograph, as confirmed by the CEP. The CEP includes an additional control for a residual solvent used in the manufacturer's synthetic route. In addition an identification test and a limit for particle size distribution have been included in the active substance specification by the applicant. The proposed particle size limits were based on the particle size results of the active substance batches used in the manufacturing of the finished product batches used for the bio-equivalence study.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standards has been provided.

Batch analyses data for two batches used for stability and/or process validation were provided. The results are consistent from batch to batch and comply with the specification in all cases.

Stability

The proposed re-test period and packaging material for amlodipine are covered by the CEP.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

Amlodipine/Valsartan Mylan is an immediate release film-coated tablet. The different tablet strengths are appropriately differentiated by their colour and/or shape as follows:
5mg/80mg film-coated tablets are light yellow, round, biconvex, debossed with "AV1" on one side and "M" on the other side;
5mg/160mg film-coated tablets are yellow, oval, biconvex, debossed with "AV2" on one side and "M" on the other side;
10mg/160mg film-coated tablets are light brown, oval, biconvex, debossed with "AV3" on one side and "M" on the other side.
The purpose of the pharmaceutical development studies was to develop a generic product bioequivalent to the reference product Exforge 5 mg /80 mg, 5 mg /160 mg and 10 mg /160 mg film-coated tablets.
The objectives of development were set so that the developed product is suitable for production for commercial scale batches and exhibit consistent quality. The product should also demonstrate acceptable stability performance in the proposed marketing packs.

The choice of the excipients has been satisfactorily justified and their levels have been chosen based on formulation optimisation studies. The compatibility of the active substance with the excipients has been adequately demonstrated.

The effect of the particle size of both active substances (AS) on tablet characteristics has been evaluated in trial batches with AS of different particle sizes. It was concluded that, within the studied ranges, the particle size of the active substances does not adversely impact dissolution. The proposed quality control (QC) dissolution method has been satisfactorily developed and justified. It has been shown to be discriminatory with regard to relevant changes in the composition of the tablets, and relevant process parameters.

The anhydrous form of amlodipine besilate is consistently manufactured by the proposed supplier and this has been confirmed by evaluating three production scale batches. The stability of the polymorphic form has been evaluated by analysing 60 months long term stability data. Valsartan is produced in its amorphous form consistently. Evidence to this effect has been provided as well as that the amorphous state does not change after 60 months under long term stability conditions.

Two bioequivalence studies have been conducted comparing Amlodipine/Valsartan Mylan 10 mg/160 mg (test) and Amlodipine/Valsartan Mylan 5 mg/160 mg (test) with the respective strengths of Exforge (reference). Comparative dissolution studies between the test and reference biobatches in the following three media were studied: 0.1N hydrochloric acid, pH 4.5 acetate buffer and pH 6.8 phosphate buffer; the latter is also the QC media. In pH 4.5 and 6.8 media the dissolution profiles of both substances were shown to be similar between the test and the reference product. In 0.1 N hydrochloric acid, the dissolution of the test product was shown to be faster but the difference was justified, as required by the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) in case of difference between the *in vitro* and *in vivo* findings. The justification was based on the difference between test and reference products with regards to the total tablet weight, the *in vivo* results where both the test and the reference products were found to be bioequivalent and the linear pharmacokinetic properties of the ASs. Hence the observed *in vitro* difference at this pH is not expected to have any clinical significance and the justification was accepted.

A strength biowaiver has been requested for Amlodipine/Valsartan Mylan 5 mg/80 mg. All the conditions specified in the Guideline on the Investigation of Bioequivalence are met. In relation to the strength biowaiver, comparative dissolution studies has been provided for Amlodipine/Valsartan Mylan 5 mg/80 mg strength and the 5mg /160 mg test bio batch in 0.1N hydrochloric acid, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The study demonstrated similarity of the dissolution profiles and thus from this point of view the biowaiver has been accepted.

A comparative impurity profile study between Amlodipine/Valsartan Mylan and the reference product exhibited similar impurity profiles.

Considering the physicochemical characteristics of both ASs and the characteristics of the pharmaceutical form, a dry granulation technique was selected as the manufacturing process. The process parameters for the compaction, milling, blending and tabletting have been optimised through a series of studies.

The finished product will be packaged in high density polyethylene (HDPE) bottle pack with white opaque polypropylene cap with aluminium induction sealing liner wad. Alternatively it may be packed in PVC/PCTFE blister pack. Bulk product is packaged for shipment in a low density polyethylene (LDPE) bag which is placed in an outer triple laminated bag along with desiccant bags (silica gel) in between the bags and sealed. The triple laminated bags are then placed in a suitable tertiary pack. All the proposed packaging materials comply with the relevant EU and Ph.Eur. requirements.

Manufacture of the product and process controls

The main steps of the manufacturing process are: sifting, pre-mixing, compaction, milling and sifting, blending, tabletting, coating and packaging. The critical steps of the process have been defined as blending, tabletting, coating and packaging. All provided in-process controls established for the manufacturing process are acceptable and justified and are considered suitable to guarantee the intended quality of the finished product. The holding time and storage conditions of the different intermediates between the process steps have been also specified.

This is a standard process. Validation of the manufacturing process was carried out for three commercial scale batches for all three strengths. In addition a satisfactory process validation protocol has been provided for larger batch sizes. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for this kind of dosage form including description, identification (TLC, HPLC), dissolution (HPLC, Ph. Eur.), uniformity of dosage units (Ph. Eur.), related substances (HPLC), assay (HPLC), water (Karl-Fischer), colour identification for titanium dioxide and iron oxide (chemical reaction) and microbial test (Ph. Eur.).

The specifications were set in line with the requirements of the Ph. Eur. general monographs, the ICH guidelines and available batch data. Identified impurities A, E and F from amlodipine besilate and impurities A and C for valstartan, as per the respective Ph. Eur. monographs, are not tested in the finished product because they are process related impurities i.e. not degradation products and because they are controlled in each active substance. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of active substances and impurities has been presented.

Batch analyses results for 9 batches of Amlodipine/Valsartan Mylan film-coated tablets (three of each strength) were provided. All batches have been analysed according to the methods valid at the time of release. All batches were found to be acceptable as per the specification valid at the time of release. Results were in line with proposed specifications and confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three commercial scale batches per strength stored under long term conditions (25 ± 2 ºC /60 ± 5% RH) for up to 24 months and under accelerated conditions (40 ± 2 ºC /75 ± 5%RH) for 6 months were provided. The stability studies were carried out in accordance with the ICH guidelines on stability. All the batches were packed in the container closure systems proposed for marketing.

The bulk shipment pack was also assessed for stability. A simulated bulk shipment pack (SBP) has been studied at accelerated and long-term stability conditions for 24 weeks and 12 months, respectively. The packaging of the SBP is essentially similar to proposed bulk shipment pack differing only in dimensions.

Samples have been tested for description, assay, dissolution, water content, related substances and microbial test. The methods used were shown to be stability indicating and were the same as for release. No significant changes were observed in any of the tested packaging and the results were found to be well within the specification.

A photo stability study has been performed on a commercial batch of each strength of Amlodipine/ Valsartan Mylan tablets as per ICH Q1B Guideline. The results indicate that there are no significant changes for description, assay, related substances and dissolution of amlodipine besilate or valsartan when exposed to light. Therefore, it was concluded that Amlodipine/ Valsartan Mylan film-coated tablets are photo stable.

A forced degradation study (under aqueous medium, acidic medium, basic medium, oxidative medium, light/UV stress heat and humidity) has shown varying degree of degradation which was more prominent in samples exposed to heat.

An in-use stability study has been conducted on a commercial batch of each strength of Amlodipine/ Valsartan Mylan tablets in compliance with the "Note for Guidance on in-use stability testing of human medicinal products" (CPMP/QWP/2934/99). Based on the results of this study, an in-use shelf life of 100 days for the product packed in HDPE bottle pack is accepted as stated in section 6.3 of the SmPC.

Based on the overall results, the proposed shelf-life of 2 years without any special storage conditions, as stated in the SmPC (section 6.3), is acceptable.

Adventitious agents

None of the materials used in the manufacture of Amlodipine/ Valsartan Mylan film-coated tablets are of human or animal origin.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview (Module 2.4) 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 and excipients content have been discussed and were considered

acceptable from toxicological point of view. The impurity profile has been discussed and was considered acceptable.

The CHMP considers that the non-clinical overview is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted.

The present application is made under article Article 10(1) generic application, i.e. Amlodipine and Valsartan Mylan 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets is a generic version of the already approved reference product Exforge 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets by Novartis Europharm Limited, which has been marketed in the UE for more than 6 years. As a generic product, it is anticipated that sales of this product will replace those of similar marketed products and no increase in environmental exposure to Amlodipine Besilate and Valsartan is likely on licensing of Amlodipine/Valsartan Mylan, film-coated tablets.

The applicant stated that the approval of the drug product will not lead to an increase of the total quantity of drug active substances into the environment. This is considered to be an acceptable justification for the absence of an environmental risk assessment in line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

The range of non-clinical data presented in the dossier is typical for generic application and include no new studies. Taking into account regulatory requirements for this category of application, there are no objections to approval of Amlodipine/Valsartan Mylan from a non-clinical point of view.

The lack of an ERA is deemed justified since the product is a generic version of an already approved one and it is not likely to change the total market of Amlodipine besilate and Valsartan.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Amlodipine/Valsartan Mylan from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Amlodipine besilate/Valsartan, 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg containing amlodipine and valsartan. To support the marketing authorisation application the applicant conducted 2 bioequivalence studies with cross-over design under fasting conditions. The bioequivalence of the test formulation versus the reference product has been investigated on the 5mg/160 mg strength (study 3064/13) and 10 mg/160 mg strength (study 3065/13).

These studies were the pivotal studies for the assessment.

- Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of control	Study 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								
BE	Project No. 3064/13	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports	Primary objective of this study was to assess the single dose bioequivalence of Amlodipine Besylate and Valsartan 5mg / 160mg tablets and Exforge® (Amlodipine Besylate and Valsartan) 5 mg/160 mg tablet of Novartis Limited UK in healthy adult subjects, under fasting conditions. Secondary objective of the present study was to monitor clinical status, adverse events and laboratory investigations and assess relative safety and tolerance of Amlodipine Besylate and Valsartan 5mg / 160mg tablets under fasting conditions.	A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Amlodipine Besylate and Valsartan 5mg / 160mg tablets and Exforge® (Amlodipine Besylate and Valsartan) 5 mg/160 mg tablet of Novartis Limited UK in healthy adult subjects, under fasting conditions.	Test Product: AMLODIPINE BESYLATE and Valsartan Tablets 5 mg/160 mg Single oral dose Reference Product: EXFORGE® amlodipine/ Valsartan Film-coated tablets 5 mg/160 mg Single oral dose	Planned- 60 Enrolled- 60 Dosed Period I: 60 Period II: 55 Completed - 55 Analyzed - 55 completed subjects for Valsartan and first 30 completed subjects for Amlodipine Withdrawn - Nil Dropped out - 05	Healthy subjects	Single dose	Complete; ICH E3 Guideline (Structure and Content of Clinical Study Reports)
PK	Not Applicable								
PD	Not Applicable								
Efficacy	Not Applicable								

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of control	Study 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								
BE	Project No. 3065/13	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports	Primary objective of this study was to assess the single dose bioequivalence of Amlodipine Besylate and Valsartan 10mg / 160mg tablets and Exforge® (Amlodipine Besylate and Valsartan) 10 mg/160 mg tablet of Novartis Limited UK in healthy adult subjects, under fasting conditions. Secondary objective of the present study was to monitor clinical status, adverse events and laboratory investigations and assess relative safety and tolerance of Amlodipine Besylate and Valsartan 10mg / 160mg tablets under fasting conditions.	A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Amlodipine Besylate and Valsartan 10mg / 160mg tablets and Exforge® (Amlodipine Besylate and Valsartan) 10 mg/160 mg tablet of Novartis Limited UK in healthy adult subjects, under fasting conditions.	Test Product: Amlodipine Besylate and Valsartan Tablets 10 mg/160 mg Single oral dose Reference Product: EXFORGE® Amlodipine/valsart an tablets 10 mg/160 mg Single oral dose	Planned- 60 Enrolled- 60 (Group 1: subject nos. 01-40 and Group 2: subject nos. 41-60) Dosed Group I oPeriod I: 40 oPeriod II: 37 Group II oPeriod I: 20 oPeriod II: 16 Completed - 52 Analyzed -56 subjects for Valsartan and first 30 completed subjects for Amlodipine Withdrawn - 04 Dropped out - 04	Healthy subjects	Single dose	Complete; ICH E3 Guideline (Structure and Content of Clinical Study Reports)
PK	Not Applicable								
PD	Not Applicable								
Efficacy	Not Applicable								

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) are of particular relevance.

GCP

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

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

Exemption

A justification for a biowaiver for Amlodipine Besilate/Valsartan, 5 mg/80 mg, film-coated tablets has been provided. According to the Guideline on the Investigation of Bioequivalence *(CPMP/EWP/QWP/1401/98 Rev. 1 – August 2010),* Amlodipine Besilate/Valsartan, 5 mg/80 mg film-coated tablets satisfy the conditions for waiver of bioequivalence studies conducted on the applied product 5 mg/160 mg and 10 mg/160 mg strength.

2.4.2. Pharmacokinetics

2.4.2.1. Study 3064/13

Study 3064/13: A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Amlodipine Besilate and Valsartan 5 mg/160 mg tablets of Mylan and Exforge® (Amlodipine Besilate and Valsartan) 5 mg/160 mg tablet of Novartis Limited UK in healthy adult subjects, under fasting conditions.

Methods

Study design

This was an open label, balanced, randomized, laboratory-blind, two period, two sequence, crossover study to assess the single dose bioequivalence of the applied Amlodipine Besilate/Valsartan, 5 mg/160 mg, film-coated tablets with the reference product Exforge® 5 mg/160 mg, film-coated tablets in healthy, adult, male subjects under fasting conditions.

The study periods were separated by a washout period of 21 days.

Test and reference products

Amlodipine Besilate/Valsartan, 5 mg/160 mg, film-coated tablets by Mylan (batch no. 2002214, expiry date: 01/2015, assay of amlodipine besilate 99.2%, assay of valsartan 100.3%, batch size 170000) has been compared to Exforge® 5 mg/160 mg, film-coated tablets by Novartis Europharm Limited, United Kingdom (batch no. B5232, expiry date: 04/2015, assay of amlodipine besilate 98.8%, assay of valsartan 99.5%).

The applicant confirms that the composition and the manufacturing process of the test product formulation used in bioequivalence study and the formulation proposed for commercial supplies to EEA is the same.

Population(s) studied

60 healthy, adult, non-smoking, human male subjects of Asian origin, between 19 and 42 years of age with a BMI 19 – 29.8 kg/m2 were enrolled and randomized. 55 subjects completed the study.

The data of 55 subjects were included for pharmacokinetic and statistical analysis for valsartan. The data of first 30 subjects were included for pharmacokinetic and statistical analysis for amlodipine.

Analytical methods

The validated HPLC/MS/MS method for the determination of valsartan concentration in K3EDTA human plasma was used over a concentration range of 50.015 ng/ml to 9002.664 ng/ml. The quality control sample (QC) concentrations of valsartan were: 150.044 ng/ml, 1700.503 ng/ml, 3401.006 ng/ml, 6802.013 ng/ml. The internal standard was olmesartan impurity.

A total of 2760 samples were received and 2640 samples were analyzed from the 55 evaluable subjects. A total of 201 samples (7.61% of the total samples analyzed) were repeated for valsartan. The incurred sample reanalysis was performed on 264 samples but the acceptance criteria was based on data generated for 263 samples. The total of 84.79% ISR samples of valsartan were found to be within ± 20% of their original assay values.

The UPLC/MS/MS method for the determination of amlodipine concentration in K3EDTA human plasma was used over a concentration range of 0.100 ng/ml to 7.021 ng/ml. The QC concentrations of amlodipine were: 0.302 ng/ml, 1.248 ng/ml, 2.495 ng/ml, 5.433 ng/ml. Amlodipine-D4 maleic acid was used as an internal standard.

A total of 2759 samples were received and 1439 samples were analyzed from the 30 evaluable subjects. A total of 9 samples (0.63% of the total samples analyzed) were repeated for amlodipine. The incurred sample reanalysis was performed on 144 samples. The total of 93.06% ISR samples of amlodipine were found to be within ± 20% of their original assay values.

Long term stability of valsartan and amlodipine at -70±15ºC was proven for the largest storage period of the study samples.

Pharmacokinetic Variables

The following pharmacokinetic parameters for amlodipine and valsartan were determined for both products by non-compartmental method of Phoenix® Version 6.3.0.395.

Amlodipine – AUC0-72, Cmax, Tmax, Kel, t1/2, NKEL, TLIN, LQCT

Valsartan – AUC0-t, AUC0-∞, Cmax, AUC ratio, Tmax, Kel, t1/2, NKEL, TLIN, LQCT

Standards for bioequivalence

The 90% confidence interval of the relative mean AUC0-72 and Cmax for amlodipine and AUC0-t and Cmax for valsartan of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

Statistical methods

In presented study the randomization schedule was generated with statistical software (SAS® version 9.2 SAS Institute Inc., Cary NC, USA). Main statistical methodology based on: sample size evaluation and statistical analysis for bioequivalence of tested and reference products.

In the study the sample size calculation was based on the observed intra-subject coefficients of variation (CV %) for valsartan and amlodipine. The parameters (CV) were obtained from sponsor's in-house study data for valsartan (Cmax and AUC not exceeding 36% and assuming the true ratio falling within 95% to 105%) and sponsor's in-house estimates and the literature data for amlodipine. Studies should have at least 54 evaluable subjects to show the bioequivalence with a power of 80% at 5% level of significance. The applicant considering dropouts and/ or withdrawals decided to enroll 60 patients into the study.

Study population in trial for valsartan pharmacokinetics variables analysis consisted of 55 healthy, adult, Asian volunteers. For the study 60 patients was enrolled but 5 was considered as dropouts (4 from I chase, 1 from II chase).

Patients were healthy, adult, Asian volunteers.

First 30 cases was an attempt to study analysis of pharmacokinetics parameters for amlodipine.

Statistical analysis of primary endpoint consisted pharmacokinetic variables/parameters.

In the study primary variables were:

- AUC0-72, Tmax and Cmax for Amlodipine

- AUC0-t and Cmax, T max for Valsartan

The following summary statistics for the pharmacokinetic parameters were to calculate for both the Test (T) and Reference (R) products: Number of observations (N), arithmetic mean (mean), standard deviation (SD), minimum, maximum, median and percentage coefficient of variation (CV%) geometric mean (GM).

The analysis consisted with data from 24 time points (blood samples).

The log-transformed pharmacokinetic parameters - AUC0-72 and Cmax of Amlodipine and AUC0-t, AUC0-∞ and Cmax of Valsartan were analyzed using General Linear Model (PROC GLM procedure) of SAS®. The ANOVA model included sequence, subjects nested within sequence, period and treatment as fixed effects. The sequence effect was tested at the 10% level of significance using the mean sum of square of subjects nested within sequence from the ANOVA as the error term, in the F-ratio of the sequence effect. All the fixed effects were tested at the 5% level of significance using the residual error (mean square error) from the ANOVA, as error term in the F-ratio for the respective main effects.

The ratio of the Test and Reference product averages (Least Square Means) was estimated for the differences in the Least Square Means (LSM) of the logtransformed data of AUC0-72 and Cmax for Amlodipine and AUC0-t,AUC0-∞ and Cmax for Valsartan, then taking the anti-log of the estimates. Consistent with Schuirmann's two one-sided tests procedure for bioequivalence, the 90% confidence interval for the ratio of the Test and Reference was estimated using the difference of least square mean between test and reference (estimate), the't' value at Mean Square Error Degrees of Freedom and the Standard Error of Estimate. The Standard Error of Estimate was calculated using the Mean Square Error and the number of reference subjects from the GLM - ANOVA Model.

Non-parametric analysis of Tmax was performed on untransformed data of Amlodipine and Valsartan, using the Wilcoxon signed-rank test with estimated median difference, 90% confidence interval is based on Hodges-Lehmann's method.

Results

Table 1: Pharmacokinetic parameters for Amlodipine (non-transformed values) (N=30)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
AUC_{0-72} (ng.h/mL)	96.13	18.604	96.59	20.431
C_{max} (ng/mL)	2.24	0.486	2.25	0.450
T_{max}* (h)	9.00	(4.50 – 12.00)	8.00	(4.50 – 36.00)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 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: Statistical analysis for Amlodipine (ln-transformed values) (N=30)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC_{0-72} (ng.h/mL)	99.93%	95.65% - 104.40%	9.99%
C_{max} (ng/mL)	99.47%	94.25% - 104.98%	12.33%
* estimated from the Residual Mean Squares			

Table 3: Pharmacokinetic parameters for Valsartan (non-transformed values) (N=55)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
AUC_{0-t} (ng.hr/mL)	27482.53	11227.417	26800.31	11638.959
$AUC_{0-\infty}$ (ng.hr/mL)	28140.34	11292.702	27428.74	11700.928
C_{max} (ng/mL)	4265.09	1674.343	4202.43	1616.902
T_{max}*	3.50	(1.00 – 6.50)	3.50	(1.00 – 6.00)
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: Statistical analysis for Valsartan (ln-transformed values) (N=55)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC_{0-t} (ng.hr/mL)	104.14%	96.37% - 112.52%	24.62%
$AUC_{0-\infty}$ (ng.hr/mL)	104.12%	96.53% - 112.30%	24.04%

The 90% confidence interval of the relative mean AUC0-72 and Cmax for amlodipine and AUC0-t and Cmax for valsartan of the test and reference product were within the acceptance range of 80.00% to 125.00% for log-transformed data.

Based on the results obtained in the study 3064/13, Amlodipine Besilate/Valsartan, 5 mg/160 mg, film-coated tablets of Mylan and Exforge® 5 mg/160 mg tablet of Novartis Limited UK were judged to be bioequivalent in healthy, adult subjects under fasting conditions

Safety data

Both the study products were found to be safe and well tolerated. There were no serious adverse events (AEs) reported in this study. Of the 19 adverse events reported during the study, 18 were considered related and 01 was considered unrelated to investigational products. 14 related adverse events occurred following administration of test product, which were mild (11) and moderate (03) to intensity. 04 related AEs were reported following administration of reference product, which were mild (03) to moderate (01) in intensity.

Pharmacokinetic conclusion

The bioequivalence of the applied product 5 mg/160 mg strength with the respective strength of the reference product Exforge® film-coated tablets has been demonstrated.

2.4.2.2. Study 3065/13

Study 3065/13: A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Amlodipine Besilate and Valsartan 10 mg/160 mg tablets of Mylan and Exforge® (Amlodipine Besilate and Valsartan) 10 mg/160 mg tablet of Novartis Limited UK in healthy adult subjects, under fasting conditions.

Methods

Study design

This was an open label, balanced, randomized, laboratory-blind, two period, two sequence, crossover study to assess the single dose bioequivalence of the applied Amlodipine Besilate/Valsartan, 10 mg/160 mg, film-coated tablets with the reference product Exforge® 10 mg/160 mg, film-coated tablets in healthy, adult, male subjects under fasting conditions.

The study periods were separated by a washout period of 24 days.

Test and reference products

Amlodipine Besilate/Valsartan, 10 mg/160 mg, film-coated tablets by Mylan (batch no. 2002188, expiry date: 01/2015, assay of amlodipine besilate 99.7%, assay of valsartan 100.2%, batch size: 170000) has been compared to Exforge® 10 mg/160 mg, film-coated tablets by Novartis Europharm Limited, United Kingdom (batch no. B0181, expiry date: 12/2013, assay of amlodipine besilate 99.7%, assay of valsartan 100.6%).

The applicant confirms that the composition and the manufacturing process of the test product formulation used in bioequivalence study and the formulation proposed for commercial supplies to EEA is the same.

Population(s) studied

60 healthy, adult, non-smoking, human male subjects of Asian origin, between 18 and 39 years of age with a BMI 18.6 – 29.9 kg/m2 were enrolled and randomized. The study was conducted in two groups: group I with subjects no. 01 – 40 and group II with subjects no. 41 – 60. 52 subjects completed the study.

The data of 52 subjects were included for pharmacokinetic and statistical analysis for valsartan. The data of first 30 subjects were included for pharmacokinetic and statistical analysis for amlodipine.

Analytical methods

The validated HPLC/MS/MS method for the determination of valsartan concentration in K3EDTA human plasma was used over a concentration range of 50.000 ng/ml to 7999.992 ng/ml. The quality control sample (QC) concentrations of valsartan were: 149.911 ng/ml, 1399.167 ng/ml, 2798.334 ng/ml, 5996.430 ng/ml. The internal standard was olmesartan impurity.

A total of 2685 samples were received and 2589 samples were analyzed from the 56 subjects who have completed both the study periods (including 97 samples from safety evaluations of subjects withdrawn due to adverse events). A total of 98 samples (3.79% of the total samples analyzed) were repeated for valsartan. The incurred sample reanalysis was performed on 254 samples. The total of 92.13% ISR samples of valsartan were found to be within ± 20% of their original assay values.

The UPLC/MS/MS method for the determination of amlodipine concentration in K3EDTA human plasma was used over a concentration range of 0.101 ng/ml to 10.111 ng/ml. The QC concentrations of amlodipine were: 0.303 ng/ml, 1.534 ng/ml, 3.836 ng/ml, 7.632 ng/ml. Amlodipine-D4 maleic acid was used as an internal standard.

A total of 2685 samples were received and 1438 samples were analyzed from the 30 evaluable subjects. A total of 18 samples (1.25% of the total samples analyzed) were repeated for amlodipine. The incurred sample reanalysis was performed on 144 samples but the acceptance criteria was based on data generated for 142 samples. The total of 98.59% ISR samples of amlodipine were found to be within ± 20% of their original assay values.

Long term stability of valsartan and amlodipine at -70±15ºC was proven for the largest storage period of the study samples.

Pharmacokinetic Variables

The following pharmacokinetic parameters for amlodipine and valsartan were determined for both products by non-compartmental method of Phoenix® Version 6.3.0.395.

Amlodipine – AUC0-72, Cmax, Tmax, Kel, t1/2, NKEL, TLIN, LQCT

Valsartan – AUC0-t, AUC0-∞, Cmax, AUC ratio, Tmax, Kel, t1/2, NKEL, TLIN, LQCT

Standards for bioequivalence

The 90% confidence interval of the relative mean AUC0-72 and Cmax for amlodipine and AUC0-t and Cmax for valsartan of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

Statistical methods

In presented study all conducted statistical analysis including preparing randomization schedule was generated with statistical software (SAS® version 9.2).

Main statistical methodology in presented studies was: sample size evaluation and statistical analysis for bioequivalence of tested and reference products.

In the study the sample size calculation was based on the observed intra-subject coefficients of variation (CV %) for valsartan and amlodipine. The parameters (CV) were obtained from sponsor's in-house study data for valsartan (Cmax and AUC not exceeding 36% and assuming the true ratio falling within 95% to 105%) and sponsor's in-house estimates and the literature data for amlodipine. Study should have at least 54 evaluable

subjects to show the bioequivalence with a power of 80% at 5% level of significance. The applicant considering dropouts and/ or withdrawals decided to enrol 60 patients into the studies.

60 healthy, adult, Asian volunteers were enrolled into the study. All of study population for valsartan pharmacokinetics variables analysis consisted of 53 subjects (dosed in both periods) and 52 subjects completed the study. In the study analysis of pharmacokinetics parameters for amlodipine concerned 30 patients only.

The statistical outlier test was performed on the pharmacokinetic data of 30 subjects for amlodipine and 52 subjects for valsartan using studentized residual test.

In the study primary variables were:

- AUC0-72 ,T max and Cmax for Amlodipine

- AUC0-t and Cmax, T max for Valsartan

and bioequivalence criteria were based on the 90% Confidence Intervals for these parameters.

The following summary statistics for the pharmacokinetic parameters were to calculate for both the Test (T) and Reference (R) products: Number of observations (N), arithmetic mean (mean), standard deviation (SD), minimum, maximum, median and percentage coefficient of variation (CV%) geometric mean (GM).

The analysis consisted with data from 24 time points (blood samples).

The log-transformed pharmacokinetic parameters - AUC0-72 and Cmax of Amlodipine and AUC0-t, AUC0-∞ and Cmax of Valsartan were analyzed using General Linear Model (PROC GLM procedure) of SAS®. The ANOVA model included sequence, subjects nested within sequence, period and treatment as fixed effects. The sequence effect was tested at the 10% level of significance using the mean sum of square of subjects nested within sequence from the ANOVA as the error term, in the F-ratio of the sequence effect. All the fixed effects were tested at the 5% level of significance using the residual error (mean square error) from the ANOVA, as error term in the F-ratio for the respective main effects.

The ratio of the Test and Reference product averages (Least Square Means) was estimated for the differences in the Least Square Means (LSM) of the logtransformed data of AUC0-72 and Cmax for Amlodipine and AUC0-t,AUC0-∞ and Cmax for Valsartan, then taking the anti-log of the estimates. Consistent with Schuirmann's two one-sided tests procedure for bioequivalence, the 90% confidence interval for the ratio of the Test and Reference was estimated using the difference of least square mean between test and reference (estimate), the't' value at Mean Square Error Degrees of Freedom and the Standard Error of Estimate. The Standard Error of Estimate was calculated using the Mean Square Error and the number of reference subjects from the GLM - ANOVA Model.

Non-parametric analysis of Tmax was performed on untransformed data of Amlodipine and Valsartan, using the Wilcoxon signed-rank test with estimated median difference, 90% confidence interval is based on Hodges-Lehmann's method.

The study was conducted in two groups, group I with subject nos. 01 - 40 and group II with subject nos. 41 – 60.

The study design established analysis of variance for combined group.

ANOVA was to be used on the log-transformed pharmacokinetic parameters- AUC0-72 and Cmax for Amlodipine and AUC0-t, AUC0-∞ and Cmax for Valsartan using a GLM ANOVA model with the main effects of

group, sequence, group*sequence, period nested within group, treatment and subject nested within group*sequence as fixed effects.

However applicant did not provide results of this analyze.

Results

Table 5: Pharmacokinetic parameters for Amlodipine (non-transformed values) (N=30)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
AUC_{0-72} (ng.h/mL) #	261.57	51.888	258.17	45.640
C_{max} (ng/mL)	6.27	1.480	6.03	1.119
T_{max}* (h)	8.00	(4.50 – 10.00)	7.00	(4.50 – 10.00)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 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)			
#	N=28			

Table 6: Statistical analysis for Amlodipine (ln-transformed values) (N=30)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC_{0-72} (ng.h/mL)	100.98%	98.10% - 103.96%	6.37%
C_{max} (ng/mL)	103.04%	99.64% - 106.56%	7.65%
* estimated from the Residual Mean Squares			

Table 7: Pharmacokinetic parameters for Valsartan (non-transformed values) (N=51) (Excluding Outlier Subject No. 53)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
AUC_{0-t} (ng.hr/mL)	24274.01	9293.848	22963.03	9164.908
$AUC_{0-\infty}$ (ng.hr/mL)	25020.80	9280.136	24087.14	8800.437
C_{max} (ng/mL)	3955.45	1451.757	3794.08	1757.598
T_{max}*	3.50	(1.00 – 5.00)	3.50	(1.00 – 5.00)
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 8: Statistical analysis for Valsartan (ln-transformed values) (N=51) (Excluding Outlier Subject No. 53)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC_{0-t} (ng.hr/mL)	108.37%	97.94% - 119.90%	31.03%
$AUC_{0-\infty}$ (ng.hr/mL)	106.44%	96.67% - 117.20%	29.20%
C_{max} (ng/mL)	110.36%	97.52% - 124.89%	38.39%
* estimated from the Residual Mean Squares			

Based on the statistical outlier test subject no. 53 was detected as an outlier for the pharmacokinetic parameters AUC0-t, AUC0-∞ and Cmax of valsartan. The statistical analysis for valsartan has been performed on both the datasets i.e. including as well as excluding the outlier.

According to the Guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr**: "Exclusion of data cannot be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone, because it is impossible to distinguish the formulation effects from other effects influencing the pharmacokinetics."

However, the case when a subject has a very low plasma concentrations of the reference medicinal product is the exception allowed by the Guideline. The AUC of the reference product is less than 5% of geometric mean AUC in the case of outlier in the study 3065/13. Therefore, the exclusion of data from this subject can be accepted.

The 90% confidence interval of the relative mean AUC0-72 and Cmax for amlodipine and AUC0-t and Cmax for valsartan (excluding outlier subject no. 53) of the test and reference product were within the acceptance range of 80.00% to 125.00% for log-transformed data.

Based on the results obtained in the study 3065/13, Amlodipine Besilate/Valsartan, 10 mg/ 160 mg, film-coated tablets of Mylan and Exforge® 10 mg/ 160 mg tablet of Novartis Limited UK were judged to be bioequivalent in healthy, adult subjects under fasting conditions.

Safety data

One medical event (soft tissue injury) was reported for subject no. 58 prior to dosing in period I, which was mild and resolved completely before dosing of the investigational product.

There were 12 adverse events reported during the study of which 11 were related and 01 was unrelated to the investigational products. Of the related adverse events, 04 occurred following administration of test product and 07 following administration of reference product. All adverse events were mild in intensity and resolved completely without sequelae.

Pharmacokinetic Conclusion

The bioequivalence of the applied product 5 mg/160 mg strength with the respective strength of the reference product Exforge® film-coated tablets has been demonstrated.

2.4.3. Pharmacodynamics

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

2.4.4. Additional data

In vitro dissolution tests were conducted using Type – II apparatus (paddle), 75 rpm, 1000 ml of three different media 0.1N Hydrochloric acid, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer comparing the test and reference biobatches used in both bioequivalence studies as well as the test biobatch Amlodipine Besilate/Valsartan 10mg/160 mg, film-coated tablet with the lower strength of the applied product i.e. Amlodipine Besilate/Valsartan 5 mg/80 mg, film-coated tablet.

Regarding in vitro dissolution tests complementary to the bioequivalence studies, the dissolution profiles of biobatches at pH 6.8 phosphate buffer and pH 4.5 acetate buffer can be considered similar as the f2 value for amlodipine and valsartan has been found between 50 and 100. There were no similarity of in vitro dissolution at 0.1 N HCl between the test and the reference biobatch 10 mg/160 mg strength. The f2 value for amlodipine and valsartan was found to be less than 50.

The results of comparative dissolution of the biobatches at 0.1 N HCl indicate that the test product show faster dissolution than the reference Exforge (which is more pronounced for amlodipine). The possible reasons for this discrepancy were discussed by the applicant. The dissimilarity of dissolution profiles between the biobatches 10 mg/160 mg strength at 0.1 N HCl is not expected to have any clinical significance, which is also confirmed by the in vivo study were both the test and the reference product were found to be bioequivalent.

The applicant has provided the additional dissolution data between the applied 5 mg/80 mg strength and the 10 mg/160 mg biobatch under the conditions described in the Guideline on the Investigation of Bioequivalence i.e. Type II apparatus (paddle), 500 rpm, 900 ml of three dissolution media (0.1 N HCl, pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer). The dissolution profiles were found to be similar in all the media studied. Therefore the biowaiver for the 5 mg/80 mg dose strength can be granted.

2.4.5. Post marketing experience

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

2.4.6. Discussion on clinical aspects

In both studies, the 90% confidence interval for the relative mean AUC0-72 and Cmax for amlodipine and AUC0-t and Cmax for valsartan (excluding outlier subject in study 3065/13) of the test and reference product were within the acceptance range of 80.00% to 125.00% for log-transformed data.

Studies submitted by the applicant include statistical analysis appropriate to bioequivalence studies. Guidelines include provisions as to compare parameters such as mean and median in theanalyses, so the use of ANOVA and Wilcoxon signed-rank test for primary endpoint was justified.

2.4.7. Conclusions on clinical aspects

The bioequivalence of the applied product Amlodipine Besilate/Valsartan, film-coated tablets, 5 mg/160 mg and 10 mg/160 mg strength with the respective strength of the reference product Exforge® film-coated tablets of Novartis Europharm Limited has been demonstrated.

An acceptable justification for a biowaiver of Amlodipine Besilate/Valsartan, 5 mg/80 mg, film-coated tablets has been provided. According to the Guideline on the Investigation of Bioequivalence *(CPMP/EWP/QWP/1401/98 Rev. 1 – August 2010),* Amlodipine Besilate/Valsartan, 5 mg/80 mg film-coated tablets satisfy the conditions for waiver of bioequivalence studies conducted on the applied product 5 mg/160 mg and 10 mg/160 mg strength.

2.5. 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.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Hyperkalaemia • Hypotension • Decreased renal function • Fetotoxicity (with use during the 2nd or 3rd trimester of pregnancy)
Important potential risk	• Teratogenicity (with use during the 1st trimester of pregnancy)
Missing information	• Use during breast feeding

Pharmacovigilance plan

Routine pharmacovilance activities only.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Hyperkalaemia	• Sections 4.4, 4.5 and 4.8 of the SPC contain adequate information on hyperkalaemia. • Sections 2 and 4 of the PIL contain adequate information on hyperkalaemia. • Product is POM only	None
Important identified risks: Hypotension	• Sections 4.3, 4.4, 4.6, 4.8 and 4.9 of the SPC contain adequate information on hypotension. • Sections 2 and 4 of the PIL contain adequate information on hypotension. • Product is POM only.	None
Important identified risks: Decreased renal function	• Sections 4.3, 4.4 and 4.5 of the SPC contain adequate information on decreased renal function. • Section 2 of the PIL contains adequate	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	information on decreased renal function. • Product is POM only.	
Important identified risks: Fetotoxicity (with use during the 2nd or 3rd trimester of pregnancy)	• Sections 4.3, 4.4 and 4.6 of the SPC contain adequate information on fetotoxicity (with use during the 2nd or 3rd trimester of pregnancy). • Section 2 of the PIL contains adequate information on fetotoxicity (with use during the 2nd or 3rd trimester of pregnancy). • Product is POM only.	None
Important potential risk: Teratogenicity (with use during the 1st trimester of pregnancy)	• Sections 4.4 and 4.6 of the SPC contain adequate information on teratogenicity (with use during the 1st trimester of pregnancy. • Section 2 of the PIL contains adequate information on teratogenicity (with use during the 1st trimester of pregnancy). • Product is POM only.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information: Use during breast feeding	• Section 4.6 of the SPC contains adequate information on use during breast feeding. • Section 2 of the PIL contains adequate information on use during breast feeding. • Product is POM only.	None

2.7. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Benefit-risk balance

Based on submitted bioequivalence studies the Amlodipine Besilate/ Valsartan Mylan film-coated tablets 5 mg/160 mg and 10 mg/160 mg are considered bioequivalent with the reference product Exforge.

An acceptable justification for a biowaiver for Amlodipine Besilate/Valsartan, 5 mg/80 mg, film-coated tablets has been provided. According to the Guideline on the Investigation of Bioequivalence *(CPMP/EWP/QWP/1401/98 Rev. 1 – August 2010),* Amlodipine Besilate/Valsartan, 5 mg/80 mg film-coated tablets satisfy the conditions for waiver of bioequivalence studies conducted on the applied product 5 mg/160 mg and 10 mg/160 mg strength.

This application concerns a generic version of amlodipine valsartan film-coated tablets. The reference product Exforge is indicated for treatment of essential hypertension, in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence studies forms the pivotal basis of this application. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Amlodipine/Valsartan Mylan 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets met the protocol-defined criteria for bioequivalence when compared with Exforge 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

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

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Amlodipine/Valsartan Mylan 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets in the treatment of essential hypertension is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.