

**DIOVAN 320MG TABLETS
PL 00101/0726**

UKPAR

TABLE OF CONTENTS

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 29
Summary of Product Characteristics	Page 30
Product Information Leaflet	Page 37
Labelling	Page 39

DIOVAN 320MG TABLETS
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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Novartis Pharmaceuticals UK Ltd a Marketing Authorisation (licence) for the medicinal product Diovan 320mg Tablets (PL 00101/0726) on 17th September 2007. This is a prescription-only medicine (POM) used for the treatment of high blood pressure.

Diovan 320mg Tablets contain the active ingredient valsartan, which belongs to a group of medicines called angiotensin receptor blockers. Angiotensin is a substance which occurs naturally in your body. It causes blood vessels to narrow. As it is harder for the blood to pass through the vessels, your blood pressure increases. Diovan 320mg Tablets prevent the action of angiotensin, causing the blood vessels to relax. This lowers your blood pressure.

The test product was considered to be a generic product of the reference product 2 x Diovan 160mg Capsules (Novartis Pharmaceuticals UK Ltd) based on the bioequivalence study submitted, and no new safety issues arose as a result of this study.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Diovan 320mg Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

**DIOVAN 320MG TABLETS
PL 00101/0726**

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 8
Clinical assessment	Page 9
Overall conclusion and risk benefit assessment	Page 28

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Novartis Pharmaceuticals UK Ltd a Marketing Authorisation for the medicinal product Diovan 320mg Tablets (PL 00101/0726) on 17th September 2007. The product is a prescription-only medicine.

This is a national application for a line extension to the existing marketing authorisations Diovan 40mg, 80mg and 160mg Film-coated Tablets (PL 00101/0599-601). The line extension is for the addition of a new 320mg strength tablet. The application was submitted as an abridged complex application according to Article 8.3 of Directive 2001/83/EC, as amended, claiming to be a generic product of the reference product 2 x Diovan 160mg Capsules (Novartis Pharmaceuticals UK Ltd), first authorised in 2002.

The product contains the active ingredient valsartan, a selective angiotensin AT1-receptor blocker, indicated for the treatment of hypertension.

Valsartan has already been authorised for use in the treatment of hypertension with a recommended starting dose of 80mg once daily and further increase up to 160mg once daily depending upon the blood pressure response. In patients with myocardial infarction the maximum recommended dose is Valsartan 160mg twice daily. In view of the recent emphasis that aggressive blood pressure management results in lower morbidity and mortality, Novartis proposes to add a 320mg dose.

The application depends upon the bioequivalence study comparing the test product with the reference product 2 x Diovan 160mg Capsules (Novartis Pharmaceuticals UK Ltd).

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

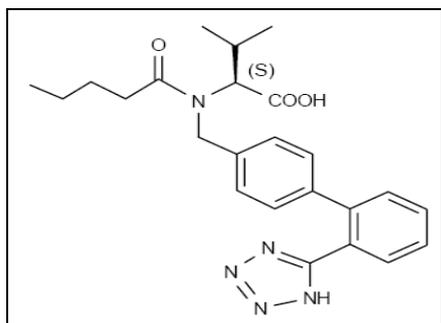
Valsartan

Nomenclature:

INN: Valsartan

Chemical name: (S)-2-{N-(1-oxopentyl)-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-amino}-3-methyl-butyric acid

Structure:



Molecular formula: C₂₄H₂₉N₅O₃

Molecular weight: 435.5

CAS No: 137862-53-4

Physical form: White to off white fine powder

Solubility: Soluble in methanol, slightly soluble in water

An appropriate drug substance specification has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active valsartan is stored in appropriate packaging. It is filled into two polyethylene bags which are placed in sealed metal drums for storage and transport. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer.

Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. This data demonstrates the stability of the drug substance and supports a retest period of 36 months, with no specific storage instructions.

DRUG PRODUCT**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely colloidal anhydrous silica, crospovidone, microcrystalline cellulose, and magnesium stearate making up the tablet core. Titanium dioxide (E171), macrogol 8000, hypromellose, red iron oxide (E172), black iron oxide (E172), yellow iron oxide (E172), and brown iron oxide make up the tablet coating premix 'Diolack brown', which is dissolved in purified water to make up the tablet coating. Appropriate justification for the inclusion of each excipient has been provided.

The excipients used comply with their respective European Pharmacopoeial monographs, with the exception of three constituents of Diolack brown, the colorants red, yellow, and black iron oxide, which comply with international standards (NF). Satisfactory certificates of analysis have been provided for all excipients of the tablet core, purified water, and Diolack brown.

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.

Pharmaceutical development

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

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on validation batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory, and complies with the in-house Novartis Testing monograph, which is satisfactory. 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. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The tablets are packed in PVC / PVDC (DPX) or PA / Al / PVC (Alu-Alu) blister packs conforming to in-house specifications. The blister strips are packaged with the PIL into cardboard boxes. The product is packaged in pack sizes of 28 and 98 tablets. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with food.

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 3 years has been set, which is satisfactory. Storage conditions are “Do not store above 30 degrees”, “Store in the original packaging”.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

Diovan 320mg Tablets have been shown to be a generic product of 2 x Diovan 160mg Capsules. The drug product corresponds to the current EU definition of a generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of the active substance, pharmaceutical form and bioequivalence.

PRECLINICAL ASSESSMENT

This is a national application for a line extension to the existing marketing authorisations Diovan 40mg, 80mg and 160mg Film-coated Tablets (PL 00101/0599-601). The line extension is for the addition of a new 320mg strength tablet, claiming to be a generic product of the reference product 2 x Diovan 160mg Capsules (Novartis Pharmaceuticals UK Ltd), first authorised in 2002.

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INDICATIONS

Treatment of hypertension.

The proposed indication is identical to that stated in the SPC of the reference product.

2. TOXICOLOGY

The toxicological profile of valsartan is well known. The proposed formulation of valsartan 320mg is authorised in the United States and has been in clinical use.

3. CLINICAL PHARMACOLOGY

General

The pharmacokinetics and pharmacodynamics of valsartan in healthy volunteers and in hypertensive patients are well established. The increase in mean AUC and C_{max} is linear and dose proportional in the dose range 80-320 mg. Total plasma clearance is approximately 2.2 L/h. The steady state volume of distribution is about 16.9 L. Following intravenous administration 30% of the dose is excreted in urine and 70% in the faeces, mainly as unchanged compound. There is very little metabolic conversion. After an oral dose of ¹⁴C-labelled dose of valsartan, about 96% of the dose is recovered in the urine and faeces within 72 hours.

The mean bioavailability of the tablet formulation used in clinical studies is 23% relative to an IV dose. In healthy elderly subjects the mean AUC and C_{max} increased by 53% and 24% respectively.

4. BIOEQUIVALENCE

The bioequivalence of new valsartan 320mg tablet and 2 × 160mg marketed Diovan Capsules was evaluated in a single centre, open-label, two-treatment, three period, repeated-measure, randomised crossover study. A total of 40 subjects (21 males, 19 females) were enrolled and completed the study. In every treatment sequence, the treatment of the second period was repeated in the third period, (i.e, ABB, or BAA). Treatments were administered after at least 10 hours overnight fast and subjects continued to fast for 4 hours after dosing. The washout period was a minimum of 3 days. The sampling period was 48 hours during which 15 pharmacokinetic samples were taken.

The results and their statistical assessment show both C_{max} and AUC to be within the recommended range of 0.80 – 1.25%.

The bioequivalence of valsartan 320mg tablet has been shown.

5. EFFICACY

Efficacy is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

The pivotal trial supporting this application is study H2301. There were additional data from ongoing studies supporting the efficacy and safety of valsartan.

All studies fully complied with the GCP requirements. Reference is also made to the statistical assessment regarding efficacy.

Overview of trials or sources of data

Source of data	Details
Controlled trials	1 active-controlled pivotal phase III trial study H2301. 3 placebo-controlled phase III trials: study 31, study C2301 and study A2201 (All adequate and well controlled)
Uncontrolled trials	1 uncontrolled trial (treatment data compared to baseline) study A2419
Long-term data	1 open label safety extension study H2301E

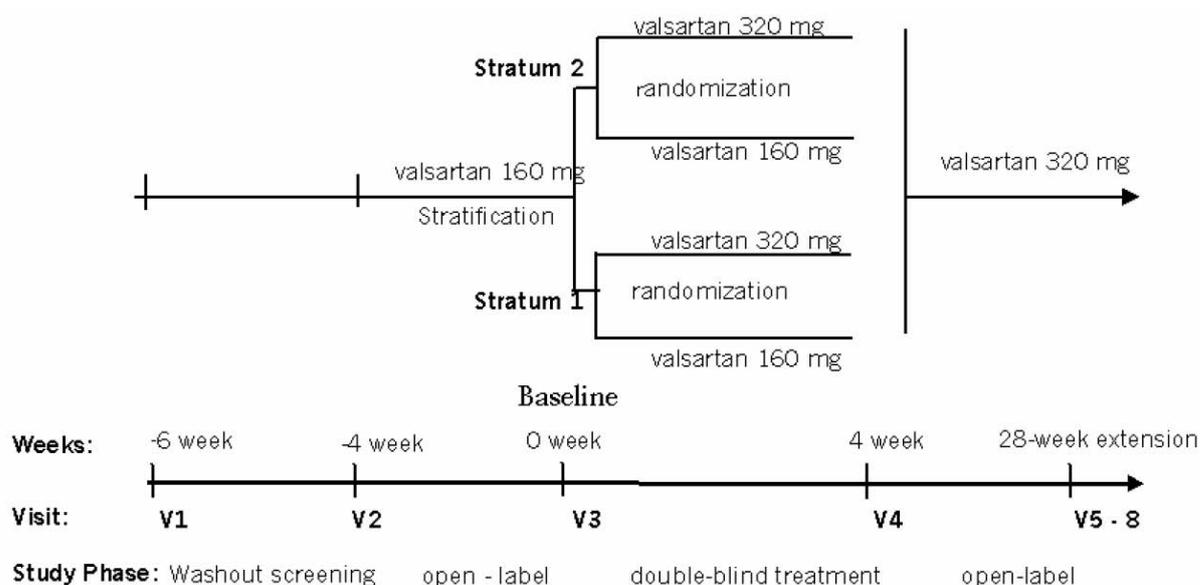
5.1 Controlled Studies

Main therapeutic study: H2301

This study investigated the efficacy and safety of valsartan 320mg and compared it with valsartan 160mg in patients with mild to moderate essential hypertension. A total of 3776 patients were recruited in the study and 3723 patients (98.6%) completed the trial. Responders (1855 patients) and non-responders (1902 patients) were separated as stratum 1 and stratum 2.

The primary endpoint was change from baseline in MSDBP in overall population and the secondary endpoint change from baseline in MSDBP in patients not adequately controlled with 160mg. The tertiary endpoints were change from baseline in MSDBP in patients controlled with 160mg; change from baseline in MSSBP; change from baseline in MSPP and response rate.

The results showed statistically significant reduction in MSDBP and MSSBP at endpoint compared to baseline and that the effect was greater with valsartan 320mg dose. In non-responders the effect was significantly greater in valsartan 320mg group compared to valsartan 160mg group.

Figure 2-1 Study H2301 design

Study 31

This study compared four doses of valsartan: 20mg, 80mg, 160mg and 320mg. This was a multi-centre, randomised, double-blind, placebo-controlled, parallel design study. A total of 736 patients were randomised, 729 included in ITT analysis and 668 completed the trial. The primary efficacy variable was change from baseline to endpoint in MSDBP.

All doses of valsartan showed statistically significant reduction in blood pressure compared to baseline. The mean difference in DBP reduction, compared to placebo, was -5.2 mm with valsartan 80mg dose, -5.32 mm with valsartan 160mg dose and -6.48 mm with valsartan 320mg. The effect on MSSBP was greater. The diastolic responder rate corresponded with dose with greatest effect observed with valsartan 320mg (50.7%).

Study C2301

This was a multicentre, double-blind, randomised, placebo-controlled, multifactorial, 8-arm parallel design study which compared the efficacy and safety of combination therapy of valsartan/HCTZ (320/12.5mg, 320/25mg, 160/12.5mg) with respective monotherapies, valsartan (160 or 320 mg), HCTZ (12.5 or 25mg) or placebo. A total of 1346 patients were randomised in DB phase. The primary efficacy variable was change in MSDBP from baseline, like other studies. Only monotherapy component was taken for this submission.

Both doses showed significant reduction in MSDBP and MSSBP but there was no difference between valsartan 160mg and 320 mg dose.

Study A2201

This was a multi-centre, double-blind, randomised, placebo-controlled, multifactorial, parallel design trial comparing eight doses of the combination therapy valsartan/amlodipine (40/2.5, 80/2.5, 80/5, 160/2.5, 160/5, 320/2.5 or 320/5mg) to their component monotherapies. A total of 1911 patients were randomised in the

double-blind treatment phase, 1898 included in ITT analysis and 1738 completed the trial. The primary efficacy variable was change in MSDBP from baseline. The current submission only looked at patients on valsartan monotherapy and placebo. A total of 128 patients were randomised to valsartan 320mg dose and 116 completed the study. All doses showed statistically significant reduction in MSDBP and MSSBP. The effect was dose related.

5.2 Uncontrolled Studies

Study A2419

This was a multi-centre, uncontrolled, open-label, forced titration study. The efficacy and safety of an escalating regimen of valsartan (valsartan 160mg, valsartan 320mg, valsartan 320/HCTZ 12.5mg) was evaluated in patients with mild to moderate hypertension.

A total of 362 patients were recruited and 304 completed the study. All patients were included in ITT analysis. The primary efficacy variable was the change in 24-hour Ambulatory Diastolic Blood Pressure (ADBP). The reduction on BP was statistically significant both at 4 weeks and 8 weeks, compared to baseline. There was no significant difference between 4 & 8 weeks for ADBP. However the change in ABSP was significant between 4 & 8 weeks.

5.3 Long-Term Data

Study H2301E

This was an open label, safety extension of study H2301. The study looked at the therapeutic effectiveness of valsartan 320 mg over 28 weeks in patients with essential hypertension. There were 642 patients in open extension phase and 595 completed this phase of the trial. The efficacy criteria were MSDBP and MSSBP.

The reduction in BP with valsartan 320mg was sustained for each time point of weeks 8, 16, 24 and 32. The baseline was taken as 4 weeks of therapy with valsartan 160mg daily.

Clinical Assessor's comments on overall efficacy

Additional effect of valsartan 320mg on reduction of blood pressure is convincingly shown in a well designed main therapeutic study. This effect being sustained over a 32 week period is also clear. The only question was that the disease characteristics in dataset A (Pooled data from DB, active or placebo controlled studies, considered a primary dataset) showed noticeable difference. There was a single case of isolated systolic hypertension in valsartan 320mg group compared to 368 in valsartan 160mg group. This, however, is not considered to affect the overall efficacy as no claim has been made for additional efficacy in isolated systolic hypertension.

5.4 Statistical Assessment

The MAH's proposed posology for the treatment of hypertension is that the recommended dose of Diovan is 80mg and that in patients whose blood pressure is not adequately controlled at this dose, then the dose should be increased to 160mg; if additional blood pressure reduction is then required the dose can be increased further to a maximum of 320mg.

This assessment concentrates on:

- a bioequivalence study (604) used to compare the proposed commercial formulation (320mg tablets) with the formulation used in the clinical trials (2×160mg capsules);
- one pivotal study (H2301) and three supportive studies (31, C2301 and A2201) used to compare the benefits of the 320mg dose of valsartan with the 160mg dose.

Bioequivalence study (604)

Design, analyses and objectives of the study

This bioequivalence study compared the proposed commercial formulation (320mg tablets-*treatment A*) with the formulation used in the clinical trials (2×160mg capsules-*treatment B*). The study was a randomised, open label, three-period cross-over study in which subjects were randomised to either sequence ABB or BAA.

AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were analysed using an ANOVA on log-transformed data with terms for sequence, subject within sequence, period and treatment. Only subjects who completed all three periods of treatment were included in the final analyses.

Results of the studies

The percentage of $AUC_{0-\infty}$ which was extrapolated was less than 20% for the majority of subjects within each period, indicating that the sampling schedule was sufficient to provide a reliable estimate of the extent of absorption.

A total of 40 subjects were randomised, all of which completed all three study periods.

Pharmacokinetic parameters

Parameter	Raw means		Adjusted ratio: Treatment group A/B	
	A	B	Point estimate	90% CI
AUC_{0-t} (mg.h/L)	41.050	38.110	1.11	1.02 -1.20
$AUC_{0-\infty}$ (mg.h/L)	42.683	39.892	1.10	1.02-1.19
C_{max} (mg/L)	6.162	6.164	1.09	0.98-1.21

Statistical assessor's comment: *The parametric 90% confidence intervals for parameters AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} show bioequivalence in accordance with the CHMP guideline as they are all contained within the 0.80-1.25% range.*

Pivotal study (H2301)

Design, analyses and objectives of the study

Study H2301 was a randomised, double-blind, parallel group study. Patients were initially treated with valsartan 160mg for 4 weeks, followed by their baseline visit at which they were classified as responders or non-responders. Patients were then randomised to receive either 160 or 320mg of valsartan for a duration of 4 weeks (the double blind treatment phase), stratified by their responder classification.

The primary endpoint for this study was the mean change from baseline in sitting diastolic blood pressure (MSDBP) using the ITT population. The primary timepoint was after the double blind treatment phase of the study. The last observation carried forward (LOCF) approach to missing data was used. Secondary analyses included using the subset of non-responding patients and the mean change from baseline in sitting systolic blood pressure (MSSBP).

Statistical assessor's comment: The design for this study is generally appropriate.

Results

Of the 4004 patients who entered the run-in phase of the study, 3776 were randomised, 1900 to valsartan 160mg and 1876 to valsartan 320mg. A total of 33 (1.7%) and 20 (1.1%) patients in the 160 and 320mg valsartan treatment groups, respectively, withdrew during the double blind treatment phase of the study.

Results from the primary analysis using the overall ITT population together with the analysis repeated using the subset of non-responder patients are given below.

Between-treatment comparison for change from baseline to endpoint in MSDBP (mmHg) (overall ITT population)				
Treatment group	N	n*	Baseline mean	LSM change from baseline (SE) M
Valsartan 160 mg	1884	1884	89.8	-0.5 (0.18)
Valsartan 320 mg	1873	1873	89.7	-1.8 (0.18)
Comparison	Difference in LS Mean Change from baseline (SE)**		95% CI	p-value
Val 320 mg vs 160 mg	-1.18 (0.231)		(-1.63,-0.72)	<0.0001

(*) N is the overall ITT population. n is the number of patients with MSDBP at both baseline and endpoint.

(**) Difference is Val 320 mg - Val 160 mg. Negative values indicate a greater BP reduction for Val 320 mg. Baseline is the mean of Week 0 readings, and endpoint is the mean of readings at Week 4 or LOCF value. Only patients with a baseline and endpoint are included. Least square means, confidence intervals, and p-values are derived from an ANCOVA model with treatment, center, responder stratum and centered baseline. (SE)M = (Standard error) of the mean.

Between-treatment comparison for change from baseline to endpoint in MSDBP (mmHg) in the non-responder (ITT population)

Treatment group	N	n*	Baseline mean	LSM change from baseline (SE) M
Valsartan 160 mg	946	946	96.9 (0.15)	-2.8 (0.25)
Valsartan 320 mg	956	956	96.8 (0.16)	-4.1 (0.25)
Comparison	Difference in LS Mean Change from baseline (SE)**		95% CI	p-value
Val 320 mg vs 160 mg	-1.29 (0.320)		(-1.91,-0.66)	<0.0001

(*) N is the non-responder ITT population; n is the number of non-responders with MSDBP at both baseline and endpoint.

(**) Difference is Val 320 mg - Val 160 mg. Negative values indicate a greater BP reduction for Val 320 mg. Baseline is the mean of Week 0 readings, and endpoint is the mean of readings at Week 4 or LOCF value. Only patients with a baseline and endpoint are included.

Least square means, confidence intervals, and p-values are derived from an ANCOVA model with treatment, center, responder stratum and centered baseline.

Statistical assessor's comment: *Statistically compelling evidence of efficacy for the 320mg dose of valsartan compared to the 160mg dose using the MSDBP endpoint has been shown. The reduction in MSDBP was slightly larger in the subset of non-responding patients than the overall population. Statistically compelling evidence of efficacy was also seen for the MSSBP endpoint, where the reduction was slightly larger in the overall ITT population than in the subset of non-responding patients.*

Supportive efficacy studies

All three supportive studies included in this submission were randomised, placebo-controlled double-blind studies. The primary endpoint for all three studies was the change from baseline in MSDBP after eight weeks of active treatment. The ITT population was considered primary and an LOCF approach to missing data was used in all three studies.

Design, analyses and objectives of the studies

Study 31 was designed to compare the efficacy of 20, 80, 160 and 320mg of valsartan versus placebo. A Bonferoni adjustment was carried out to account for multiple comparisons.

Study A2201 was designed as a valsartan/amlodipine combination study where patients were randomised equally to all possible combinations of 0, 40, 80, 160 and 320mg of valsartan together with 0, 2.5 and 5mg of amlodipine (i.e. 15 treatment groups in total).

Study C2301 was designed to compare the efficacy of the 320/12.5mg and 320/25mg combinations of valsartan/HCTZ with their corresponding monotherapies.

Statistical assessor's comment: *None of these studies were designed to make comparisons between the 320mg and 160mg doses of valsartan. However, the design of these studies means that their results are considered to be adequate as supportive data for the proposed indication and only relevant treatment comparisons are presented.*

Results of the studies

Patients' dispositions are given in the table below.

	Placebo		Valsartan 80mg		Valsartan 160mg		Valsartan 320mg	
	R	W	R	W	R	W	R	W
Study 31	148	20 (14%)	150	10 (7%)	148	12 (8%)	150	11 (7%)
Study A2201	128	28 (22%)	124	11 (9%)	128	10 (8%)	128	12 (9%)
Study C2301	169	32 (19%)	-	-	166	13 (8%)	170	33 (19%)

R-randomised, W-withdrew from the study.

Statistical assessor's comment: For all three studies more patients withdrew from the placebo than the active treatment arm. For studies 31 and A2201 a similar number of patients withdrew from each of the active treatment arms. In study C2301, more patients withdrew from the 320mg valsartan treatment group than the 160mg treatment group.

The table below shows the results for the MSDBP endpoint.

Table 3-6 Least squares mean change from baseline in MSDBP (mmHg) at endpoint (placebo-controlled trials – ITT population)

Study	31		A2201		C2301	
	Difference	98.75% CI	Difference	95% CI	Difference	95% CI
valsartan 320 mg vs. placebo	-6.5 ^P	(-8.8; -4.1)	-6.7 ^P	(-8.4; -4.9)	-4.4 ^P	(-6.1; -2.6)
valsartan 160 mg vs. placebo	-5.3 ^P	(-7.7; -3.0)	-4.5 ^P	(-6.1; -2.5)	-4.7 ^P	(-6.5; -2.9)
valsartan 80 mg vs. placebo	-5.2 ^P	(-7.5; -2.9)	-3.0 ^P	(-4.8; -1.2)	-	-

^P indicates a statistically significant difference vs. placebo

Placebo response was -2.0 mmHg in study 31, -6.4 mmHg in study A2201 and -7.0 mmHg in study 2301

Statistical assessor's comment: For the MSDBP endpoint, there is an increase in efficacy between the 320mg and 160mg doses of valsartan apart from in study C2301. One possible reason for seeing no increase in efficacy between the 320 and 160mg doses of valsartan in study C2301, is that the amount of missing data in the 320mg valsartan treatment group was larger than in the 160mg group. For this reason, more missing data is imputed in the 320mg than the 160mg treatment group, and could explain the non-monotonic dose response. Similar conclusions were seen in all three studies when using the MSSBP endpoint.

Statistical assessor's conclusions

The pivotal study assessed both the overall population and the subset of patients who did not respond to the 160mg dose of valsartan. Both these populations showed statistically compelling evidence of efficacy for the 320mg dose when compared to the 160mg dose of valsartan. The three supportive studies were not designed to compare the 320 mg and 160 mg doses of valsartan. However, two of these studies showed an increase in efficacy between the 320mg and 160mg doses of valsartan.

In addition, bioequivalence has been shown between the proposed marketed formulation and the formulation used in the clinical trials.

6 SAFETY

Safety is reviewed in the Clinical Expert Report.

Safety data has been extracted from various trials for higher doses of 160mg and 320mg valsartan given as monotherapy. This was compared with data from the current dosing of valsartan 80mg and 160mg and also from placebo and comparator products (amlodipine and lisinopril).

Additional evidence has been provided from studies performed on an ongoing basis and designed to support the efficacy and safety of valsartan across the 80mg to 320mg dose range: VAL489A2419, H2301, extension study H2301E and a published study (Hermida et al. 2003). Data from most comparator groups and from combination therapy were omitted. Several pooling strategies were used resulting in several datasets, detailed as follows:

Dataset A: Pooled data from DB, active or placebo controlled studies

Dataset B: Pooled data from placebo controlled studies. This was a subset of A.

Dataset C: DB, active-controlled study with open label active run-in phase

Dataset D: Open-label extension trial

Dataset E: Open-label and publication studies

The overall exposure of patients on 320mg dose of valsartan was 447 in dataset A, 447 in dataset B, 1876 in dataset C and 642 in dataset D. The mean exposure duration on the proposed higher dose of 320mg in datasets A & B were 7.6 weeks, in dataset C 4 weeks and in dataset D 27.1 weeks.

Disease characteristics in dataset A (considered a primary dataset) showed a noticeable difference. There was a single patient (0.2%) with isolated systolic hypertension in valsartan 320mg group compared to 368 (15.5) in valsartan 160mg group. The majority of patients (88.4%) in valsartan 160mg group had stage II hypertension while in valsartan 320mg they were approximately equally distributed between stage I (43.8%) and stage II (56.2).

6.1 Withdrawals

Dataset A showed discontinuation to be higher (12.3%) in patient group on valsartan 320mg compared to 4% for valsartan 160mg group, 4.3 % for valsartan 80mg group 5.2% for amlodipine group and 10.2% for lisinopril group. An even higher rate for the placebo group (16.6%) is not surprising as this may be due to inadequate therapeutic effect. In addition, a higher percentage of patients on 320mg valsartan were reported to have unsatisfactory therapeutic effect, lost to follow up and had abnormal laboratory values compared to patients on valsartan 160mg.

A similar pattern of discontinuation is reported in dataset B. There was no significant difference between valsartan 160mg and 320mg groups in dataset C. Discontinuations due to adverse events were higher in valsartan 320mg group (4.9%) compared to 1.5% for valsartan 160mg, 3.4% for amlodipine and 4.3% for lisinopril

groups. Discontinuations due to cardiac disorders and ear and labyrinth disorders were also higher in valsartan 320mg group compared to other groups.

6.2 Adverse Events

The Company believes that the new dose of valsartan allows for additional BP lowering in hypertensive patients not adequately controlled with valsartan 160mg and the safety profile of the higher dose remains similar to that observed with placebo. For patients who were titrated from valsartan 160mg to 320mg (Pivotal trial H2301), the high dose was well controlled. The MAH claimed that the AE profile of valsartan 320mg did remain similar to that of the approved 160mg dose and the frequency of AEs was not increased significantly between the two treatment doses.

To demonstrate the safety of valsartan 320mg, the applicant focuses on datasets A and B which are briefly described below:

- Dataset A, data were pooled from double blind, active or placebo controlled studies. In these studies the valsartan doses were 80mg or 160mg or 320mg and the populations were a combination of a total of 5216 patients with mild to moderate or moderate to severe hypertension.
- Dataset B was more selective and only data from double blind, placebo controlled studies were pooled. In these studies the valsartan doses were 80mg or 160mg or 320mg and the 2145 patients from this dataset were all mild to moderate hypertensives.

In dataset A, the frequencies of AEs with valsartan 320mg was higher than in the other treatment groups. However, the frequencies of AEs seen with valsartan 320mg remain in the range of those observed with placebo. The applicant suggests that this information should be interpreted with caution because of the heterogeneity of the trials pooled.

The groups in dataset B are better matched in terms of background demographic and disease characteristics and this dataset confirms in a smaller more balanced population the information presented in dataset A. In dataset B, the safety profile of valsartan 320mg remains similar to that of the lower doses of valsartan and is in the range of that seen with placebo.

6.2.1 Overall Common Adverse Events

The most common adverse events were upper respiratory complaints (pharyngitis, cough etc), dizziness, nausea, headache & diarrhoea. It is claimed that these were similar to that noted with placebo but it is clear in dataset A & dataset B that valsartan 320mg group showed higher adverse event rates than valsartan 160mg or comparator products amlodipine or lisinopril.

6.2.2 Most Frequently Observed Adverse Events

In dataset A, headache, dizziness, upper respiratory tract infection, nasopharyngitis, cough, arthralgia, fatigue, sinusitis, diarrhoea, influenza, nausea and anxiety were all reported to be higher in valsartan 320mg group than in valsartan 160mg group. Most of these adverse events except cough were higher in valsartan 320mg group than in amlodipine and lisinopril groups.

The pattern was similar in dataset B. In dataset C the most frequent adverse events, defined as $\geq 0.5\%$, were similar in both groups (valsartan 160mg & valsartan 320mg). In extension phase (dataset D), bronchitis, back pain, eczema, nasopharyngitis and headache remained the most frequently reported adverse events (defined as $>1.0\%$) indicating consistency of adverse events reported with valsartan 320mg.

6.2.3 Drug related Adverse Events

In dataset A, patient reported adverse events were noted in 53.2% patients on valsartan 320mg as opposed to 27.8% on valsartan 160mg, 32.6% on amlodipine and 24.0% on lisinopril. The incidence of drug related adverse events attributed by the investigators was higher (7.2%) in valsartan 320mg compared to valsartan 160mg (5.9%). The incidence in both amlodipine and lisinopril groups were even higher (9.3% & 10.7% respectively).

6.2.4 Deaths/Serious Adverse Events

The overall incidence of severe adverse events in dataset A was highest in valsartan 320mg group (3.1%). The respective figures for valsartan 160mg, amlodipine & lisinopril were 1.5%, 1.8% and 1.3%.

The only death reported was in the valsartan 320mg group. A 72 year old female had a cardiac arrest and died from arrhythmia on day 8 of the double blind treatment period. Although it is alleged that death was not suspected to be related to the study, the assessor wonders how the possibility of hyperkalaemia leading to arrhythmic death has been ruled out.

Serious adverse events excluding deaths were similar in valsartan 160mg, valsartan 320mg, amlodipine, and lisinopril groups.

Assessor's comments:

The applicant has emphasised their claim that the adverse events with valsartan 320mg were similar to those observed in the placebo group, although this is not considered as the issue. The dose of 320mg valsartan will be used by up-titration from valsartan 160mg daily. The clinical alternatives are to add another therapy e.g., thiazide or amlodipine. The safety analysis should demonstrate unequivocally that the safety profile of valsartan 320mg dose is no worse than valsartan 160mg dose and that valsartan 320mg is comparatively safer or no worse than add-on thiazide or amlodipine.

Study H2301 showed incidence of diarrhoea (11/1876, 0.6% vs 6/1898, 0.3%) and asthenia (9/1876, 0.5% vs 3/1898, 0.2%) to double in valsartan 320mg group, compared to valsartan 160mg group. Similarly, vertigo (4/1876, 0.2% vs 1/1898, 0.1%) and asthenia (3/1876, 0.2% vs 1/1898, 0.1%) were reported with greater frequency in valsartan 320mg group than 160mg group although the numbers were small.

The data provided show that adverse events are worse with valsartan 320mg compared to valsartan 160mg dose and also to amlodipine and lisinopril groups. There is a clear trend for higher adverse events in valsartan 320mg dose group in data from study H2301, dataset A, and dataset B, as shown in the table below:

Adverse events higher than placebo and higher than valsartan 160mg

DATASET A	Placebo %	Valsartan 160mg %	Valsartan 320mg %
Dizziness	3.9	1.8	6.7
Upper Resp Tract Inf	3.4	0.9	4.7
Nasopharyngitis	2.6	2.0	3.6
Cough	0.6	1.1	2.9
Arthralgia	1.1	0.7	2.9
Fatigue	2.0	1.3	2.7
Sinusitis	1.9	0.3	2.2
Diarrhoea	1.5	0.9	2.0
Influenza	0.7	0.9	2.0
Nausea	1.5	0.8	2.0
Anxiety	0.4	0.5	2.0
DATASET B			
Dizziness	3.9	3.0	6.7
Upper Resp Tract Inf	3.4	3.3	4.7
Arthralgia	1.1	1.9	2.9
Cough	0.6	1.7	2.9
Fatigue	2.0	1.9	2.7
Sinusitis	1.9	1.1	2.2
Influenza	0.7	1.1	2.0
Anxiety	0.4	0.2	2.0

The safety of the higher dose and the positive risk:benefit need further proof. The majority of patients with hypertension are asymptomatic. Any symptoms as part of adverse events has a negative impact on risk:benefit.

Further data and analysis of adverse events

The individual AEs in study H2301 occurred at very low frequencies in both treatment groups during the double-blind phase (Table 1-1). Headache was the most frequently reported adverse event followed by nasopharyngitis, dizziness and back pain. In addition, despite an increase in the incidence of some of these AEs such as diarrhoea or asthenia, there was no evidence of dose dependency in the overall valsartan tolerability profile when comparing the 320mg dose to the 160mg dose.

In dataset A and B there appears to be a trend towards a small increase of selected events in the 320mg group compared to 160mg group. However, there is no evidence of a dose-adverse experience relationship in the company's global database. The observed small increase in adverse events with valsartan 320mg compared to

valsartan 160mg may be explained by the fact that the 447 patients in the valsartan 320 mg group were treated with this dose directly. These patients were not titrated up from 160mg as is recommended in the Diovan 320mg SPC proposed by the company. This titration step is expected to ensure that the new 320mg dose is well tolerated, in line with what was observed in study H2301.

Table 1-1 Number (%) of patients with most frequent ($\geq 0.5\%$ in either treatment group) AEs (Safety population, double blind phase – Study H2301)

Adverse events (preferred Term)	Val 160mg N=1898 n (%)	Val 320mg N=1976 n (%)
Total no.with an AE	270 (14.2)	266 (14.2)
Headache	26 (1.4)	27 (1.4)
Nasopharyngitis	16 (0.8%)	17 (0.9)
Diarrhoea	6 (0.3)	11 (0.6)
Asthenia	3 (0.2)	9 (0.5)
Dizziness	14 (0.7)	9 (0.5)
Back pain	12 (0.6)	8 (0.4)
Fatigue	10 (0.5)	8 (0.4)
Arthralgia	9 (0.5)	3 (0.2)

- AEs are listed by preferred term and by most frequent in 320 mg dose.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- Patients are counted if an adverse event has not occurred previous to entering the current phase or if an existing adverse event changes in severity or relation to study drug during the current phase.

Source: PTT 10.1 – 1e

The incidence of SAEs and AEs leading to discontinuation, in clinical programme, is a key feature of the risk:benefit profile of a drug. In the pivotal study H2301 (Table 1-2 below), there were very few SAEs overall and they were equally split across treatment doses. Discontinuations occurred at similar frequencies in the 160mg and in the 320mg group.

Table 1-2 Deaths, SAEs and significant events during the double-blind phase. (Study H2301)

	Val 160mg N=1898 n (%)	Val 320mg N=1976 n (%)
Deaths	0	0
SAEs	6 (0.3)	6 (0.3)
AEs leading to discontinuation	7 (0.4)	5 (0.3)
SAEs leading to discontinuation	2 (0.1)	1 (0.1)

Source: PTT 10.2-1b 10.2-2b and 10.2-3b; PTL 10.2-2

As regards diarrhoea and asthenia, the tolerability profile should be looked at not just by their incidence but also by their level of severity. The severity of diarrhoea reported in the 320mg group is generally lower than in the 160mg group (table 1-3). All cases reported in the 320mg group were of mild severity. This is valid for the pivotal study H2301 as well as datasets A & B.

Table 1-3 Severity of Diarrhoea (study H2301, Dataset A and Dataset B)

	Placebo n (%)	Val 80mg n (%)	Val 160mg n (%)	Val 320mg n (%)
Study H2301	-	-	N = 1898	N = 1876
Mild	-	-	4 (0.2)	11 (0.6)
Moderate	-	-	1 (0.1)	0 (0.0)
Severe	-	-	1 (0.1)	0.(0.0)
Dataset A	N = 537	N = 628	N = 2379	N = 447
Mild	6 (1.1)	8 (1.3)	12 (0.5)	9 (0.2)
Moderate	2 (0.4)	2 (0.3)	10 (0.4)	0 (0.0)
Severe	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Dataset B	N = 537	N = 370	N = 538	N = 447
Mild	6 (1.1)	6 (1.6)	6 (1.1)	9 (2.0)
Moderate	0.(0.0)	0.(0.0)	0 (0.0)	0.(0.0)
Severe	0.(0.0)	0.(0.0)	0.(0.0)	0.(0.0)

Source: SCS Table 4.4-1.1 and 4.4-1.2

With respect to asthenia, table 1-4 shows that asthenia tends to be of low severity with 320mg, similar to what is observed with the lower doses of valsartan and with placebo. In addition, the incidence of diarrhoea and asthenia is in the range of 1%. This is similar to what is known for other AT1-receptor blockers as evidenced in their respective SPCs (Olmesartan, Irbesartan and Telmisartan).

Table 1-4 Severity of Asthenia (study H2301, Dataset A and Dataset B)

	Placebo n (%)	Val 80mg n (%)	Val 160mg n (%)	Val 320mg n (%)
Study H2301	-	-	N = 1898	N = 1876
Mild	-	-	2 (0.1)	7 (0.4)
Moderate	-	-	1 (0.1)	2 (0.1)
Severe	-	-	0 (0.0)	0.(0.0)
Dataset A	N = 537	N = 628	N = 2379	N = 447
Mild	5 (0.9)	1 (0.2)	8 (0.3)	0 (0.0)
Moderate	1 (0.2)	1 (0.2)	2 (0.1)	1 (0.2)
Severe	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Dataset B	N = 537	N = 370	N = 538	N = 447
Mild	5 (0.9)	1 (0.3)	0 (0.0)	0 (0.0)
Moderate	1.(0.2)	1.(0.3)	0 (0.0)	1.(0.2)
Severe	0.(0.0)	1.(0.3)	0.(0.0)	0.(0.0)

Source: SCS Table 4.2-1.1 and 4.2-1.2

Having provided this further data, the applicant concludes that the valsartan 320mg dose has a positive risk:benefit ratio. Even if for selected events there is a trend towards a small increase with this dose as compared to the 160mg dose, they remain of mild or moderate severity and the observed difference between the 320mg and 160mg groups in datasets A and B is likely to be attributable to the absence of adequate treatment titration.

The applicant accepts that hypertensive patients are asymptomatic. However, they argue that the benefit of treatment goes beyond BP reduction. International guidelines on the management of hypertension have underlined the importance of lowering the BP of hypertensive patients in order to lower associated morbidity and mortality.

Assessor's comments

The company's argument regarding mild severity of adverse events like diarrhoea and asthenia is accepted. The discontinuations due to AEs and SAEs are similar between 160mg and 320mg group. No drug related death has been reported. The company's argument that a positive risk:benefit of valsartan 320mg has been established is accepted.

Valsartan 320mg Vs Valsartan 160mg + other antihypertensive therapy.

The 320mg dose is likely to be used by uptitration from valsartan 160mg dose. Therefore, justification is required that the adverse profile of the 320mg dose is no worse than if the patients were switched to valsartan 160mg + HCTZ or valsartan + other antihypertensive therapy.

Although the company does not have head-to-head data comparing the safety/tolerability profile of the two treatment approaches, data from two well designed large trials looking individually at the two treatment options do not suggest that the adverse event profile observed when titrating patients to valsartan 320mg is worse than if patients not controlled on valsartan 160mg were switched to a combination with HCTZ.

- In study H2301, patients not controlled with valsartan 160mg were uptitrated to valsartan 320 mg. A total of 3776 patients were randomised into the double-blind treatment phase. This trial allows for an assessment of the safety of a 160mg to 320mg treatment strategy.
- Study 201 was a multicentre, double-blind, double-dummy, randomised, 3-arm active-controlled, parallel group trial in patients with mild to moderate essential hypertension not adequately controlled on valsartan 160mg. In the double blind phase of this trial, patients not controlled on valsartan 160mg were randomised to one of the following treatment arms: valsartan 160mg or valsartan 160mg + HCTZ 12.5mg or 25mg. A total of 2002 patients were randomised into the double blind treatment phase. This trial allows for an assessment of the safety of a 160mg to 160mg + HCTZ combination treatment strategy.

In study H2301, no significant difference between valsartan 160mg and valsartan 320mg strengths were observed in the safety profiles.

In study 201, the overall incidence of AEs was relatively low and the same proportion of patients in each of the treatment groups (valsartan 160mg and valsartan 160mg/HCTZ 12.5mg) reported adverse events (22.7%, 23.3% respectively). An overview of deaths, SAEs and AEs that led to discontinuation of medication showed no difference to be observed between valsartan 160mg and valsartan 160mg + HCTZ 12.5mg.

In conclusion, the studies described show that patients not adequately controlled on valsartan 160mg do not experience significantly more adverse events when the dose

of valsartan is increased to 320mg than when a diuretic is added. Therefore, the above trials do not suggest that the adverse event profile observed when titrating patients to 320mg is worse than that observed when switching patients to a combination with HCTZ.

Assessor's comments

The point has not been directly addressed. The issue was regarding the adverse event profile of valsartan 320mg monotherapy vs valsartan 160mg + HCTZ combination therapy. The company accepts not having head-to-head comparative data for valsartan 320mg and valsartan 160mg + HCTZ but goes on to conclude that adverse event profile is no worse than when switching patients to a combination with HCTZ. This assumption seems to be based on study 201 which has not used valsartan 320mg dose.

Assessor does not agree with the company's assumption that combining two agents with a complimentary mechanism of actions leads to additional BP reductions but usually bears the risks of cumulative adverse reactions of the individual agents, and that patients may therefore benefit from moving to a higher dose of monotherapy. On the contrary, combinations sometimes have better safety profile because a satisfactory control of blood pressure could be achieved with lower doses of each component.

This point was resolved by amending a statement in section 4.2 of the SPC, to "Further blood pressure reduction may be achieved either by increasing the dose of valsartan to a maximum of 320mg or by adding in a thiazide diuretic".

6.3 Laboratory parameters

The effect of valsartan 320mg on laboratory parameters was presented in some detail. As was done for other safety parameters, pivotal information was gathered from study H2301 and additional supportive information is available from pooled datasets.

For all of the clinical laboratory variables, the following were analysed:

- mean change from baseline to final visit
- Shift analysis of number of patients who experienced a shift from baseline to any post-baseline visit of low/normal to high, or normal/high to low values.

In study H2301, mean and median changes from baseline at endpoint were clinically unremarkable in all groups for the biochemistry parameters during the double blind and extension phases of the study.

Shift analysis data in dataset A did not show any significant changes from baseline to any post-baseline visit in dataset A.

Assessor's comments

Laboratory parameters did not show any adverse effects of clinical concern. The only parameters noted with higher incidence in valsartan 320mg group than in the other treatment groups or the placebo group were potassium and glucose levels (dataset A).

Overall the company's detailed analysis provided does not show any cause for concern regarding laboratory parameters.

6.4 Safety in individual studies

Safety in Study 301

This study compared four doses of valsartan/HCTZ combination (80/12.5, 80/25, 160/12.5 & 160/25mg) with component monotherapies or placebo. Treatment was given for a total period of 8 weeks to 871 patients. Data from only valsartan monotherapy (99 in valsartan 80mg group and 99 in valsartan 160mg group) and placebo (94) has been discussed in this submission.

The incidence of adverse events was similar (52 – 57%) in each group except for 160 mg valsartan group which had lower incidence (47%).

Safety in Study B2401

A total of 1213 patients in this trial received either valsartan 160mg or lisinopril 20mg o.d. for 4 weeks. Patients who were controlled continued on this therapy while those not controlled were switched either to a combination of valsartan/HCTZ 160mg/12.5 mg or lisinopril/HCTZ 20/12.5mg for 12 weeks.

In this submission data from patients on valsartan (604) or lisinopril (609) from first 4 weeks have been discussed.

A similar proportion of patients in each group reported adverse events.

Safety in Study 2403

This was a forced titration study but the safety issue addressed in this submission has considered only the first 4 weeks of treatment phase during which valsartan 80mg was compared with valsartan 160mg. There were no differences in adverse events between the groups.

Safety in Study 2405

This study compared valsartan 160mg o.d. with amlodipine 5mg o.d. followed by up-titration to combination of valsartan + HCTZ or amlodipine 10mg. A total of 1088 patients were recruited in this study. This submission considered only the first period of the trial. There was no difference between the groups as regards adverse events.

Safety in Study Hermida et al, 2003

This study aimed at evaluating the time-dependent effects of administration of valsartan 160mg o.d., either at awakening or before bedtime in the circadian BP profile.

6.5 Post-marketing data

Valsartan 320mg was authorised in the US in 1996. The safety profile of this dose was no different from that of other doses.

6.6 Long term safety.

Concerning long-term safety, the ICH requirement of generating 1-year safety data in > 100 patients was not met by the company. However, study H2301 was prolonged by a 6-month extension (VAL489H2301 & E1) during which 642 patients were treated with valsartan 320mg and monitored for safety. During the extension of study H2301 no event was reported as study drug related for $\geq 0.5\%$ of the population (Study

H2301 PTT 10.1-2c). Overall, during this period, the AE pattern was not different from that observed during short term exposure.

In addition, valsartan 320mg is approved and has been marketed in the US since 1996 and post-marketing surveillance data show that neither the distribution of preferred terms nor the associated estimates of incidence suggest a safety profile of the 320mg daily dosage of valsartan different from that of lower doses (Safety Expert Statement). Therefore the company believes that the 6-months safety extension provides adequate safety evidence for a new dose of valsartan which is a well-known and widely used substance for which no major safety concern was raised.

Assessor's comments

The post-marketing experience revealed that the total amount of Diovan 320mg sold until 31 January 2005 corresponded to 141,475,000 daily doses or approximately 387,603 patient-treatment years. A total of 294 events were reported in 118 patients. The most frequently reported events were disease progression (n=9), blood pressure inadequately controlled (n=9), dizziness (n=8), headache (n=8), surgery (n=7), drug ineffective (n=5), cough (n=5), fatigue (n=4), muscle cramp (n=4), and dyspnoea (n=4). Although the incidence rate based on estimated exposure is low, adverse events like dizziness, headache and fatigue confirm the trend noted in earlier studies

Although the long-term safety data has not been provided in line with the ICH guidance, post-marketing experience has been accepted as a reasonable substitute.

7 EXPERT REPORT

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

8 PRODUCT INFORMATION

8.1 Summary Of Product Characteristics

Sections 1, 2, 3, and 6 of the SPC are in line with the current SPC for the reference products and the updated and approved SPC is satisfactory.

8.2 Patient Information Leaflet

The PIL is in line with the approved SPC and is satisfactory. It has been formatted according to Article 59(1) of directive 2001/83/EC, as amended. Results of User testing (Article 59(3)) were submitted and acceptable.

8.3 Labelling

Colour mock-ups of the blister pack and the carton have been provided. The labelling is satisfactory.

9. DISCUSSION

The clinical pharmacology of valsartan is well known. The bioequivalence of valsartan 320mg tablets with 2 x marketed Diovan 160mg Capsules has been shown. The currently authorised maximal dose of valsartan in hypertension is 160mg once daily. The efficacy of further up-titration to valsartan 320mg once daily for the treatment of hypertension has been demonstrated. Diovan is already licensed at the doses of 160mg twice daily in patients with myocardial infarction.

Safety concerns and adverse events rates have been discussed and resolved. The long-term safety has been established. A Marketing authorisation should be granted for this product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Diovan 320mg 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 preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Diovan 320mg Tablets, and the reference product 2 x Diovan 160mg Capsules (Novartis Pharmaceuticals UK Ltd).

Any safety concerns relating to the application have been resolved.

The SPC, PIL and labelling are satisfactory and consistent with that for Diovan 160mg Capsules.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the reference product are interchangeable. The risk benefit is, therefore, considered to be positive.

**DIOVAN 320MG TABLETS
PL 00101/0726**

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 9 th September 2005
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 30 th September 2005
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 5 th April 2006, and further information relating to the clinical dossier on 7 th April 2006
4	The applicant responded to the MHRA's requests, providing further information for the clinical sections and the quality sections on 27 th August 2006
5	Following assessment of the response the MHRA requested further information relating to the clinical dossier on 17 th November 2006
6	The applicant responded to the MHRA's request, providing further information for the clinical sections on 6 th January 2007
7	The application was determined on 17 th September 2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Diovan 320mg Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Diovan® 320 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: (S)-N-valeryl-N-{{2'-(1H-tetrazol-5-yl)biphenyl-4-yl}methyl}-valine (INN = valsartan).

One tablet contains 320 mg valsartan.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Dark grey-violet, ovaloid with bevelled edges, one side with debossing DXL and NVR on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension

Treatment of hypertension

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Hypertension

The recommended dose of Diovan is 80 mg once daily for most patients. The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg. Further blood pressure reduction may be achieved either by increasing the dose of valsartan to a maximum of 320 mg or by adding in a thiazide diuretic.

Diovan may also be administered with other antihypertensive agents.

Use in patients over 75 years:

A lower starting dose of 40 mg once daily is recommended.

Use in renal impairment:

No initial dose adjustment is required in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine less than 20 ml/min) or patients on dialysis, a lower starting dose of 40 mg once daily is recommended.

Use in patients with intravascular volume depletion:

For those patients who have intravascular volume depletion (e.g. those treated with high dose diuretics who are unable to have their dose of diuretic reduced) a starting dose of 40 mg is recommended.

Use in patients with mild to moderate hepatic impairment:

Treatment should commence at a dose of 40 mg once daily. A daily dose of 80 mg should not be exceeded. Patients with severe hepatic impairment, cirrhosis or biliary obstruction should not use Diovan (see Section 4.3 "**Contraindications**").

Use in children and adolescents:

The safety and efficacy of Diovan have not been established in children and adolescents (below the age of 18 years).

4.3 CONTRAINDICATIONS

Hypersensitivity to valsartan or to any of the excipients of Diovan.

Pregnancy (see Section 4.6. "**Pregnancy and lactation**").

Severe hepatic impairment, cirrhosis, biliary obstruction.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypertension

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 Diovan. For those patients whose diuretic dose cannot be reduced in order to correct their sodium and/or volume depletion a starting dose of 40 mg is recommended.

Renal artery stenosis:

Short-term administration of Diovan 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, since other drugs that affect the renin-angiotensin-aldosterone system may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis, monitoring is recommended as a safety measure.

Hepatic impairment:

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of valsartan in mild to moderately hepatically impaired patients, a lower dose is recommended in patients with hypertension (see Section 4.2 "**Posology and method of administration**"). In these patients the dose of 80 mg should not be exceeded. Patients with severe hepatic impairment, cirrhosis, biliary obstruction are contra-indicated from using Diovan (see Section 4.3 "**Contraindications**").

Renal function impairment:

As a consequence of inhibiting the renin-aldosterone-angiotensin system, increases of blood urea and serum creatinine and changes in renal function including renal failure (very rarely) have been reported particularly in patients with pre-existing renal dysfunction or those with severe cardiac insufficiency.

Serum potassium should be monitored in renally impaired or elderly patients if they are also taking potassium supplements (see Section 4.8 "Undesirable Effects").

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Compounds which have been studied in clinical trials include cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide. Used together with cimetidine, the systemic exposure of valsartan may be marginally increased. A combination with glibenclamide may cause a decrease in the systemic exposure to valsartan.

As Diovan is not metabolised to a significant extent, clinically relevant drug-drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, *in vitro* studies have not shown any interaction at this level with a range of molecules which are also highly protein-bound, such as diclofenac, furosemide, and warfarin.

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium. Comedication is not advisable.

Combination with NSAIDs: When Angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors,

acetylsalicylic acid (>3g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of Angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme (ACE) inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and valsartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

4.6 PREGNANCY AND LACTATION

Due to the mechanism of action of angiotensin II antagonists, a risk factor for the fetus cannot be excluded. In utero exposure to ACE inhibitors (a specific class of drugs acting on the RAAS) during the second and third trimesters has been reported to cause injury and death to the developing fetus. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan. As for any drug that also acts directly on the RAAS, Diovan should not be used during pregnancy (see section 4.3 “Contraindications”) or in women planning to become pregnant. Healthcare professionals prescribing Diovan should counsel women of child-bearing potential about the potential risk of this product during pregnancy. If pregnancy is detected during therapy, Diovan should be discontinued as soon as possible.

It is not known whether valsartan is excreted in human milk. Valsartan was excreted in the milk of lactating rats. Thus, it is not advisable to use Diovan in lactating mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data to suggest that Diovan affects the ability to drive or use machines. When driving vehicles or operating machines, it should be recognised that occasionally dizziness or weariness may occur during treatment with any antihypertensive agent.

4.8 UNDESIRABLE EFFECTS

In clinical trials in hypertensive patients, adverse experiences have been mild and transient in nature. The incidence of AEs showed no association with gender, age or race.

The following table of AEs is based on 10 placebo-controlled clinical trials in patients with hypertension (N=2316) and on post-marketing reports. All AEs with an incidence of 1% or more in the Diovan treatment group in placebo-controlled clinical studies are included in Table 1. The table also includes non-fatal serious adverse events (SAEs) with suspected study drug relationship reported with an incidence of $\geq 0.1\%$ in a clinical study in patients with post-myocardial infarction (N=14,703).

Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10\ 000$, $< 1/1000$); very rare ($< 1/10\ 000$).

Infections and infestations

Common:	Viral infections
Uncommon:	Upper respiratory tract infection, pharyngitis, sinusitis
Very rare:	Rhinitis

Blood and lymphatic system disorders

<u>Common</u>	Neutropenia
Very rare:	Thrombocytopenia

Immune system disorders	
Very rare:	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Uncommon:	Hyperkalaemia*
Psychiatric disorders	
Uncommon:	Insomnia, libido decrease
Nervous system disorders	
Uncommon:	Syncope*
Rare:	Dizziness
Very rare:	Headache, mild and transient taste disturbance
Ear and labyrinth disorders	
Uncommon:	Vertigo
Cardiac disorders	
Uncommon:	Cardiac failure*
Vascular disorders	
Uncommon:	Hypotension*
Very rare:	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough, epistaxis
Gastrointestinal disorders	
Uncommon:	Diarrhoea, abdominal pain
Very rare:	Nausea
Hepatobiliary Disorders	
Very rare:	Liver function abnormalities
Skin and subcutaneous tissue disorders	
Very rare:	Angioneurotic oedema**, rash, pruritus
Musculoskeletal and connective tissue disorders	
Uncommon:	Back pain
Very rare:	Arthralgia, myalgia
Renal and urinary disorders	
Very rare:	Renal impairment**, acute renal failure**, renal insufficiency**
General disorders and administration site conditions	
Uncommon:	Fatigue, asthenia, oedema

*reported in post-myocardial infarction indication

** reported as uncommon in post-myocardial infarction indication

Post-myocardial infarction

In the VALIANT study valsartan was initiated at a dose of 20mg BD and titrated, by dose doubling, to a target dose of 160mg BD as tolerated.

In the double-blind, randomized, active-controlled, parallel-group VALIANT trial comparing the efficacy and safety of long-term treatment with valsartan, captopril and their combination in high-risk patients after myocardial infarction, the safety profile of valsartan was consistent with the pharmacology of the drug and the background diseases, cardiovascular risk factors, and clinical course of patients treated in the post-myocardial infarction setting.

Serious adverse events (SAEs) were primarily cardiovascular and generally related to the underlying disease as reflected in the primary efficacy endpoint of all-cause mortality. Non-

fatal SAEs with suspected study drug relationship observed with an incidence of $\geq 0.1\%$ are included in Table 1 above.

The percentage of permanent discontinuations due to adverse events was 5.8% in valsartan-treated patients and 7.7% in captopril-treated patients.

Laboratory findings:

In controlled clinical trials in hypertensive patients, Diovan was rarely associated with decreases in haemoglobin and haematocrit.; neutropenia was observed in 1.9% of patients treated with valsartan versus 1.6% of patients treated with an ACE inhibitor. Six percent (6.0%) of valsartan treated patients had a $>100\%$ increase in total bilirubin compared to 12.9% of patients treated with an ACE inhibitor, 0.8% of valsartan treated patients had a $>50\%$ increase in creatinine compared to 1.6% of ACE inhibitor treated patients and 4.4% of valsartan treated patients had a $>20\%$ increase in serum potassium compared to 6.4% of ACE inhibitor treated patients.

No special monitoring of laboratory parameters is necessary for patients with essential hypertension receiving valsartan therapy; however, serum potassium should be monitored in renally impaired or elderly patients if they are also taking potassium supplements (see Section 4.4 "Special Warnings and Precautions for Use").

In post-myocardial infarction patients, 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.

4.9 OVERDOSE

Overdosage with Diovan, may result in marked hypotension, which could lead to depressed levels of consciousness, circulatory collapse and/or shock. If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be intravenous infusion of normal saline solution.

Valsartan is unlikely to be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic groups: angiotensin II antagonists (valsartan) (ATC code: C09C A03).

The active hormone of the RAAS is angiotensin II, which is formed from angiotensin I through ACE. Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including in particular both direct and indirect involvement in the regulation of blood pressure. As a potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition it promotes sodium retention and stimulation of aldosterone secretion.

Diovan (valsartan) is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The AT2 subtype is unrelated to cardiovascular effects. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor.

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 cough. 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 ($P < 0.05$). Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hypertension

Administration of Diovan 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 maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

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

In multiple dose studies in hypertensive patients valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

5.2 PHARMACOKINETIC PROPERTIES

Absorption of valsartan after oral administration is rapid, although the amount absorbed varies widely. Mean absolute bioavailability for Diovan is 23%. Valsartan shows multi-exponential decay kinetics ($t_{1/2\alpha} < 1\text{h}$ and $t_{1/2\beta}$ about 9 h).

The pharmacokinetics of valsartan are linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration, and little accumulation when dosed once daily. Plasma concentrations were observed to be similar in males and females.

Valsartan is highly bound to serum protein (94-97 %), mainly serum albumin. Steady-state volume of distribution is low (about 17 L). Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 30 L/h). After oral dosing, 83% is excreted in the faeces and 13% in the urine, mainly as unchanged compound.

Diovan may be given with or without food.

Special populations

Elderly:

A somewhat higher systemic exposure to valsartan was observed in some elderly subjects compared with young subjects; and a lower starting dose (40 mg) is recommended for the elderly.

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 mild renal impairment (creatinine clearance 20-50 ml/min). Limited data are available in patients with moderate-severe impairment of renal function and a starting dose of 40 mg is recommended for these patients. No studies have been performed in patients undergoing dialysis. However, valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment:

In a pharmacokinetics trial in patients with mild to moderate hepatic dysfunction, exposure to valsartan was increased approximately 2-fold compared with healthy volunteers.

5.3 PRECLINICAL SAFETY DATA

In a variety of preclinical safety studies conducted in several animal species, there was no evidence of systemic or target organ toxicity, apart from fetotoxicity. Offspring from rats given 600 mg/kg during the last trimester and during lactation showed a slightly reduced survival rate and a slight developmental delay (see Section 4.6. "**Pregnancy and lactation**"). The main preclinical safety findings are attributed to the pharmacological action of the compound, and have not been demonstrated to have any clinical significance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

6 PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS**Core

Microcrystalline cellulose
Crospovidone
Colloidal anhydrous silica
Magnesium stearate

Film-coat

Hypromellose
Titanium dioxide (E171)
Macrogol 8000
Red iron oxide (E172)
Yellow iron oxide (E172)
Black iron oxide (E172)
Brown iron oxide (mixture of red iron oxide and black iron oxide).

6.2 INCOMPATIBILITIES

None known.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PVDC blister packs

Pack sizes of 28 and 98 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No specific instructions for use/handling.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited
Trading as: Ciba Laboratories
Frimley Business Park
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GU16 7SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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17/09/2007

10 DATE OF REVISION OF THE TEXT

17/09/2007

PATIENT INFORMATION LEAFLET



Patient Information leaflet

What you need to know about Diovan 320 mg Tablets

Your doctor has decided that you need this medicine to help treat your condition.

Please read this leaflet carefully before you start to take your medicine. It contains important information. Keep the leaflet in a safe place because you may want to read it again.

If you have any other questions, or if there is something you don't understand, please ask your doctor or pharmacist.

This medicine has been prescribed for you. Never give it to someone else. It may not be the right medicine for them even if their symptoms seem to be the same as yours.

In this leaflet:

1. What Diovan Tablets are, and what they are used for
2. Things to consider before you start to take Diovan Tablets
3. How to take Diovan Tablets
4. Possible side effects
5. How to store Diovan Tablets
6. Further information

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

Diovan Tablets are used to treat high blood pressure (also known as hypertension).

Valsartan, the active ingredient in Diovan Tablets, is one of a group of medicines called angiotensin receptor blockers.

Angiotensin is a substance which occurs naturally in your body. It causes blood vessels to narrow. Because it is harder for the blood to pass through the vessels your blood pressure increases. Diovan Tablets prevent the action of angiotensin, causing the blood vessels to relax. This lowers your blood pressure.

Even if you have no symptoms, raised blood pressure should be treated because it can cause damage to the heart and blood vessels. This damage can increase the risk of a stroke, heart attack, heart failure or kidney failure.

As well as giving you this medicine your doctor may also suggest 2021976 GB some changes to your lifestyle so that you can help yourself to reduce your blood pressure. These may include losing weight, stopping smoking, reducing the amount of salt in your diet and the amount of alcohol you drink, taking regular exercise, and avoiding stress. It is important to follow your doctor's advice.

2. THINGS TO CONSIDER BEFORE YOU START TO TAKE DIOVAN TABLETS

Some people MUST NOT take Diovan Tablets. Talk to your doctor if:

- You think you may be allergic to valsartan or to any of the other ingredients of Diovan Tablets. (These are listed at the end of the leaflet.)
- You are pregnant or trying to become pregnant.
- You have severe liver disease or any obstruction of the bile duct.

You should also ask yourself these questions before taking Diovan Tablets:

- Are you suffering from vomiting or diarrhoea?
- Do you suffer from any kidney or liver disease?
- Are you breast feeding?
- Are you taking cimetidine (for stomach problems) or glibenclamide (for diabetes)?
- Are you taking potassium supplements, salt substitutes containing potassium or potassium-sparing diuretics (water tablets such as spironolactone, triamterene or amiloride)?

If the answer to any of these questions is YES, tell your doctor or pharmacist because Diovan Tablets might not be the right medicine for you.

Are you taking other medicines?

Some medicines can interfere with your treatment. Tell your doctor or pharmacist if you are taking any of the following:

- Lithium for depression
- Non-steroidal anti-inflammatory painkillers (NSAIDs), COX-2 inhibitors or more than 3g per day of aspirin

Always tell your doctor or pharmacist about all the medicines you are taking. This means medicines you have bought yourself as well as medicines on prescription from your doctor."

Will there be any problems with driving or using machinery?

Diovan Tablets will probably not affect your ability to drive or use machinery. However, since some medicines used to treat high blood pressure can cause dizziness or tiredness, do not drive or use machinery if you are affected.

Diovan Tablets are not suitable for children.



3. HOW TO TAKE DIOVAN TABLETS.

Always take Diovan Tablets exactly as your doctor has told you to. The instructions should be on the pharmacist's label. If you are not sure how many tablets to take or when to take them, ask your doctor or pharmacist. Keep taking your tablets for as long as you have been told unless you have any problems. In that case, check with your doctor.

Swallow your tablets whole with a glass of water.

To treat high blood pressure (hypertension)

The usual starting dose for Diovan is 80 mg once a day. Some people may need a higher dose of 160 or 320 mg a day to control their blood pressure. Some people, such as the elderly, those taking diuretics, people who are severely dehydrated, or who have liver or kidney disease may be told to start on a lower dose of 40 mg once a day.

You may also have been given other tablets to take at the same time.

What if you forget to take a dose?

If you forget to take a dose, do not worry. Take the next dose at the usual time. Do not take a double dose.

What if you take too many tablets?

If you accidentally take too many Diovan Tablets, tell your doctor or your nearest hospital casualty department immediately. Take your medicine with you.

4. POSSIBLE SIDE EFFECTS

Diovan is suitable for most people. However, like all other medicines, it may occasionally cause side effects in a few people.

Possible side effects:

The following side effects are very rare, but you must speak to your doctor straight away if you notice them:

Hypersensitivity or allergic reactions including swollen throat, face, eyelids or lips, or inflamed blood vessels. This reaction may start soon after you first take Diovan, or it might start later.

Kidney problems or kidney failure. You may feel sick or notice that you are passing less urine.

Changes in liver function which may give symptoms of jaundice such as yellow skin or eyes or itchy skin, or which may not produce any symptoms but will show on blood tests.

The side effects listed below have also been reported. If any of the symptoms become troublesome, or if you notice anything else not mentioned here, please go and see your doctor. He/she may want to give you a different medicine. The side-effects below have occurred in patients taking Diovan, but are not necessarily attributable to taking Diovan.

Up to 1 in 10 people may catch a viral infection, or find that, because of changes in the blood cells, they bruise or bleed more easily. 2021976 GB

Up to 1 in 100 people may experience the following:

Upper respiratory tract infections including sore throat, runny nose or sinus pain.

Nose bleed. Cough.

Weakness, tiredness or sleep problems.

Low blood pressure causing light-headedness, dizziness or fainting especially when getting up from sitting or lying down.

Change in sex drive.

Back pain and, very rarely, muscle or joint pain.

High blood potassium levels which can cause abnormal heart rhythm but will probably only show on blood testing.

Heart failure which can cause shortness of breath or swollen ankles.

Very rarely (up to 1 in 10,000) people may experience the following:

Rash or itching.

Nausea, diarrhoea or stomach ache.

Headache. Taste disturbance.

5. HOW TO STORE DIOVAN TABLETS

Keep your tablets in their original pack at a temperature below 30°C and out of the reach and sight of children. Do not take the tablets after the expiry date which is printed on the carton. Do not dispose of any unused tablets yourself, return them to your pharmacist for safe disposal.

6. FURTHER INFORMATION

Diovan Tablets contain 320 mg of the active ingredient valsartan. They also contain the following inactive ingredients: microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide (E171), macrogol 8000 and iron oxides (E172).

Diovan 320 mg Tablets are oval-shaped and dark grey/violet in colour.

The tablets come in blister packs of 28 and 98.

Diovan Tablets are manufactured by: Novartis Pharmaceuticals UK Limited
Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom

The product licence holder is: Novartis Pharmaceuticals UK Limited

Trading as: Ciba Laboratories

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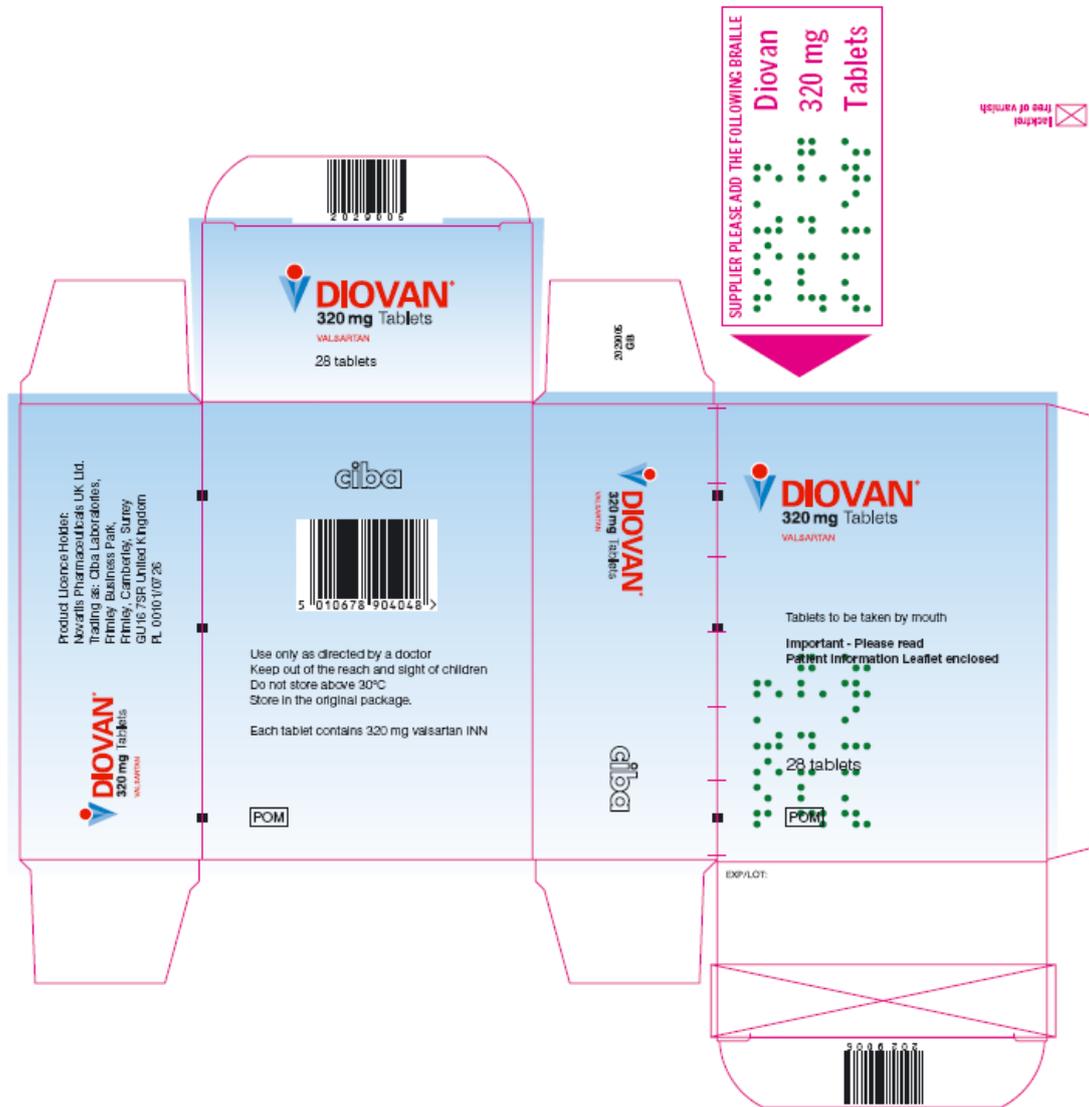
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If you would like any more information please contact
Medical Information at Novartis Pharmaceuticals UK Ltd,
telephone number 01276 698370.

LABELLING

Diovan 320mg Tablets – pack size 28



Diovan 320mg Tablets – pack size 98

