Valsartan 40mg film-coated tablets
Valsartan 80mg film-coated tablets
Valsartan 160mg film-coated tablets

(valsartan)

PL 20092/0045-7

UK Public Assessment Report

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Valsartan 40mg, 80mg and 160mg film-coated tablets (valsartan)
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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Lupin (Europe) Limited Marketing Authorisations (licences) for the medicinal products Valsartan 40mg, 80mg and 160mg film-coated tablets (PL 20092/0045-7) on 25th February 2010. These are prescription-only medicines (POM).

The active ingredient in Valsartan Tablets is valsartan. This is one of a group of medicines called angiotensin antagonists.

Valsartan tablets can all be used for the following:

- **to treat people after a recent heart attack**
- **to treat heart failure**. Heart failure symptoms include shortness of breath, and swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

Valsartan tablets can also be used for the following:

- **to treat high blood pressure**

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of Valsartan 40mg, 80mg and 160mg film-coated tablets outweigh the risks; hence Marketing Authorisations have been granted.

Valsartan 40mg, 80mg and 160mg film-coated tablets (valsartan)
PL 20092/0045-7

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Lupin (Europe) Limited Marketing Authorisations for the medicinal products Valsartan 40mg, 80mg and 160mg film-coated tablets (PL 20092/0045-7) on 25th February 2010. These are prescription-only medicines (POM).

These are applications for Valsartan 40mg, 80mg and 160mg film-coated tablets, submitted under Article 10.1 of Directive 2001/83/EC claiming to be generic versions of the reference products, Diovan 40mg tablets (PL 00101/0599), Diovan 80mg capsules (PL 00101/0525), and Diovan 160mg capsules (PL 00101/0526), authorised to Novartis Pharmaceuticals UK Ltd on 22/03/2002, 31/10/1997, and 31/10/1997, respectively. The innovator product is Diovan 40mg Capsules, granted to Ciba-Geigy plc on 16th October 1996; it has been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Valsartan film-coated tablets are indicated for the following:

Hypertension - Treatment of essential hypertension.

Recent myocardial infarction - Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction.

Heart failure - Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used.

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 (about 20,000 fold) 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.

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food. Valsartan does not distribute into tissues extensively and is highly bound to serum proteins (94–97%), mainly serum albumin. Valsartan is not bio-transformed to a high extent as only about 20% of dose is recovered as metabolites. Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. The half-life of valsartan is 6 hours.

These applications for Valsartan 40mg, 80mg and 160mg film-coated tablets all depend on the single bioequivalence study presented comparing the applicant's 160mg product with the Novartis reference product, Tareg 160mg tablets, sourced from the French market. Consequently, all sections of the Scientific Discussion refer to all three products. As the test products, Valsartan 40mg, 80mg and 160mg film-coated tablets, were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 160mg strength were extrapolated to the other tablet strengths.

The MHRA considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH 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.

The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of an Environmental Risk Assessment is justified since the application is for a generic version of an approved product and it is not likely to change the total market of valsartan.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Valsartan

Nomenclature:

INN: Valsartan

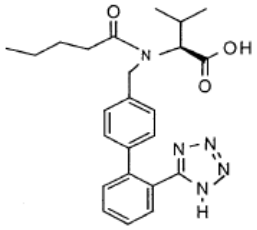
Chemical names:

(i) N-(1-oxopentyl)-N-[[2'(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L valine

(ii) N-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-n-valeryl-L-valine

(iii) (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-methyl]amine

Structure:



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

Molecular weight: 435.52 g/mol

CAS No: 137862-53-4

Physical form: White to off-white hygroscopic powder

Solubility: Soluble in methanol and ethanol

The active substance, valsartan, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided for three batches and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is packed in clear LDPE bags which are purged with nitrogen, tied and twisted and placed along with a silica gel bag inside a HM-HDPE/LDPE/LLDPE bag which is heat sealed. The pack is then further placed inside a triple-laminated Al bag before being heat sealed and stored in HM-HDPE containers. The specifications and Certificates of Analysis for all the packaging materials were provided and the specifications for the LDPE bag in contact with the drug substance included testing for identification and extractables. A statement was provided from the supplier of the LDPE bag to state compliance with EC Directive 2002/72/EC, as amended, and Ph Eur monograph 3.1.3 Polyolefines.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 2 years, with no specific storage conditions.

MEDICINAL PRODUCT

Description and Composition

The medicinal products are presented as biconvex, film-coated tablets containing 40mg, 80mg, or 160mg of valsartan (see SmPCs / patient information leaflet for full descriptions of individual tablets). The 40mg strength tablets have a break-line on one side and can be divided into equal halves. The 80mg and 160mg strength tablets have scorelines but these are only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, crospovidone, colloidal anhydrous silica, and magnesium stearate making up the tablet cores; and hypromellose (E464), titanium dioxide (E171), and macrogol 8000 constituting the film-coating. In addition, the 40mg tablets contain iron oxide yellow (E172), the 80mg tablets contain iron oxide red (E172), and the 160mg tablets contain iron oxide yellow and iron oxide red (E172). Appropriate justification for the inclusion of each excipient has been provided.

All excipients of the tablet cores comply with their respective European Pharmacopoeia monographs. The film-coatings (including iron oxide colouring agents) comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Comparative dissolution and impurity data were provided for the test and appropriate reference products. The dissolution and impurity profiles were found to be acceptable, with all impurities within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. A commitment has been made by the MAH that process validation will be conducted on the first three commercial batches.

Finished product specification

The finished product specifications are provided for both release and shelf life and are acceptable, they provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory Certificates of Analysis have been provided for three pilot scale batches and are accepted. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The tablets are licensed for marketing in PVC (polyvinylchloride) - Aclar / aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in carton pack sizes of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 90, 98, and 100 film-coated tablets. The MA Holder has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are “Store below 30°C, store in the original package to protect from moisture”.

Bioequivalence Study

A single bioequivalence study was submitted comparing the test product, Valsartan 160mg film-coated tablets, to the reference product, Tareg 160mg tablets (Novartis, France).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling and PIL have been provided. The labelling fulfils the statutory requirements for Braille

Conclusion

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant's claim that Valsartan 160mg film-coated tablets is a generic medicinal product of Tareg 160mg tablets appears justified. As the test products, Valsartan 40mg, 80mg and 160mg film-coated tablets, meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 160mg strength were extrapolated to the 40mg and 80mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It was, therefore, recommended that Marketing Authorisations be granted.

PRE-CLINICAL ASSESSMENT

These abridged applications, submitted under Article 10.1 of Directive 2001/83/EC, as amended, are for Valsartan 40mg, 80mg and 160mg film-coated tablets, products claiming to be generic medicinal products of Diovan 40mg tablets, Diovan 80mg capsules, and Diovan 160mg capsules (Novartis Pharmaceuticals UK Ltd) respectively.

No new pre-clinical data have been supplied with these applications and none are required for applications of this type.

A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

CLINICAL ASSESSMENT

INDICATIONS

Valsartan film-coated tablets are indicated for the following:

- *Hypertension* - Treatment of essential hypertension.
- *Recent myocardial infarction* - Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction.
- *Heart failure* - Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used.

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist (ATC Code C09C A03). 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.

Pharmacokinetics

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Valsartan does not distribute into tissues extensively and is highly bound to serum proteins (94–97%), mainly serum albumin. Valsartan is not bio-transformed to a high extent as only about 20% of dose is recovered as metabolites. Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. The half-life of valsartan is 6 hours.

Pharmacokinetics - Bioequivalence study

The applicant presented a single bioequivalence study comparing the test product, Valsartan 160mg film-coated tablets, to the reference product, Tareg 160mg tablets (Novartis, France). Satisfactory Certificates of Analysis for the test and reference products were provided. The study was conducted in accordance with current standards of Good Clinical Practice.

This was a randomised, open-label, two-treatment, two-period, two-sequence, single dose crossover bioavailability and bioequivalence study. The study was conducted in 48 healthy, adult, male, human volunteer subjects, under fasting conditions. Following an overnight fast, a single 160mg dose of the investigational products was administered orally with 240 ml of water to each subject in each period. A satisfactory washout period of 11 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 36.0 hours after administration of test or reference product. Plasma levels of valsartan were detected by a validated LC-MS/MS method.

An adequate statistical plan was provided and the planned statistical methods were conventional. Log-transformed data for $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} were analysed by ANOVA. The protocol specified bioequivalence acceptance ranges of 80-125% for AUC and C_{max} which is acceptable.

Biostudy outcome and results:

All 48 volunteers who were dosed in period I completed the study and all data were analysed. No significant protocol deviations were reported. There were no serious or significant adverse events reported in the study.

The summary of the results of the bioequivalence study are tabulated below:

Summary pharmacokinetic data for a randomised, open-label, two-way, single dose crossover study between the test and reference products. n=48 healthy subjects, dosed fasted; t=36 hours. Wash-out period: 11 days – Valsartan

Parameters	**Geometric Least Squares Mean**			
	Tareg 160mg (Reference)	**Lupin's 160mg tablets (Test)**	**Ratio (Test/Ref) %**	**90% CI (Parametric)**
C_{max} (ng/ml)	3944.859	4003.292	101.5%	90.92 – 113.27
AUC_{0-t} (ng.h/ml)	26444.963	28009.410	105.9%	97.06 – 115.58
$AUC_{0-\infty}$ (ng.h/ml)	27036.235	28555.002	105.6%	96.87 – 115.15

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test and reference products are bioequivalent under fasting conditions as the confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for valsartan fall within the acceptance criteria range of 80-125% in line with current guidelines.

The multiple dose waiver criteria are met and hence this study is accepted as demonstrating bioequivalence for the other product strengths.

Satisfactory justification is provided for a bio-waiver for Valsartan 40mg and 80mg tablets. As Valsartan 40mg, 80mg, and 160mg film-coated tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 160mg strength can be extrapolated to the 40mg and 80mg strength tablets.

EFFICACY

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of valsartan is well-established from its extensive use in clinical practice.

SAFETY

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of valsartan is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics

The approved SmPCs are consistent with those for the reference products and are acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and bioequivalence of the 160mg strength test and reference products was shown with 90% Confidence Intervals within general acceptance limits. The conditions, as detailed in CPMP/EWP/QWP/1401/98, for a single bioequivalence study to cover multiple strengths of a product have been met, so the results and conclusions of this bioequivalence study were extrapolated to the 40mg and 80mg strength tablets.

Sufficient clinical information has been submitted to support these applications. When used as indicated, valsartan has a favourable benefit-to-risk ratio. The grant of Marketing Authorisations was, therefore, recommended on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Valsartan 40mg, 80mg and 160mg 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.

PRECLINICAL

No new pre-clinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Valsartan 160mg film-coated tablets, and the reference product Tareg 160mg tablets (Novartis, France).

As the test products were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 160mg strength were extrapolated to the 40mg and 80mg tablet strengths. Thus, no separate bioequivalence studies were necessary for these strengths.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

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 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.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new pre-clinical or clinical safety concerns have been identified. The bioequivalence study and the valid extrapolation of its results and conclusions support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with valsartan is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.

Valsartan 40mg, 80mg and 160mg film-coated tablets (valsartan)
PL 20092/0045-7

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation applications on 5th February 2007

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 9th March 2007

3 Following assessment of the applications the MHRA requested further information relating to the quality dossier on 11th July 2007, 4th March 2008, 4th August 2008, and 6th October 2009

4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 12th February 2008, 23rd June 2008, 8th September 2009, and 9th December 2009 respectively

5 The applications were determined on 25th February 2010

Valsartan 40mg, 80mg and 160mg film-coated tablets (valsartan)
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STEPS TAKEN AFTER AUTHORISATION

Not applicable

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Valsartan 40mg, 80mg & 160mg film-coated tablets is as follows – Differences are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Valsartan 40mg film-coated tablets

Valsartan 80mg film-coated tablets

Valsartan 160mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 40 mg of valsartan

One film-coated tablet contains 80 mg of valsartan

One film-coated tablet contains 160 mg of valsartan

3 PHARMACEUTICAL FORM

Film coated Tablet

Valsartan 40 mg Tablets:
Yellow, capsule shaped, film coated biconvex tablets debossed with '40' on one side and scoreline on the other side.
The tablet can be divided in to equal halves

Valsartan 80 mg Tablets:
Pink, round, film coated, biconvex tablets debossed '80' on one side and scoreline on the other side. The scorline is only to facilitate breaking for ease of swallowing and not to divide it into equal doses.

Valsartan 160 mg Tablets:
Yellow capsule shaped, film coated, biconvex tablets debossed '160' on one side and scoreline on the other side. The scoreline is only to facilitate breaking for ease of swallowing and not to divide it into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of essential hypertension.

Recent myocardial infarction
Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction (see sections 4.4 and 5.1).

Heart failure
Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Posology

Hypertension
The recommended starting dose of valsartan is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In

some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg and to a maximum of 320 mg.

Valsartan may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.

Recent myocardial infarction
In clinically stable patients, therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan should be titrated to 40 mg, 80 mg, and 160 mg twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet. The target maximum dose is 160 mg twice daily. In general, it is recommended that patients achieve a dose level of 80 mg twice daily by two weeks after treatment initiation and that the target maximum dose, 160 mg twice daily, be achieved by three months, based on the patient's tolerability. If symptomatic hypotension or renal dysfunction occur, consideration should be given to a dosage reduction.

Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta blockers, statins, and diuretics. The combination with ACE inhibitors is not recommended (see sections 4.4 and 5.1). Evaluation of post-myocardial infarction patients should always include assessment of renal function.

Heart failure
The recommended starting dose of valsartan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, a beta blocker and valsartan is not recommended (see sections 4.4 and 5.1).

Evaluation of patients with heart failure should always include assessment of renal function.

Method of administration
Valsartan may be taken independently of a meal and should be administered with water.

Additional information on special populations

Elderly
No dose adjustment is required in elderly patients.

Renal impairment
No dosage adjustment is required for patients with a creatinine clearance >10 ml/min (see sections 4.4 and 5.2)

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, the dose of valsartan should not exceed 80 mg. Valsartan is contraindicated in patients with severe hepatic impairment and in patients with cholestasis (see sections 4.3, 4.4 and 5.2).

Paediatric patients
Valsartan is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications

-Hypersensitivity to the active substance or to any of the excipients.
-Severe hepatic impairment, biliary cirrhosis and cholestasis.
-Second and third trimester of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Hyperkalaemia
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Sodium- and/or volume-depleted patients
In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with valsartan. Sodium and/or volume depletion should be corrected before starting treatment with valsartan, for example by reducing the diuretic dose.

Renal artery stenosis

In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of valsartan has not been established.

Short-term administration of valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

Kidney transplantation
There is currently no experience on the safe use of valsartan in patients who have recently undergone kidney transplantation.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with valsartan as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Impaired renal function
No dosage adjustment is required for patients with a creatinine clearance >10 ml/min. There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 5.2).

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan should be used with caution (see sections 4.2 and 5.2).

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Recent myocardial infarction
The combination of captopril and valsartan has shown no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies (see sections 4.2 and 5.1). Therefore, the combination of valsartan with an ACE inhibitor is not recommended.

Caution should be observed when initiating therapy in post-myocardial infarction patients. Evaluation of post-myocardial infarction patients should always include assessment of renal function (see section 4.2).

Use of valsartan in post-myocardial infarction patients commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).

Heart Failure
In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and valsartan has not shown any clinical benefit (see section 5.1). This combination apparently increases the risk for adverse events and is therefore not recommended.

Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function (see section 4.2).

Use of valsartan in patients with heart failure commonly results in some reduction in blood pressure,but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).

In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia and in rare cases with acute renal failure and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of valsartan may be associated with impairment of the renal function.

Other conditions with stimulation of the renin-angiotensin system
In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia and in rare cases with acute renal failure and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of valsartan may be associated with impairment of the renal function.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs

When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Others
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

4.6 Pregnancy and lactation

Pregnancy

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia); see also section 5.3 “Preclinical safety data”.

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also sections 4.3 and 4.4).

Lactation
Because no information is available regarding the use of valsartan during breastfeeding, valsartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

In controlled clinical studies in patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

The ADRs reported from clinical studies, post-marketing experience and laboratory findings are listed below according to system organ class.

Adverse reactions are ranked by frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a "not known" frequency.

- **Hypertension**

Blood and lymphatic system disorders	
Not known	Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Increase of serum potassium
Ear and labyrinth system disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepato-biliary disorders	
Not known	Elevation of liver function values including increase of serum bilirubin
Skin and subcutaneous tissue disorders	
Not known	Angioedema, Rash, Pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, Elevation of serum creatinine
General disorders and administration site conditions	
Uncommon	Fatigue

The safety profile seen in controlled-clinical studies in patients with post-myocardial infarction and/or heart failure varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in post-myocardial infarction and/or heart failure patients are listed below:

- **Post-myocardial infarction and/or heart failure**

Blood and lymphatic system disorders	
Not known	Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Uncommon Not known	Hyperkalaemia Increase of serum potassium
Nervous system disorders	
Common Uncommon	Dizziness, Postural dizziness Syncope, Headache
Ear and labyrinth system disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Cardiac failure
Vascular disorders	
Common	Hypotension, Orthostatic hypotension
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough

Gastrointestinal disorders	
Uncommon	Nausea, Diarrhoea
Hepato-biliary disorders	
Not known	Elevation of liver function values
Skin and subcutaneous tissue disorders	
Uncommon	Angioedema,
Not known	Rash, Pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Common	Renal failure and impairment
Uncommon	Acute renal failure, Elevation of serum creatinine
Not known	Increase in blood urea nitrogen
General disorders and administration site conditions	
Uncommon	Asthenia, Fatigue

4.9 Overdose

Symptoms
Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock.

Treatment
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms; stabilisation of the circulatory condition is of prime importance.

If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken.

Valsartan is unlikely to be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC code: C09CA03

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 (about 20,000 fold) 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. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($P<0.05$) less in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor ($P<0.05$).

Hypertension
Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks and persist during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 μg/min; amlodipine: 55.4 μg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 μmol/l). At 24 weeks, UAE was reduced ($p<0.001$) by 42% (–24.2 μg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (–1.7 μg/min; 95% CI: –5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.

The Diovan Reduction of Proteinuria (DROP) study further examined the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 μg/min; 20-700 μg/min) and preserved renal function (mean serum creatinine = 80 μmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

Recent myocardial infarction

The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) was a randomised, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction (manifested as an ejection fraction ≤40% by radionuclide ventriculography or ≤35% by echocardiography or ventricular contrast angiography). Patients were randomised within 12 hours to 10 days after the onset of myocardial infarction symptoms to valsartan, captopril, or the combination of both. The mean treatment duration was two years. The primary endpoint was time to all-cause mortality.

Valsartan was as effective as captopril in reducing all-cause mortality after myocardial infarction. Allcause mortality was similar in the valsartan (19.9%), captopril (19.5%), and valsartan + captopril (19.3%) groups. Combining valsartan with captopril did not add further benefit over captopril alone. There was no difference between valsartan and captopril in all-cause mortality based on age, gender, race, baseline therapies or underlying disease. Valsartan was also effective in prolonging the time to and reducing cardiovascular mortality, hospitalisation for heart failure, recurrent myocardial infarction, resuscitated cardiac arrest, and non-fatal stroke (secondary composite endpoint). The safety profile of valsartan was consistent with the clinical course of patients treated in the postmyocardial infarction setting. Regarding renal function, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients, 4.8% of valsartan+captopril-treated patients, and 3.4% of captopril-treated patients. Discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients, 1.3% in valsartan+captopril patients, and 0.8% of captopril patients. An assessment of renal function should be included in the evaluation of patients post-myocardial infarction.

There was no difference in all-cause mortality, cardiovascular mortality or morbidity when beta blockers were administered together with the combination of valsartan + captopril, valsartan alone, or captopril alone. Irrespective of treatment, mortality was lower in the group

of patients treated with a beta blocker, suggesting that the known beta blocker benefit in this population was maintained in this trial.

Heart failure

Val-HeFT was a randomised, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 5,010 NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF <40% and left ventricular internal diastolic diameter (LVIDD) >2.9 cm/m^2. Baseline therapy included ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of valsartan in Val-HeFT was 254 mg. The study had two primary endpoints: all cause mortality (time to death) and composite mortality and heart failure morbidity (time to first morbid event) defined as death, sudden death with resuscitation, hospitalisation for heart failure, or administration of intravenous inotropic or vasodilator agents for four hours or more without hospitalisation.

All cause mortality was similar (p=NS) in the valsartan (19.7%) and placebo (19.4%) groups. The primary benefit was a 27.5% (95% CI: 17 to 37%) reduction in risk for time to first heart failure hospitalisation (13.9% vs. 18.5%). Results appearing to favour placebo (composite mortality and morbidity was 21.9% in placebo vs. 25.4% in valsartan group) were observed for those patients receiving the triple combination of an ACE inhibitor, a beta blocker and valsartan.

In a subgroup of patients not receiving an ACE inhibitor (n=366), the morbidity benefits were greatest. In this subgroup all-cause mortality was significantly reduced with valsartan compared to placebo by 33% (95% CI: –6% to 58%) (17.3% valsartan vs. 27.1% placebo) and the composite mortality and morbidity risk was significantly reduced by 44% (24.9% valsartan vs. 42.5% placebo). In patients receiving an ACE inhibitor without a beta-blocker, all cause mortality was similar (p=NS) in the valsartan (21.8%) and placebo (22.5%) groups. Composite mortality and morbidity risk was significantly reduced by 18.3% (95% CI: 8% to 28%) with valsartan compared with placebo (31.0% vs. 36.3%).

In the overall Val-HeFT population, valsartan treated patients showed significant improvement in NYHA class, and heart failure signs and symptoms, including dyspnoea, fatigue, oedema and rales compared to placebo. Patients treated with valsartan had a better quality of life as demonstrated by change in the Minnesota Living with Heart Failure Quality of Life score from baseline at endpoint than placebo. Ejection fraction in valsartan treated patients was significantly increased and LVIDD significantly reduced from baseline at endpoint compared to placebo.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution:

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Biotransformation:

Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Excretion:
Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

In Heart failure patients:
The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and C_{max} values of valsartan are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 l/h. Age does not affect the apparent clearance in heart failure patients.

Special populations

Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.

Impaired renal function
As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment (creatinine clearance >10 ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 4.4). Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment
Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Valsartan has not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Cellulose Microcrystalline
Crospovidone
Silica, Colloidal Anhydrous
Magnesium stearate

Tablet Film-Coating:
Hypromellose (E 464)
Titanium dioxide (E 171)
Macrogol 8000

Valsartan 40 mg Tablets:
Iron Oxide Yellow (E 172)

Valsartan 80 mg Tablets:
Iron Oxide Red (E 172)

Valsartan 160 mg Tablets:
Iron Oxide Red & Iron Oxide Yellow (E 172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C, store in the original package to protect from moisture.

6.5 Nature and contents of container

Valsartan Tablets are packed in blister packs, using PVC/Aclar as forming (base) material / 0.025mm hard tampered aluminium foil (as lidding material) which are further packed in cartons.

Tablets are available in packs of 1,7,10,14,20,28,30,50,56,60,90,98, and 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited
Victoria Court, Bexton Road
Knutsford,
Cheshire,
WA 16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20092/ 0045

PL 20092/ 0046

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/02/2010

10 DATE OF REVISION OF THE TEXT

25/02/2010

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
Valsartan 40 mg, 80 mg and 160 mg tablets
Valsartan

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for **you**. Do **not** pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In This Leaflet:

1. WHAT VALSARTAN TABLETS ARE AND WHAT THEY ARE USED FOR.

The **active** ingredient in Valsartan Tablets is Valsartan. This is one of a group of medicines called Angiotensin II Antagonists, which help to control high blood pressure. 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. For the **other** ingredients, see section **6.**

Valsartan 40 mg film-coated tablets **can be used for two different conditions:**
- **to treat people after a recent heart attack** (myocardial infarction). "Recent" here means between 12 hours and 10 days.
- **to treat symptomatic heart failure**. Valsartan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or it may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used.

  Heart failure symptoms include shortness of breath, and swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

Valsartan 80 mg film-coated tablets and Valsartan 160 mg film-coated tablets **can be used for three different conditions:**
- **to treat high blood pressure.** 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 your blood pressure to normal reduces the risk of developing these disorders.
- **to treat people after a recent heart attack** (myocardial infarction). "Recent" here means between 12 hours and 10 days.
- **to treat symptomatic heart failure.** Valsartan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or it may be used in addition to ACE inhibitors when beta blockers (another medication to treat

heart failure) cannot be used.

Heart failure symptoms include shortness of breath, and swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

2. BEFORE YOU USE VALSARTAN TABLETS

Do not use these tablets :

- if you are **allergic** (hypersensitive) to Valsartan, or any of the other ingredients of these tablets.
- if you have **severe liver disease**
- if you are **more than 3 months pregnant** (it is also better to avoid these tablets in early pregnancy-see pregnancy section)

If any of these apply to you, do not take Valsartan Tablets

Take special care with these tablets

- if you have liver disease.
- if you have severe kidney disease or if you are undergoing dialysis.
- if you are suffering from a narrowing of the kidney artery.
- if you have recently undergone kidney transplantation (received a new kidney).
- if you are treated after a heart attack or for heart failure, your doctor may check your kidney function.
- if you have severe heart disease other than heart failure or heart attack.
- if you are taking medicines that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin. It may be necessary to check the amount of potassium in your blood at regular intervals.
- if you suffer from aldosteronism. This is a disease in which your adrenal glands make too much of the hormone aldosterone. If this applies to you, the use of valsartan is not recommended.
- if you have lost a lot of fluid (dehydration) caused by diarrhoea, vomiting, or high doses of water pills (diuretics).
- the use of valsartan in children and adolescents is not recommended (below the age of 18 years).
- you must tell your doctor if you think you are (or might become) pregnant. Valsartan is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

If any of these apply to you, tell your doctor before you take valsartan tablets.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The effect of the treatment can be influenced if valsartan is taken together with certain other medicines. It may be necessary to change the dose, to take other precautions, or in some cases to stop taking one of the medicines. This applies to both prescription and non-prescription medicines, especially:

- **other medicines that lower blood pressure**, especially **water pills** (diuretics).
- **medicines that increase the amount of potassium** in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin.

- **certain type of pain killers** called non-steroidal anti-inflammatory medicines **(NSAIDs)**.
- **lithium**, a medicine used to treat some types of psychiatric illness.

In addition:
- if you are being **treated after a heart attack,** a combination with **ACE inhibitors** (a medication to treat heart attack) is not recommended.
- if you are being **treated for heart failure,** a triple combination with **ACE inhibitors and betablockers** (medications to treat heart failure) is not recommended.

Taking valsartan with food and drink
You can take valsartan with or without food.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
- **You must tell your doctor if you think that you are (or might become) pregnant**. Your doctor will normally advise you to stop taking valsartan before you become pregnant or as soon as you know you are pregnant, and will advise you to take another medicine instead of valsartan. Valsartan is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if it is used after the third month of pregnancy
- **Tell your doctor if you are breast-feeding or about to start breast-feeding**. Valsartan tablets are not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machinery
Before you drive a vehicle, use tools or operate machines, or carry out other activities that require concentration, make sure you know how valsartan affects you. Like many other medicines used to treat high blood pressure, valsartan may in rare cases cause dizziness and affect the ability to concentrate.

3. HOW TO TAKE VALSARTAN TABLETS
Always take Valsartan Tablets exactly as your doctor has told you in order to get the best results and reduce the risk of side effects. You should check with your doctor or pharmacist if you are not sure. People with high blood pressure often do not notice any signs of this problem. Many may feel quite normal. This makes it all the more important for you to keep your appointments with the doctor even if you are feeling well.

High blood pressure: The usual dose is 80 mg daily. In some cases your doctor may prescribe higher doses (e.g. 160 mg or 320 mg). Your doctor may also combine valsartan with an additional medicine (e.g. a diuretic).

After a recent heart attack: After a heart attack the treatment is generally started as early as after 12 hours, usually at a low dose of 20 mg twice daily. You obtain the 20 mg dose by dividing the 40 mg tablet. Your doctor will increase this dose gradually over several weeks to a maximum of 160 mg twice daily. The final dose depends on what you as an individual patient can tolerate.

Valsartan can be given together with other treatment for heart attack, and your doctor will decide which treatment is suitable for you.

Heart failure: Treatment starts generally with 40 mg twice daily. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice daily. The final dose depends on what you as an individual patient can tolerate.

Valsartan can be given together with other treatment for heart failure, and your doctor will decide which treatment is suitable for you.

You can take valsartan with or without food. Swallow valsartan with a glass of water.

Take valsartan at about the same time each day.

If you take more tablets than you should

If you experience severe dizziness and/or fainting, lay down and contact your doctor immediately. If you have accidentally taken too many tablets, contact your doctor, pharmacist, or hospital

If you forget to take your tablets

Do not take a double dose to make up for a forgotten tablet.
If you forget to take a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the dose you missed.

If you stop taking these tablets

Stopping your treatment with valsartan may cause your disease to get worse. Do not stop taking your medicine unless your doctor tells you to.

If you have any further questions on the use of these tablets, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS-

Like all medicines, Valsartan tablets can cause side effects, although not everybody gets them.

These side effects may occur with certain frequencies, which are defined as follows:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Some symptoms need immediate medical attention:

You may experience symptoms of angioedema, such as

- swollen face, tongue or throat
- difficulty in swallowing
- hives and difficulties in breathing

If you get any of these, see a doctor immediately.
Other side effects include:
Common:

- dizziness, postural dizziness
- low blood pressure with symptoms such as dizziness
- decreased kidney function (signs of renal impairment)

Uncommon*:*

- allergic reaction with symptoms such as rash, itching, dizziness, swelling of face or lips or tongue or throat, difficulty breathing or swallowing (signs of angioedema)
- sudden loss of consciousness
- spinning sensation
- severely decreased kidney function (signs of acute renal failure)
- muscle spasms, abnormal heart rhythm (signs of hyperkalaemia)
- breathlessness, difficulty breathing when lying down, swelling of the feet or legs (signs of cardiac failure)

- headache
- cough
- abdominal pain
- nausea
- diarrhoea
- tiredness
- weakness

Not known:

- rash, itching, together with some of the following signs or symptoms: fever, joint pain, muscle pain,swollen lymph nodes and/or flu-like symptoms (signs of serum sickness)
- purplished-red spots, fever, itching (signs of inflammation of blood vessels also called vasculitis)
- unusual bleeding or bruising (signs of thrombocytopenia)
- muscle pain (myalgia)
- fever, sore throat or mouth ulcers due to infections (symptoms of low level of white blood cells also called neutropenia)
- decrease of level of haemoglobin and decrease of the percentage of red blood cells in the blood (which can, in severe cases, lead to anaemia)
- increase of level of potassium in the blood (which can, in severe cases, trigger muscle spasms,abnormal heart rhythm)
- elevation of liver function values (which can indicate liver damage) including an increase of bilirubin in the blood (which can, in severe cases, trigger yellow skin and eyes)
- increase of level of blood urea nitrogen and increase of level of serum creatinine (which can indicate abnormal kidney function)

The frequency of some side effects may vary depending on your condition. For example, side effects such as dizziness, and decreased kidney function, were seen less frequently in patients treated with high blood pressure than in patients treated for heart failure or after a recent heart attack.

If any of the side effects becomes serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE VALSARTAN TABLETS

Keep out of the reach and sight of children.
Do not use Valsartan Tablets after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Store below 30 ^{0}C.
Keep your tablets in the original package to protect from moisture.
Do not use Valsartan Tablets if you notice that the pack is damaged or shows signs of tampering.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

What these tablets contain:
The active ingredient is **Valsartan.**
The other ingredients are:
Tablet Core:
Cellulose Microcrystalline
Crospovidone
Silica, Colloidal Anhydrous

Magnesium stearate
Tablet Film-Coating:
Hypromellose (E 464)
Titanium dioxide (E 171)
Macrogol 8000

Valsartan 40 mg Tablets
Iron Oxide Yellow (E 172)

Valsartan 80 mg Tablets
Iron Oxide Red (E 172)

Valsartan 160 mg Tablets
Iron Oxide Red & Iron Oxide Yellow (E 172)

What these tablets look like and the contents of the pack
Valsartan Tablets are available in three strengths.

- Valsartan 40 mg Tablets
  Yellow, capsule shaped, film coated biconvex tablets debossed with "40" on one side and "scoreline" on the other side.
  The tablet can be divided in to equal halves.
- Valsartan 80 mg Tablets
  Pink, round, film coated, biconvex tablets debossed '80' on one side and "scoreline" on the other side
  The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
- Valsartan 160 mg Tablets
  Yellow, capsule shaped, film coated, biconvex tablets debossed '160' on one side and "scoreline" on the other side.

  The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Valsartan 40mg, 80mg and 160mg Tablets are available in the following pack sizes:
1,7,10,14,20,28,30,50,56,60,90,98 and 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Lupin (Europe) Limited,
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WA16 OPF
United Kingdom

This leaflet was last approved in

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Code No. GO/DRUGS/654

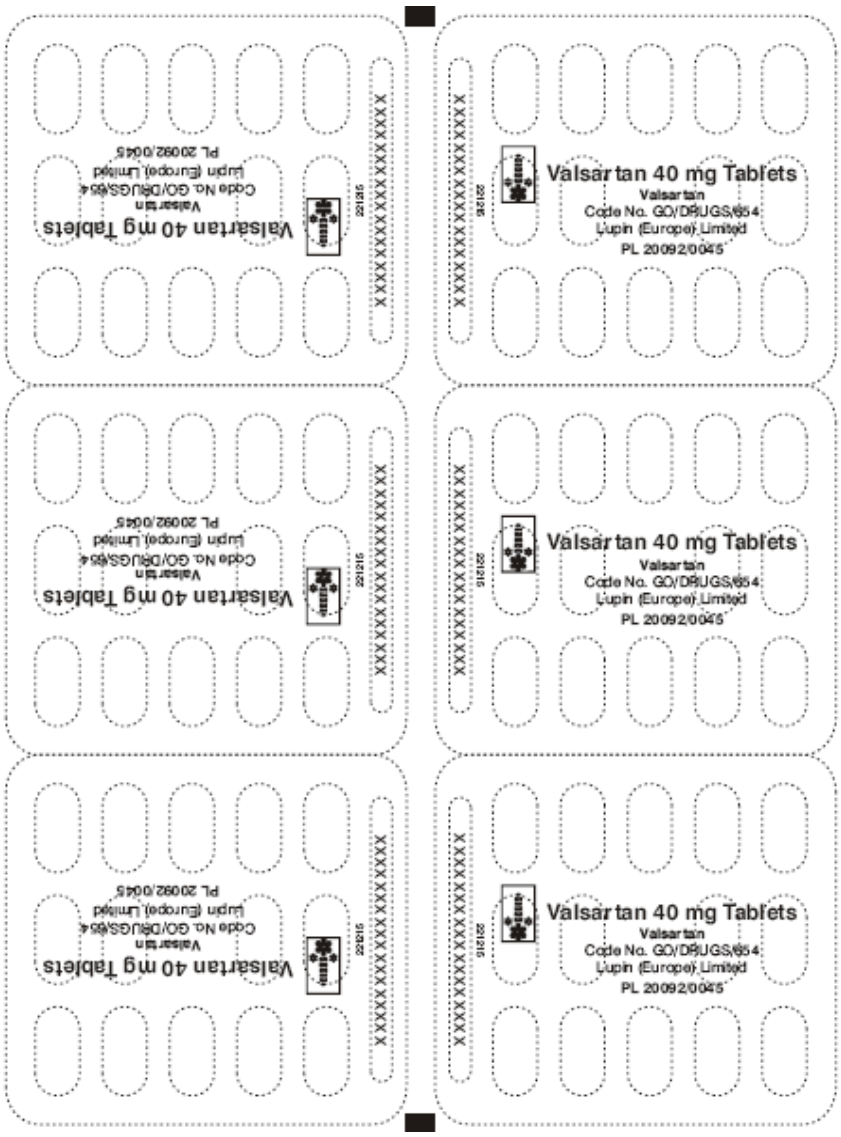
LABELLING

Valsartan 40mg film-coated tablets

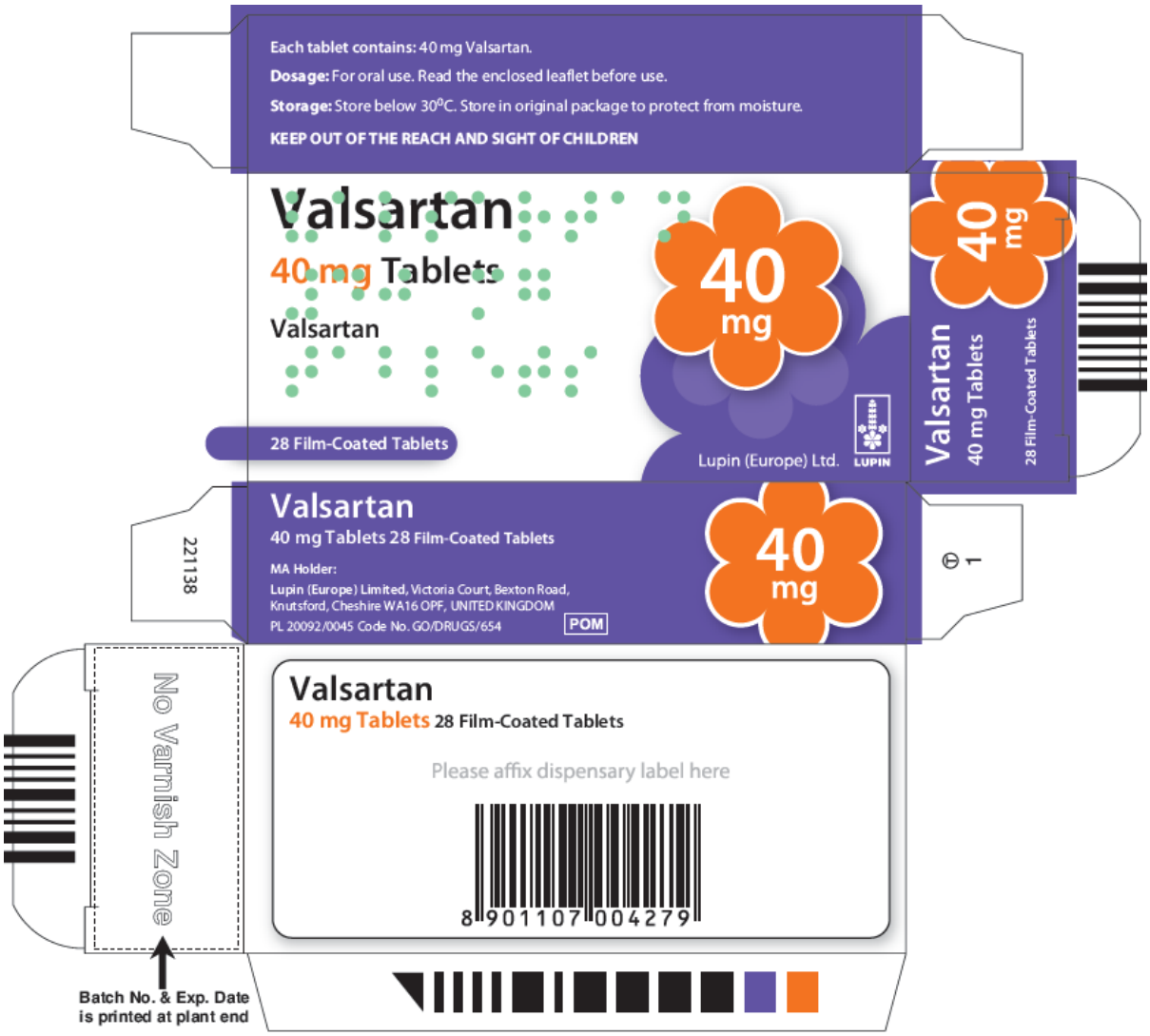
Carton for blisters, with braille

Braille translation

Blisters foils



Carton for blisters, with Braille – alternate carton



Braille translation

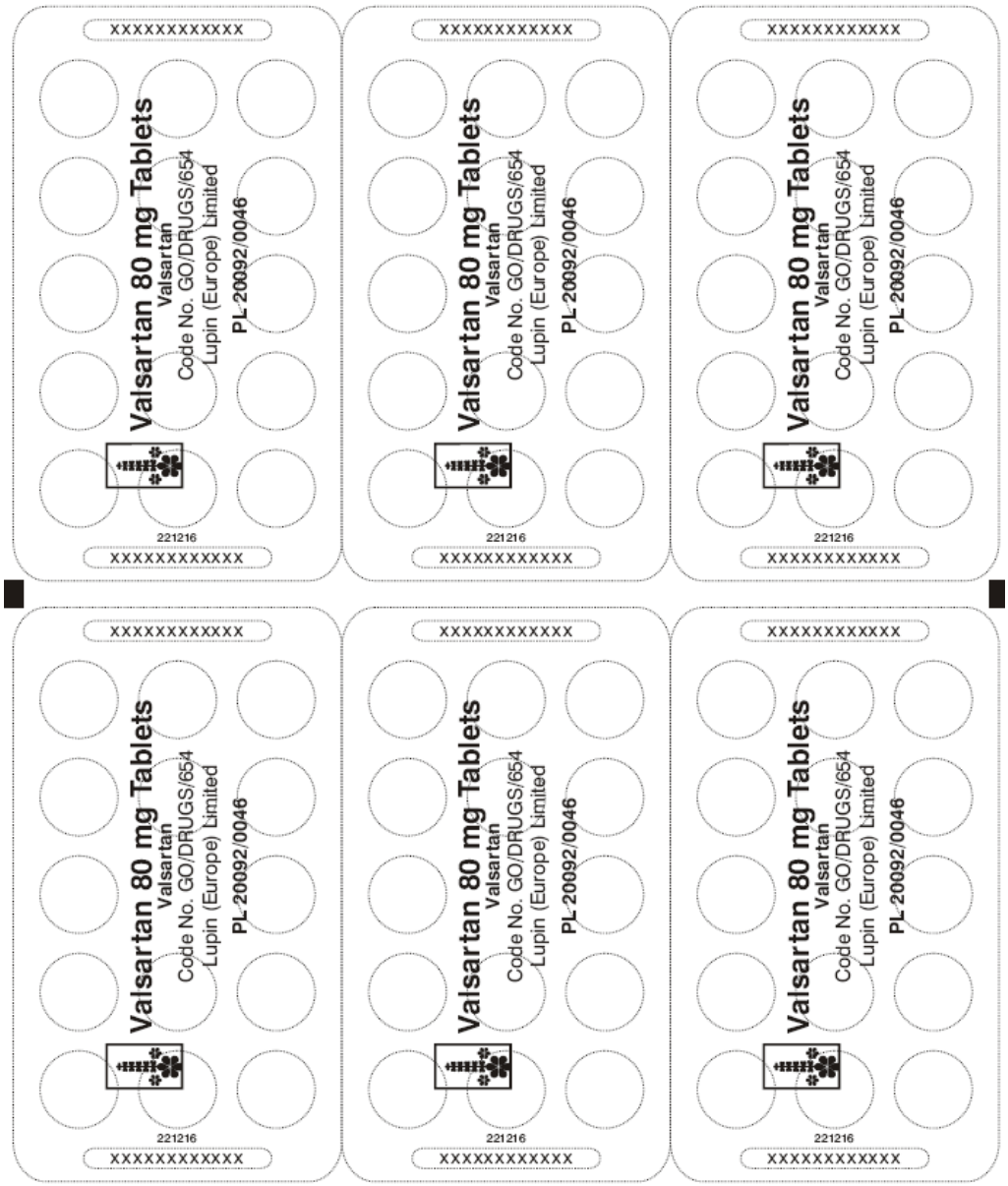
Blisters foils

Valsartan 80mg film-coated tablets

Carton for blisters, with braille

Braille translation

Blisters foils



Carton for blisters, with Braille – alternate carton

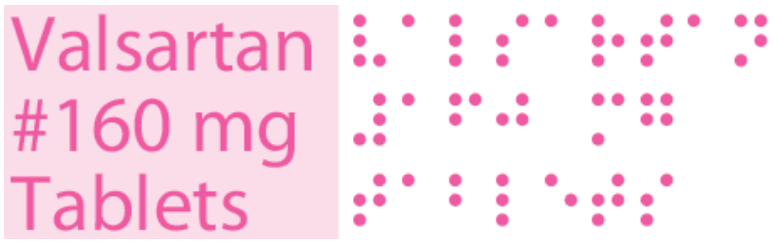
Braille translation

Blisters foils

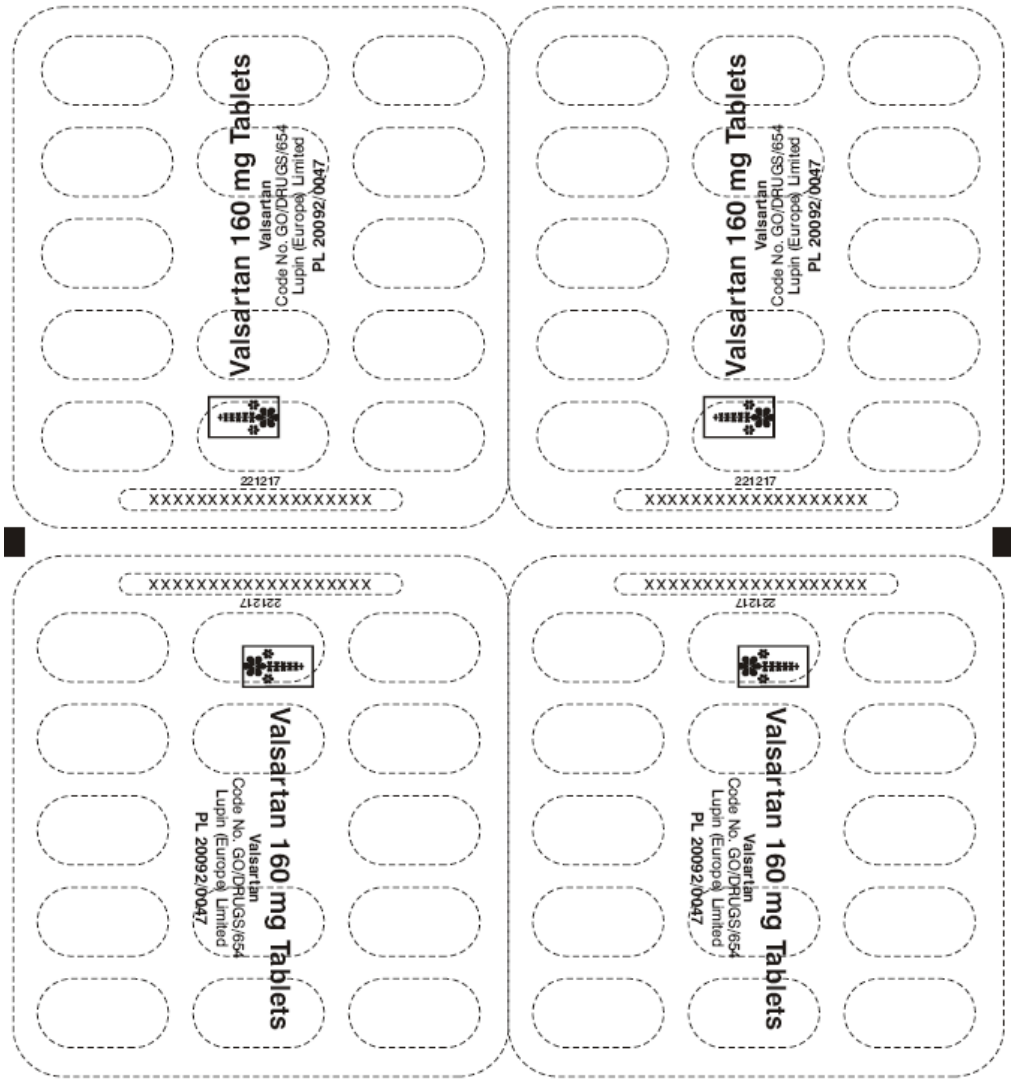
Valsartan 160mg film-coated tablets

Carton for blisters, with braille

Braille translation



Blisters foils



Carton for blisters, with Braille – alternate carton

Braille translation

Blisters foils