COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Valsartan Mylan 40 mg, 80 mg, 160 mg and 320 mg, film-coated tablets (valsartan)

## NL/H/4552/001-004/DC

## Date: 27 February 2023

**This module reflects the scientific discussion for the approval of Valsartan Mylan 40 mg, 80 mg, 160 mg and 320 mg, film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/4518/001-004/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.**

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

# Public Assessment Report

## Decentralised Procedure

**Valsartan 40 mg Film-coated Tablets**
**Valsartan 80 mg Film-coated Tablets**
**Valsartan 160 mg Film-coated Tablets**
**Valsartan 320 mg Film-coated Tablets**

**Procedure No: UK/H/4518/001-4/DC**

**UK Licence No: PL 04569/1175-8**

**Generics (UK) Limited**

# LAY SUMMARY

**Valsartan 40 mg Film-coated Tablets**
**Valsartan 80 mg Film-coated Tablets**
**Valsartan 160 mg Film-coated Tablets**
**Valsartan 320 mg Film-coated Tablets**

(valsartan, film-coated tablets, 40 mg, 80 mg, 160 mg or 320 mg)

This is a summary of the Public Assessment Report (PAR) for Valsartan 40 mg, 80 mg, 160 mg, and 320 mg Film-coated Tablets (PL 04569/1175-8; UK/H/4518/001-4/DC). It explains how Valsartan 40 mg, 80 mg, 160 mg, and 320 mg Film-coated Tablets were assessed and their authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Valsartan 40 mg, 80 mg, 160 mg, and 320 mg Film-coated Tablets.

The products will be collectively referred to as Valsartan Tablets throughout the remainder of this PAR.

For practical information about using Valsartan Tablets patients should read the package leaflet or contact their doctor or pharmacist.

**What are Valsartan Tablets and what are they used for?**
Valsartan Tablets are 'generic medicines'. This means that Valsartan Tablets are similar to 'reference medicines' already authorised in the European Union (EU) called Diovan 40 mg, 80 mg, 160 mg and 320 mg Tablets (Novartis Pharmaceuticals UK Limited, UK).

Valsartan 40mg Film-coated Tablets can be used to treat:
- high blood pressure in children and adolescents aged 6 to 18yrs
- adult patients after a recent heart attack (myocardial infarction). Recent here means between 12 hours and 10 days.
- symptomatic heart failure in adult patients.

Valsartan 80mg and 160mg Film-coated Tablets can be used to treat:
- high blood pressure in adults, and in children and adolescents aged 6 to 18yrs
- adult patients after a recent heart attack (myocardial infarction). Recent here means between 12 hours and 10 days.
- symptomatic heart failure in adults.

Valsartan 320mg Film-coated Tablets can be used to treat:
- high blood pressure in adults, and in children and adolescents aged 6 to 18yrs

High blood pressure increases the workload on the heart and arteries. If not treated it can damage the blood vessels of the brain, heart, and kidneys, and may result in a stroke, heart failure, or kidney failure. High blood pressure increases the risk of heart attacks. Lowering blood pressure to normal reduces the risk of developing these disorders.

Heart failure occurs when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body. Heart failure symptoms include shortness of breath, and swelling of the feet and legs owing to fluid build-up. Valsartan Tablets are used for heart failure when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors

(a medication to treat heart failure) cannot be used or Valsartan Tablets may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used.

**How do Valsartan Tablets work?**
This medicine contains the active ingredient valsartan, which belongs to a class of medicines known as 'angiotensin II receptor antagonists'. Angiotensin II is a substance in the body that causes vessels to tighten, thus causing your blood pressure to increase. Valsartan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.

**How are Valsartan Tablets used?**
The pharmaceutical form of these medicines are film-coated tablet and the route of administration is oral (by mouth).

**Dose:**
The recommended dose of these medicines will depend on the patient's age, weight and the reason why they have been prescribed these medicines.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

These medicines can only be obtained with a prescription.

**What benefits of Valsartan Tablets have been shown in studies?**
Because Valsartan Tablets are generic medicines, studies in patients have been limited to tests to determine that each strength is bioequivalent to its respective reference medicine, Diovan 40 mg, 80 mg, 160 mg and 320 mg Tablets (Novartis Pharmaceuticals UK Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Valsartan Tablets?**
Because Valsartan Tablets are generic medicines, their benefits and possible side effects are taken as being the same as their respective reference medicines.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Valsartan Tablets, see Section 4 of the package leaflet available on the MHRA website.

**Why were Valsartan Tablets approved?**
It was concluded that, in accordance with EU requirements, Valsartan Tablets have been shown to have comparable quality and to be comparable to Diovan 40 mg, 80 mg, 160 mg and 320 mg Tablets (Novartis Pharmaceuticals UK Limited, UK). Therefore, the MHRA decided that, as for Diovan 40 mg, 80 mg, 160 mg and 320 mg Tablets (Novartis Pharmaceuticals UK Limited, UK), the benefits are greater than its risk and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Valsartan Tablets?**

A risk management plan (RMP) has been developed to ensure that Valsartan Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Valsartan Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Valsartan Tablets**

Austria, Belgium, Cyprus, Germany, Greece, Spain, France, Ireland, Italy, Luxembourg, the Netherlands Portugal and the UK agreed to grant Marketing Authorisations for Valsartan 40 mg, 80 mg and 160 mg Film-coated Tablets (PL 04569/1175-7; UK/H/4518/001-3/DC) on 06 July 2011. Marketing Authorisations were granted in the UK on 05 August 2011.

Austria, Belgium, Cyprus, Germany, Greece, Spain, Ireland, Italy, Luxembourg, the Netherlands, Portugal and the UK agreed to grant Marketing Authorisations for Valsartan 320 mg Film-coated Tablets (PL 04569/1178; UK/H/4518/004/DC) on 06 July 2011. Marketing Authorisations were granted in the UK on 05 August 2011.

The full PAR for Valsartan Tablets follows this summary.

For more information about treatment with Valsartan Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2016.

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# I INTRODUCTION

***Please note that the below scientific discussion consists of the original assessment of this product licence, plus a summary of key post approval changes at the end of this introduction section to improve the accuracy of this Public Assessment Report.***

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Valsartan 40 mg, 80 mg, 160 mg, and 320 mg Film-coated Tablets (PL 04569/1175-8; UK/H/4518/001-4/DC) could be approved. The products are prescription-only medicines (POM).

Valsartan 40 mg Film-coated Tablets are indicated for the treatment of:
- hypertension in children and adolescents 6 to 18 years of age
- clinically stable adult patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction
- symptomatic heart failure in adult patients when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used.

Valsartan 80mg and 160mg Film-coated Tablets are indicated for the treatment of:
- essential hypertension in adults, and hypertension in children and adolescents 6 to 18 years of age
- clinically stable adult patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction
- symptomatic heart failure in adult patients when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used.

Valsartan 320mg Film-coated Tablets are indicated for the treatment of:
- essential hypertension in adults, and hypertension in children and adolescents 6 to 18 years of age.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Belgium, Cyprus, Germany, Greece, Spain, France, Ireland, Italy, Luxembourg, the Netherlands and Portugal as Concerned Member States (CMS). These applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Diovan 40 mg, 80 mg, 160 mg and 320 mg Tablets (Novartis Pharmaceuticals UK Limited, UK), which were first authorised in the UK on 13 May 1996.

Valsartan Film-coated Tablets contain the active ingredient valsartan. Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the $AT_1$ receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following $AT_1$ receptor blockade with valsartan may stimulate the unblocked $AT_2$ receptor, which appears to counterbalance the effect of the $AT_1$ receptor. Valsartan does not exhibit any partial agonist activity at the $AT_1$ receptor and has much greater affinity for the $AT_1$ receptor than for the $AT_2$ receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Valsartan does not inhibit ACE (also known as kininase II), which converts Ang I to Ang II and degrades bradykinin.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.
One single-dose, bioequivalence study was submitted to support these applications, comparing the test product Valsartan 320 mg Film-coated Tablets (Generics (UK) Limited, UK) versus the reference product Diovan 320 mg Tablets (Novartis Pharmaceuticals UK Limited, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 06 July 2011. After a subsequent national phase, licences were granted in the UK on 05 August 2011.

Summary of key post-approval changes:
The following post-approval variations have been granted for these licences:

1. To add the following pack sizes '28, 56 and 98 tablets' for the HDPE bottles, in order to meet commercial needs. As a consequence, section 6.5 (container) of the SmPC and section 6 of the PIL have been updated (PL 04569/1175-0011, PL 04569/1176-0009, PL 04569/1177-0009 & PL 04569/1178-0010). Approved on 19/12/2012.
2. To add a new blister pack: PVC/PE/PVDC. Consequently, section 6.5 (Container) of the SPC has been updated and the limits for water content of the finished product at release are tightened. The product description has been updated as requested during Procedure UK/4518/002-003/1B/012 (40mg and 320mg strengths only). Section 3 of the SmPC and Section 6 of the PIL are accordingly updated (PL 04569/1175-0023, PL 04569/1176-0021, PL 04569/1177-0021 & PL 04569/1178-0022). Approved on 18/02/2015.

# II QUALITY ASPECTS

## II.1 Introduction

Each film-coated tablet contains 40 mg, 80 mg, 160 mg or 320 mg of valsartan.

Other ingredients consist of the pharmaceutical excipients in the tablet core and film coating, namely microcrystalline cellulose, crospovidone, povidone, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, hypromellose (E464), titanium dioxide (E171), Macrogol/PEG 8000, iron oxide yellow (E172), iron oxide black (E172) (40 mg, 160 mg and 320 mg tablets only), iron oxide red (E172) (80 mg, 160 mg and 320 mg tablets only). Appropriate justifications for the inclusion of each excipient have been provided.

The tablets are packaged in either:

1. cold form blister strips, comprising of cold form laminate (aluminium foil laminated to oriented polyamide on one side and to polyvinylchloride on the other side i.e. OPA/Al/PVC) on one side and hard tempered alumium foil coated with heat seal laquer on the other side, in pack sizes of 7, 10, 14, 28, 30, 56, 90, 98 and 100 film-coated tablets.
2. white high-density polyethylene (HDPE) bottles, with white polypropylene closures and induction sealing liners, in pack sizes of 500 and 1000 film-coated tablets.

Not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before marketing any pack size.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Directive 2002/72/EC, as amended) concerning materials in contact with foodstuff.

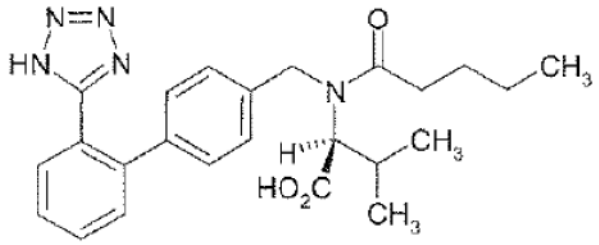
## II.2. Drug Substance

INN: Valsartan

Chemical Name: (2S)-3-methyl-2-[pentanoyl[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]butanoic acid;
N-(1-oxopentyl)-N-[[2'(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L valine;
N-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-n-valeryl-L-valine;
S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-methyl]amine

Molecular formula: $C_{24}H_{29}N_5O_3$

Structure:




Molecular mass: 435.5

Appearance: A white or almost white hygroscopic powder, practically insoluble in water, freely soluble in anhydrous ethanol and sparingly soluble methylene chloride.

Valsartan is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

## II.3. Medicinal Product

### Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Diovan 40 mg, 80 mg, 160 mg and 320 mg Tablets (Novartis Pharmaceuticals UK Limited, UK).

Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for these products and their respective reference products.

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of iron oxide yellow (E172), iron oxide black (E172) and iron oxide red (E172). These are controlled to National Formulary specifications and are in compliance with Directive 2008/128/EC concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

### Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation on future full-scale (commercial) batches.

**Finished Product Specification**
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been proposed, with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling**
The SmPCs, PIL and labelling are pharmaceutically satisfactory.

**MAA Forms**
All aspects of the MAA forms are pharmaceutically satisfactory.

**Expert Report**
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that Marketing Authorisations are granted for these applications.

# III NON-CLINICAL ASPECTS

## III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of valsartan are well-known, no further non-clinical studies are required and none have been provided.

## NON-CLINICAL EXPERT REPORT

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology

## III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

## III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

## III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

## III.5 Ecotoxicity/environmental risk assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

## III.6 Discussion on the non-clinical aspects

The grant of Marketing Authorisations is recommended.

# IV CLINICAL ASPECTS

## IV.1 Introduction

The clinical pharmacology of valsartan is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

## IV.2 Pharmacokinetics

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

**A randomised, single-dose, two-treatment, two-sequence, two-period, crossover study comparing the pharmacokinetics of the test product Valsartan 320 mg Film-coated Tablets (Generics (UK) Limited, UK) and the reference product Diovan 320 mg Tablets (Novartis Pharmaceuticals UK Limited, UK) in healthy male and female adult subjects under fasting conditions.**

The subjects were given a single dose of either treatment with 240ml of water after at least a 10-hour overnight fast. Blood samples were collected before and up to 36 hours after each administration. The washout period between the treatment arms was 10 days. The pharmacokinetic results (presented as geometric means, ratios and 90% confidence intervals) are presented below:

**Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) of valsartan**

| | Valsartan 320 mg (Test) | Diovan 320 mg (Reference) | Test/Ref Ratio (%) | 90% CI |
|---|---|---|---|---|
| **$AUC_{0-t}$ (ng h/mL)** | 57663.87 | 55365.88 | 104.1506 | 93.5034-116.0101 |
| **$AUC_{0-inf}$ (ng.h/mL)** | 59344.04 | 57698.20 | 102.8525 | 93.2595-113.4322 |
| **$C_{max}$ (ng/mL)** | 8262.40 | 7734.67 | 106.8230 | 95.9602-118.9155 |

$AUC_{0-inf}$ 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
$C_{max}$ maximum plasma concentration
Geometric mean taken as the antilog (exponential) of the least square mean of of the log-transformed data
Ratios and 90% CI calculated from log-transformed data

The *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80% to 125% for $C_{max}$ and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{max}$ lie within the acceptable limits. Thus, the data support the claim that the test product Valsartan 320 mg Film-coated Tablets (Generics (UK) Limited, UK) is bioequivalent to the UK reference product Diovan 320 mg Tablets (Novartis Pharmaceuticals UK Limited, UK).

As the 40 mg, 80 mg, 160 mg and 320 mg strength products meet all the criteria specified in the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1) for (bio) waiver, the results and conclusions from the bioequivalence study with the 320 mg tablet strength can be extrapolated to the 40 mg, 80 mg and 160 mg tablet strengths.

## IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

## IV.4 Clinical efficacy

The efficacy of valsartan is well-known. No new efficacy data have been submitted and none are required for applications of this type.

## IV.5 Clinical safety

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence study.

## IV.6 PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN

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.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

## SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with those for the originator products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

## CLINICAL EXPERT REPORT

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

## IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended.

## V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

## VI Overall conclusion, benefit/risk assessment and recommendation

### QUALITY

The important quality characteristics of Valsartan 40mg, 80mg, 160mg, and 320mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### NON-CLINICAL

No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of valsartan are well-known, no additional data were required.

### EFFICACY

With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant's 320 mg strength tablet and the reference product Diovan 320 mg Tablets (Novartis Pharmaceuticals Limited, UK). As the 40 mg, 80 mg, 160 mg and 320 mg strengths of the product meet all the criteria specified in the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions from the bioequivalence study with the 320 mg tablet strength can be extrapolated to the 40 mg, 80 mg and 160 mg tablet strengths.

### SAFETY

With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of valsartan is well known, no additional data were required. No new or unexpected safety concerns were raised from the bioequivalence study.

### PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

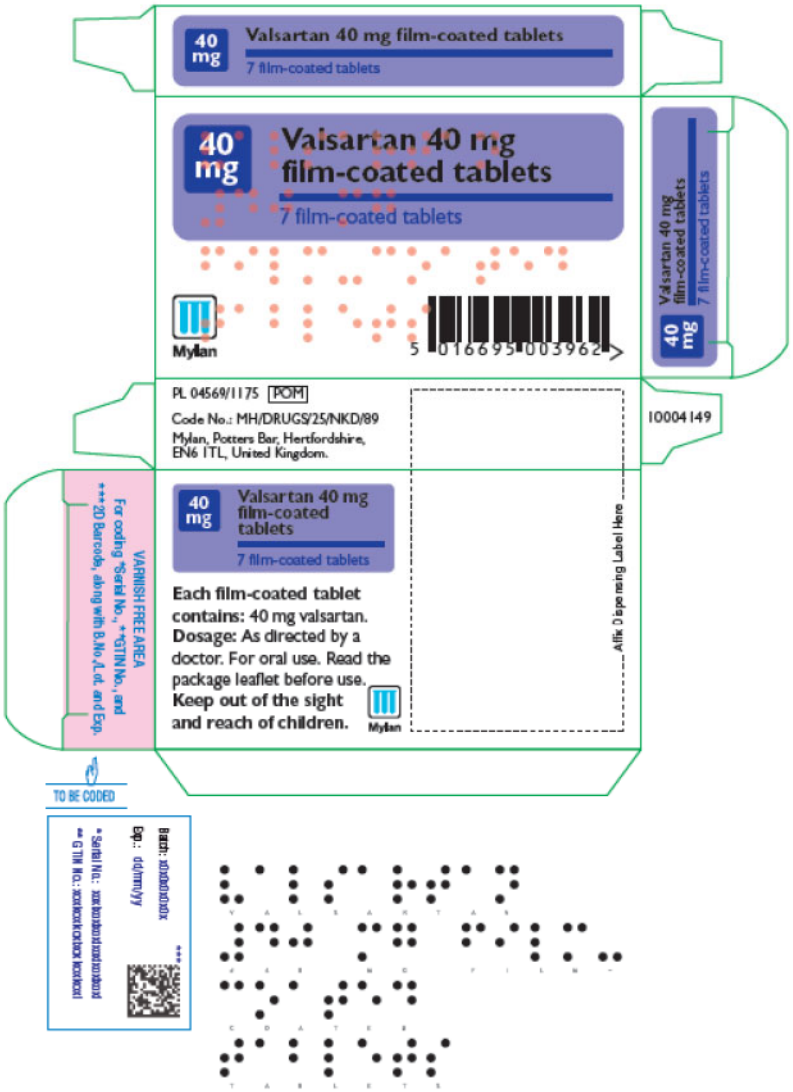
### BENEFIT/RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with valsartan is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.

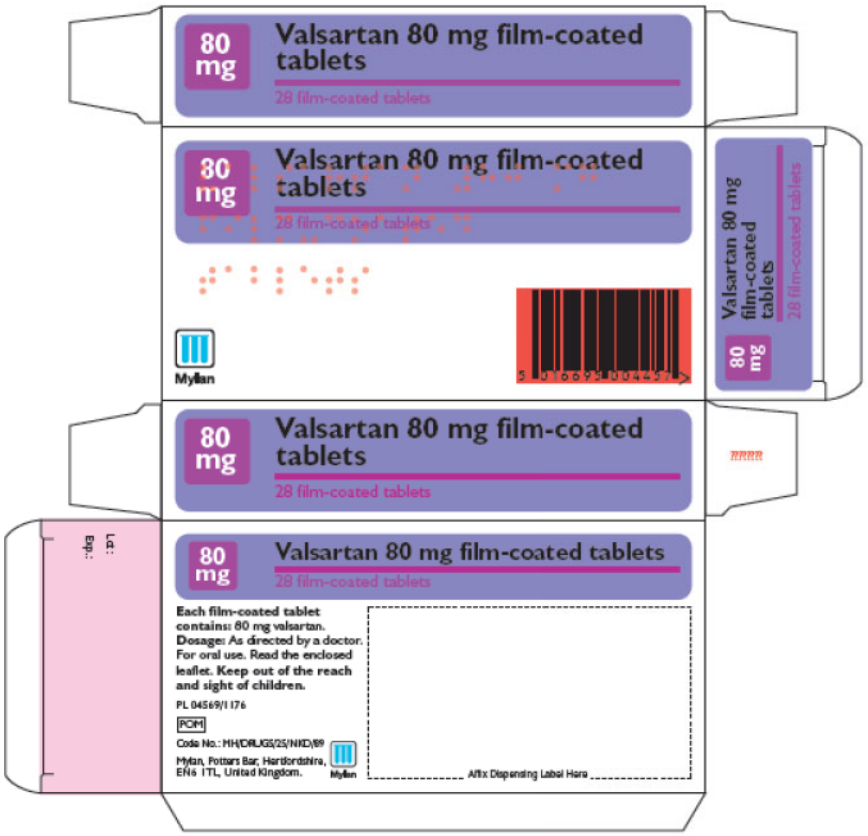
**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

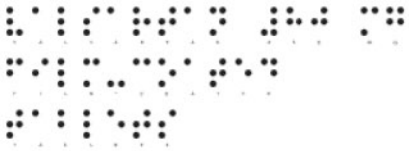
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

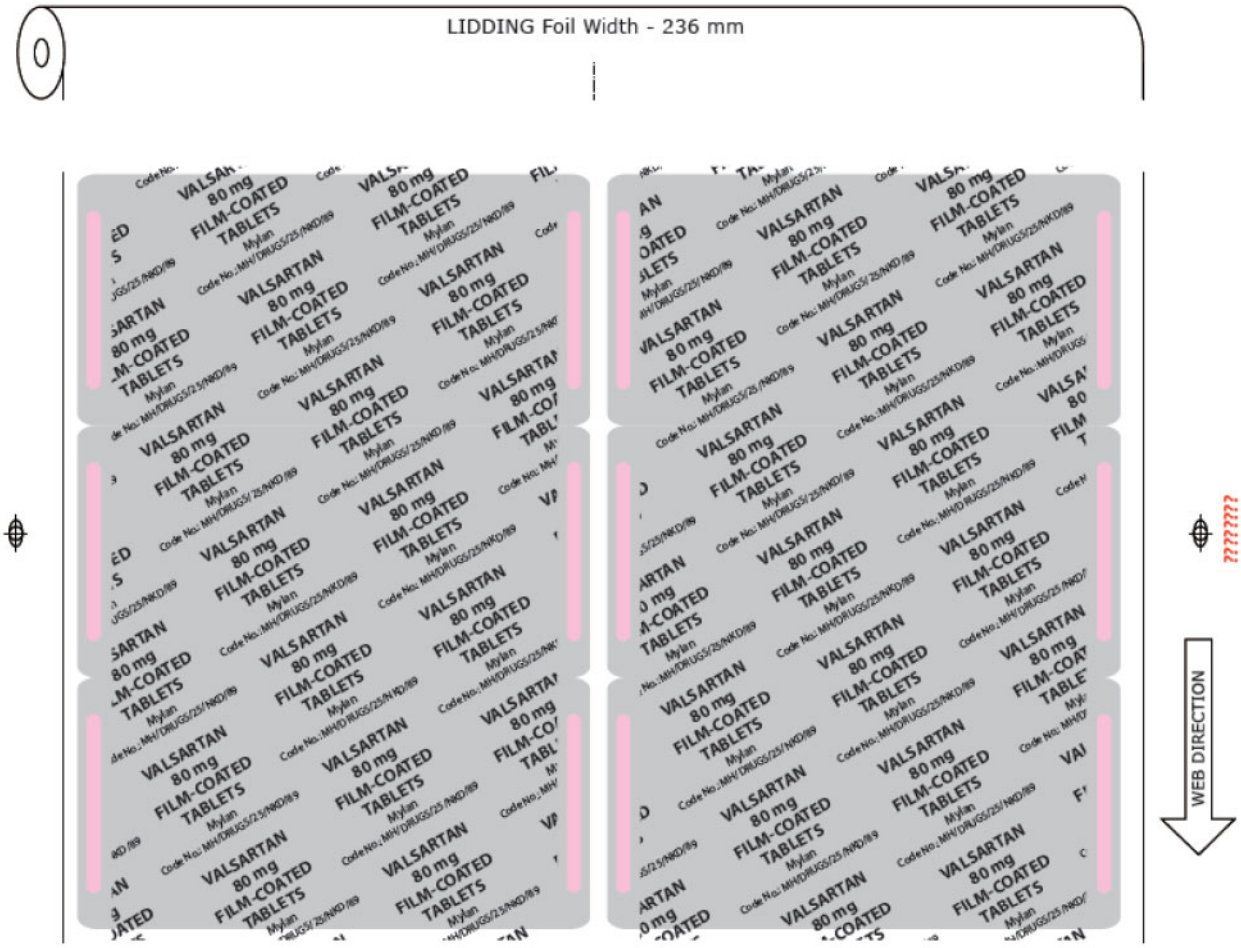
The current approved labelling for this medicine is presented below:

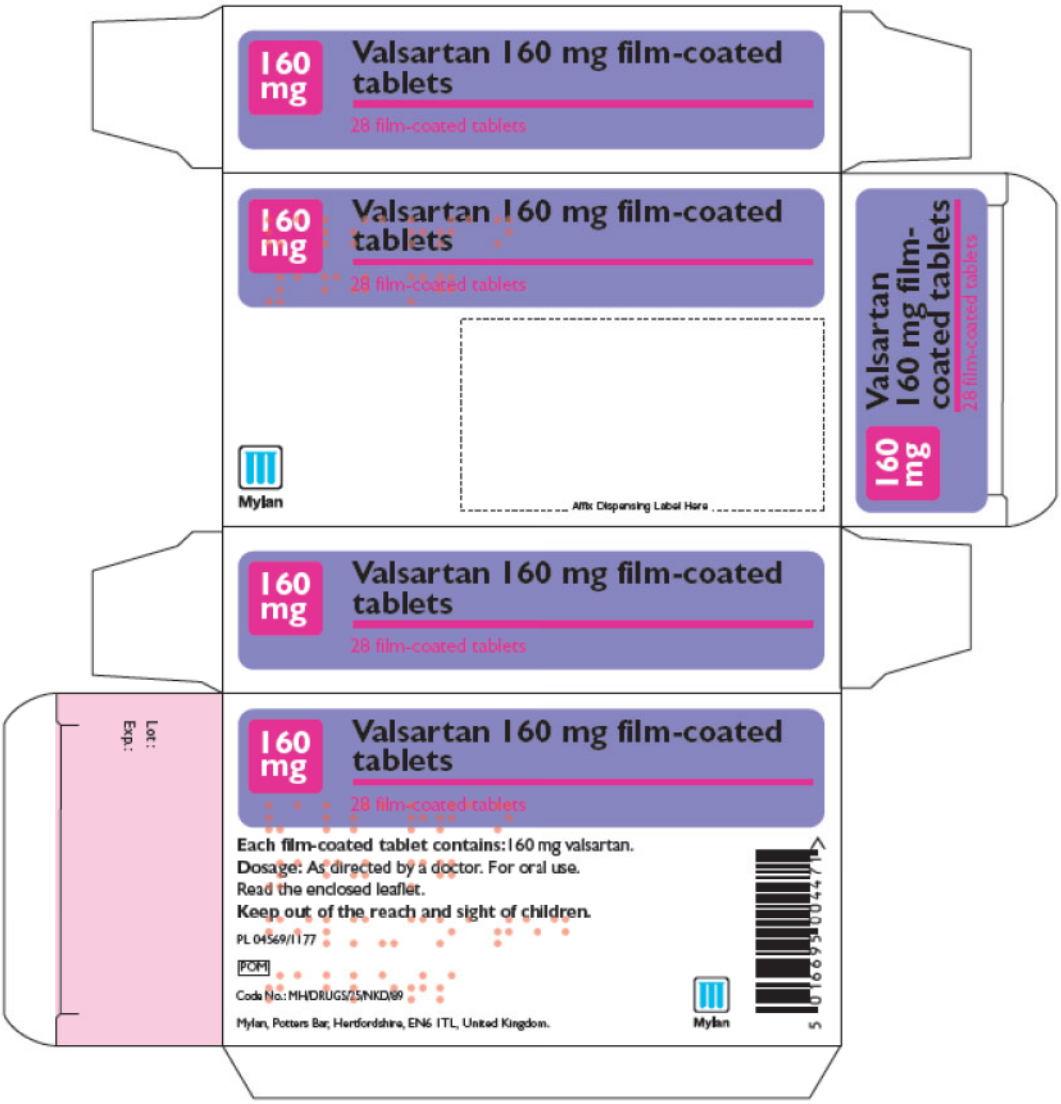


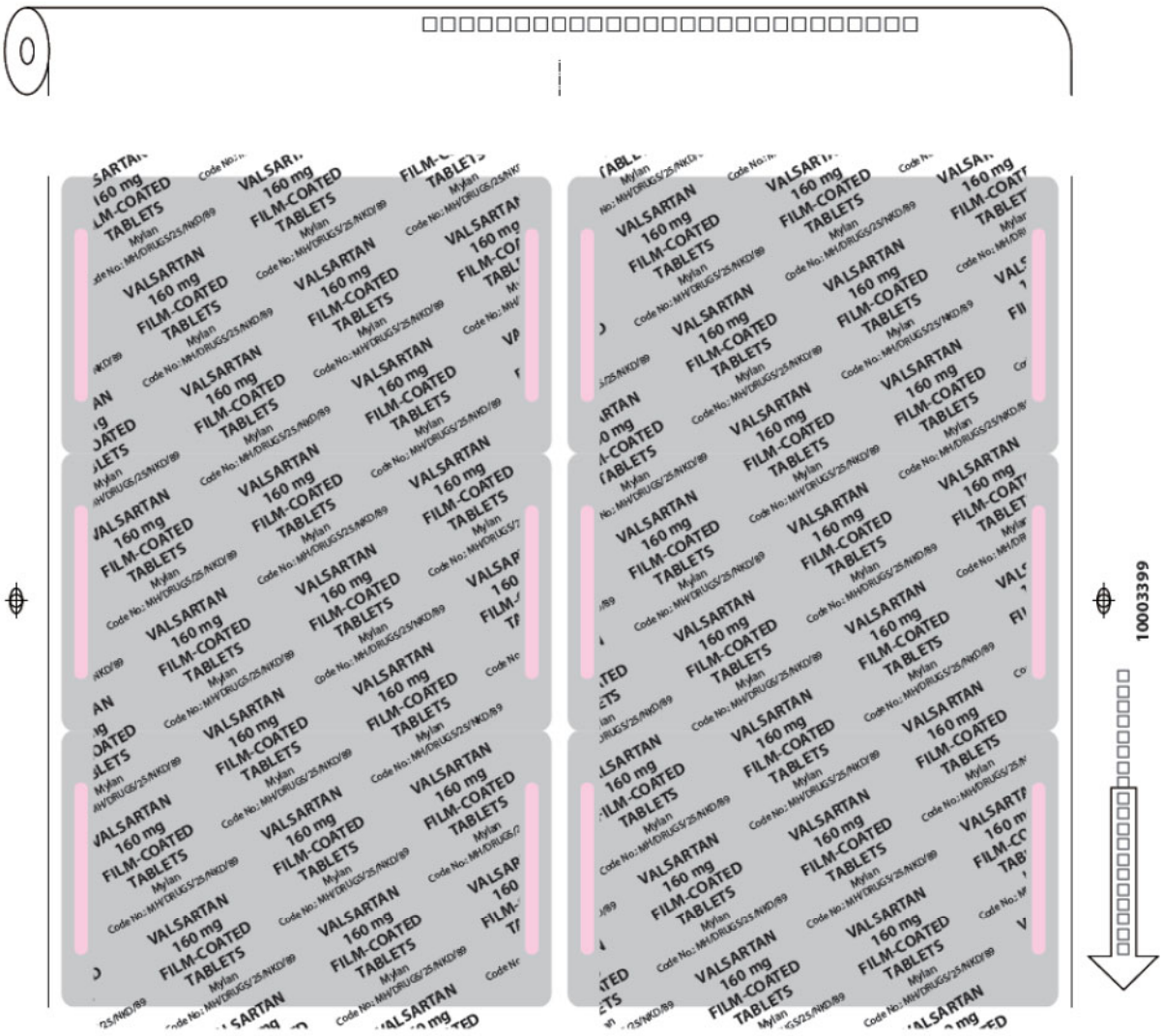

VALSARTAN
40 mg
FILM-COATED
TABLETS
Mylan


80 mg
Valsartan 80 mg film-coated tablets
28 film-coated tablets
Mylan
Valsartan 80 mg film-coated tablets
28 film-coated tablets
Each film-coated tablet contains: 80 mg valsartan.
Dosage: As directed by a doctor. For oral use. Read the enclosed leaflet. Keep out of the reach and sight of children.
PL 04569/1176
POM
Code No.: MH/DRUGS/25/NKD/89
Mylan, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom.
Affix Dispensing Label Here

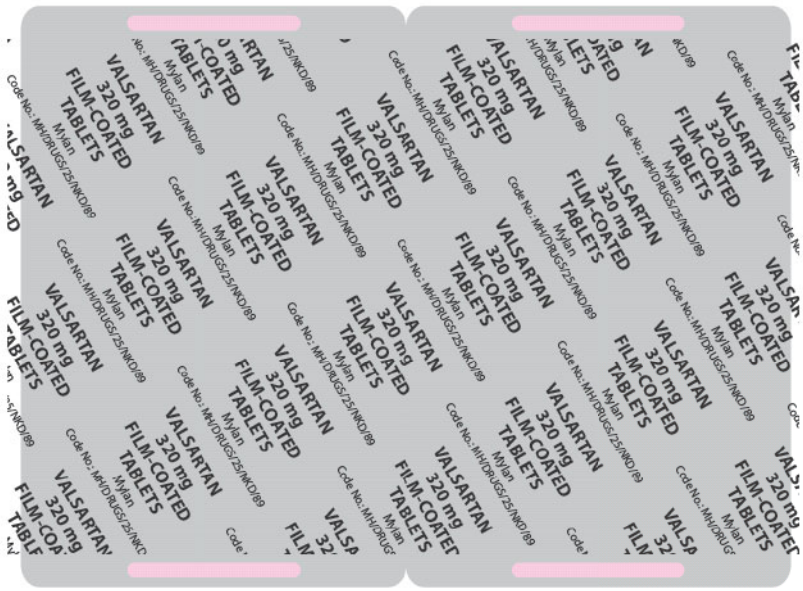



LIDDING Foil Width - 236 mm
VALSARTAN
80 mg
FILM-COATED
TABLETS
Mylan
WEB DIRECTION
???????


160 mg
Valsartan 160 mg film-coated tablets
28 film-coated tablets
Valsartan 160 mg film-coated tablets
160 mg
28 film-coated tablets
Affix Dispensing Label Here
Mylan
Valsartan 160 mg film-coated tablets
160 mg
28 film-coated tablets
Lot:
Exp:
Each film-coated tablet contains: 160 mg valsartan.
Dosage: As directed by a doctor. For oral use.
Read the enclosed leaflet.
Keep out of the reach and sight of children.
PL 04569/1177
POM
Coda No.: MHDRUGS/25/NKD/09
Mylan, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom.
Mylan


10003399


320 mg
Valsartan 320 mg film-coated tablets
28 film-coated tablets
Mylan
Affix Dispensing Label Here
10004151
Each film-coated tablet contains: 320 mg valsartan.
Dosage: As directed by a doctor. For oral use. Read the package leaflet before use.
Keep out of the sight and reach of children.
PL 04569/1178
POM
Code No.: MH/DRUGS/25/NKD/89
Mylan, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom.


VALSARTAN
320 mg
FILM-COATED
TABLETS
Mylan
Code No.: MH/DRUGS/25/NKD/89

# Annex 1

# Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

| Scope | Procedure number | Product information affected | Date of start of the procedure | Date of end of procedure | Approval/ non approval | Assessment report attached Y/N (version) |
|---|---|---|---|---|---|---|
| To update the SmPC fragments 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.2, 5.3, 6.4 and 10 in line with the reference product Diovan 40 mg, 80 mg, 160 mg, 320 mg film-coated tablets from Novartis. Consequential changes have been made to the PILs. | UK/H/4518/001-004/IB/024 | SmPCs and PILs | | | Approved on 29/11/2016 | Yes-see Annex 1 |

## ANNEX 1

| | |
|---|---|
| **Our Reference:** | PL 04569/1175-0035<br>PL 04569/1176-0034<br>PL 04569/1177-0034<br>PL 04569/1178-0033 |
| **Product:** | Valsartan 40 mg, 80 mg, 160 mg, and 320 mg Film-coated Tablets |
| **Marketing Authorisation Holder:** | Generics (UK) Limited |
| **Active Ingredient(s):** | Valsartan |
| **Type of Procedure:** | Mutual Recogniton |
| **Submission Type:** | Variation |
| **Submission Category:** | Type IB |
| **Submission Complexity:** | Standard |
| **EU Procedure Number (if applicable):** | UK/H/4518/001-004/IB/024 |

**Reason:**
To update the SmPC fragments 4.1,4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.2, 5.3, 6.4 and 10 in line with the reference product Diovan 40 mg, 80 mg, 160 mg, 320 mg film-coated tablets from Novartis. Consequential changes have been made to the patient information leaflets (PILs).

**Supporting Evidence**
Revised SmPC fragments and PILs.

**Evaluation**
The proposed changes to the SmPCs and PILs are acceptable. The updated SmPC fragments and PILs have been incorporated into the Marketing Authorisations.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

**Conclusion**
Approved on 29 November 2016.