Australian Government

Department of Health and Ageing

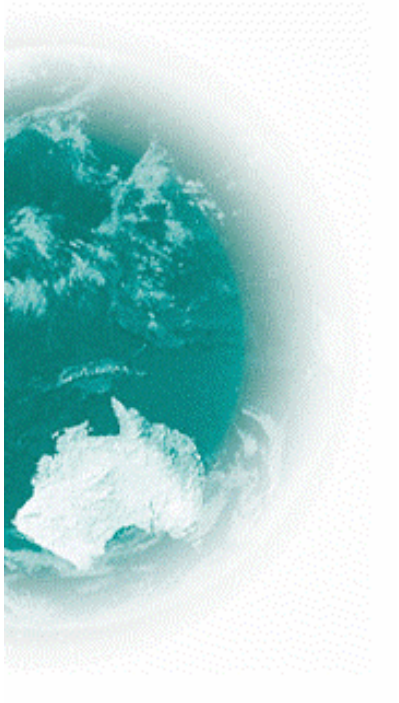
Therapeutic Goods Administration

Australian Public Assessment Report for Telmisartan

Proprietary Product Name: Micardis/Pritor

Submission No: PM-2009-00165-3-3

Sponsor: Boehringer Ingelheim Pty Ltd



April 2010

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I. Introduction to Product Submission

Product Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	19 February 2010
Active ingredient(s):	Telmisartan
Product Name(s):	Micardis/Pritor
Sponsor's Name and Address:	Boehringer Ingelheim Pty Ltd 78 Waterloo Road North Ryde NSW 2113
Dose form(s):	Tablet
Strength(s):	40 mg and 80 mg
Container(s):	Blister pack
Pack size(s):	7, 28, 56, 98 tablets
Approved Therapeutic use:	Prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes with evidence of end organ damage (see Clinical Trials).
Route(s) of administration:	Oral
Dosage:	Hypertension: 40 mg daily Prevention: 80 mg daily

Product Background

Telmisartan is a specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor to which it binds selectively.

Telmisartan (with the two trade names Micardis and Pritor) is currently approved for marketing in Australia, and the formulations that are the subject of the present application are registered in Australia. At its 203rd meeting on 3-4 June 1999, the Australian Drug Evaluation Committee (ADEC) recommended that there were no objections to approval of the application by Boehringer Ingelheim Pty Limited to register both Micardis and Pritor, containing telmisartan 40 mg and 80 mg, for the treatment of mild to moderate hypertension. The sponsor is applying to extend the indications for telmisartan, and in the same application is making changes to the Product Information document.

The current approved indications are as follows:

Micardis (and Pritor) is indicated for the treatment of hypertension

The proposed indications are:

Micardis (and Pritor) is indicated for:

- *Treatment of hypertension*

- *Prevention of cardiovascular morbidity and mortality in patients 55 years or older at high risk for cardiovascular disease.*

Regulatory Status

Micardis and Pritor have been on the ARTG since 27 August 1999.

A similar application to the current Australian submission was approved in the US on 16 October 2009. The approved indication is as follows:

MICARDIS is indicated for reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors.

Similar applications have been submitted, and are currently under evaluation, in the European Union (10 December 2008), Canada (10 December 2008), New Zealand (9 April 2009) and Switzerland (13 January 2009).

A positive opinion was issued by the EU on 22 October 2009 for the indication:

Reduction of cardiovascular morbidity in patients with:

i) manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or

ii) type 2 diabetes mellitus with documented organ damage

The data submitted in Australia differ from those submitted in the EU, USA and Canada by the inclusion of data for Study U08-1362-01.

A similar application has also been approved in Argentina, Bolivia, Mexico, Paraguay and the Philippines

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There were two studies, conducted in 126 subjects, all of whom were exposed to telmisartan and which were submitted in support of bioequivalence or pharmacokinetics. These were the result of the fact that the formulation of ramipril used in the ONTARGET trial, namely Delix, is not the formulation approved for marketing in Australia. As the bioequivalence study did not investigate different formulations of the telmisartan tablet, the quality evaluator was of the opinion that it need not be formally evaluated by the pharmaceutical chemistry evaluation section.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There is no requirement for a nonclinical evaluation in an application of this type.

IV. Clinical Findings

Introduction

The data presented in the submission are from five studies, conducted in 52004 subjects, of whom 30270 were exposed to telmisartan.

There were two studies, conducted in 126 subjects, all of whom were exposed to telmisartan, submitted in support of bioequivalence or pharmacokinetics:

- ***Trial No. 1236.5***: a single dose bioequivalence study conducted in 84 healthy volunteers
- ***Trial No. 1236.6***: a steady state pharmacokinetic interaction study conducted in 42 healthy volunteers

There were three studies, conducted in 51878 subjects, 30144 of whom were exposed to telmisartan for a treatment duration of up to 5.5 years, submitted in support of efficacy:

- ***Trial No. 502.373: ONTARGET*** was the pivotal study and included 25620 subjects, 17044 of whom were treated with telmisartan
- ***Trial No. 502.373: TRANSCEND*** included 5926 subjects, 2954 of whom were treated with telmisartan
- ***Trial No. 9.159: PRoFESS***, involving a total of 20332 subjects, 10146 of whom were treated with telmisartan

There were no additional data submitted in support of safety. There were no post-marketing surveillance data contained in the submission.

The formulation of telmisartan used in the ONTARGET, TRANSCEND and PRoFESS trials was the formulation approved for marketing in Australia.

The sponsor stated that the studies conducted by the sponsor were performed according to the principles of the Declaration of Helsinki and conformed to Good Clinical Practice.

Pharmacokinetics

A single bioequivalence study was performed to establish bioequivalence between the formulation of ramipril used in the ONTARGET trial (Delix, the commercially available formulation in Europe) and the formulation available in the USA (Altace). However, neither of these formulations are approved for marketing in Australia. The formulation of ramipril approved for marketing in Australia is Tritace. Tritace and Altace were compared in an *in vitro* dissolution study.

The sponsor argues that ramipril has a high therapeutic index and uncomplicated pharmacokinetics, both for absorption and excretion. The dissolution profiles for Tritace and Altace were similar at pH 1, 4.5 and 6.8 for three different batches of each drug. Altace is manufactured in the USA under licence from Sanofi Aventis, which markets Tritace in Australia. On the basis of these arguments the sponsor justified the use of a non-Australian reference product.

Trial No. 1236.5 was an open-label, randomised, single dose, three way crossover, bioequivalence study (Table 1). The aim of the study was to demonstrate bioequivalence between the fixed dose combination of telmisartan 80 mg/ ramipril 10 mg with Micardis (Mic) and Altace (Alt) given separately and Micardis and Delix (Del) given separately. The study treatments were:

1.) 80 mg telmisartan/10 mg ramipril, fixed-dose combination (FDC) tablet

2.) Telmisartan 80 mg (Micardis) tablet and ramipril 10 mg (Altace) capsule

3.) Telmisartan 80 mg (Micardis) tablet and ramipril 10 mg (Delix) capsule

The treatments were given by oral administration after an overnight fast of at least 10 hours, with 240 mL water.

A total of 84 subjects, all healthy volunteers, were enrolled, and 82 completed. One withdrew because of drug hypersensitivity, and one withdrew consent. There were 47 (56%) females and 37 (44%) males. The age range was 19 to 55 years. The pharmacokinetic parameters for telmisartan, ramiprilat and ramipril were similar for all three treatments. The three treatments were bioequivalent for telmisartan, ramiprilat and ramipril (Table 2).

Table 1: Details of Trial No. 1236.5

Study Design	Medication	No. of Volunteers Entered (M/F) Age range	Adverse Reactions
Open-label, randomised, single dose, three way crossover, bioequivalence study	1.) 80 mg telmisartan/10 mg ramipril, fixed-dose combination tablet 2.) Telmisartan 80 mg (Micardis) tablet and ramipril 10 mg (Altace) capsule 3.) Telmisartan 80 mg (Micardis) tablet and ramipril 10 mg (Delix) capsule Oral administration after an overnight fast of at least 10 hours, with 240 mL water	84 subjects enrolled, 82 completed. One withdrew because of drug hypersensitivity, one withdrew consent Healthy volunteers 47 (56%) female, 37 (44%) male Age range 19 to 55 years	55 (65.5%) subjects reported at least one adverse event (AE) There were no deaths or serious AEs (SAEs) The most frequently reported AEs were headache (32.1%), fatigue (28.6%), dizziness (21.4%), nausea (9.5%), diarrhoea (8.3%), and somnolence (6.0%) One subject had elevated creatinine, none had elevated potassium

Table 2: Relative bioavailability of telmisartan for the comparison between the FDC (Test) and the monocomponent treatments (Reference 1: Mic+Alt, Reference 2: Mic+Del)

	Adjusted gMean ratio (Test/reference) [%]	Two-sided 90% CI		Intra-individual gCV
		Lower limit [%]	Upper limit [%]	
FDC vs Mic + Alt				
C_{max}	91.67	84.00	100.04	35.0
$AUC_{0-\infty}$	94.31	89.90	98.94	18.8
AUC_{0-24}	93.02	89.21	96.99	16.4
FDC vs Mic + Del				
C_{max}	94.20	86.29	102.85	35.0
$AUC_{0-\infty}$	98.58	93.95	103.44	18.8
AUC_{0-24}	97.54	93.53	101.73	16.4

Mic: Micardis, Alt: Altace, Del: Delix, C_{max}: maximal plasma concentration, $AUC_{0-\infty}$: area under the plasma concentration time curve from time zero to infinity, AUC_{0-24}: area under the plasma concentration time curve from time zero to 24 hours

There were four bioanalytical reports submitted, in support of Trial No. 1236.5.

- ***Report U07-1609*** described an analytical study cross validating an analytical method for the simultaneous determination of ramipril and ramiprilat in human EDTA plasma with a fully validated method using human heparin plasma. The method used solid phase extraction, reverse phase liquid chromatography and tandem mass spectrometry. There was no interference between telmisartan and ramipril or ramiprilat.

- ***Report U00-1775*** described an analytical study validating an enzyme linked immunosorbent assay (ELISA) method for quantifying telmisartan in human plasma.
- ***Report U07-1745*** described an analytical study validating a high pressure liquid chromatography (HPLC) method for determining telmisartan in human plasma. The method used liquid/liquid extraction and fluorescence detection.
- ***Report U07-1483*** described a validation study for an ELISA method for quantifying telmisartan in human EDTA plasma. The original method was described in Report U00-1775, but because of several minor modifications was revalidated. Hydrochlorotriazole, lacidipine, amlodipine, ramipril, simvastatin, Aggrenox (acetyl-salicylic acid 25 mg + dipyridamole ER 200 mg) and clopidogrel did not show any interference in the assay.

Trial No. 1236.6 was an open-label, randomised, multiple dose (steady state), three way crossover, pharmacokinetic interaction study (Table 3). The study treatments and other details are described in the Table.

At steady state, exposure to telmisartan was decreased by approximately 16%, to ramipril doubled and to ramiprilat increased by approximately 47% with co-administration (Tables 4, 5 and 6). There did not appear to be any pharmacokinetic effect of co-administration on telmisartan with the first dose but at steady state there was a clear decrease in telmisartan area under the plasma concentration time curve (AUC). There were increases in ramipril and ramiprilat AUCs from the first dose that persisted at steady state.

Table 3: Details of Trial No. 1236.6

Study Design	Medication	No. of Volunteers Entered (M/F) Age range	Adverse Reactions
Open-label, randomised, multiple dose (steady state), three way crossover, pharmacokinetic interaction study	1. Telmisartan 80 mg (Micardis) 2. Ramipril 10 mg (Delix) 3. Telmisartan 80 mg (Micardis) and Ramipril 10 mg (Delix) Once daily administration Treatment duration was 5 days Ramipril arms were preceded by 3 day run-in period of 5 mg ramipril daily, wash-out phase of at least 3 days after the telmisartan treatment, and wash-out phases of at least 11 days after the ramipril and telmisartan + ramipril treatments	42 healthy volunteers, 21 male and 21 female Age range 22 to 52 years 41 completed One subject discontinued because of an AE during the first run-in period with ramipril: flushing	33 (78.6%) subjects experienced at least one AE during the study 20 (47.6%) subjects experienced AEs during telmisartan alone, 9 (22.0%) during ramipril alone, and 16 (39.0%) during combination The commonest AEs were headache, dizziness and postural dizziness There were no SAEs or deaths reported Two subjects in the co-administration group had elevated serum potassium: 6.20 mmol/L and 5.54 mmol/L There were no other clinically significant laboratory abnormalities All three treatments resulted in clinically significant decreases in SBP, DBP and BP

Table 4: Adjusted by-treatment geometric mean ratios of primary pharmacokinetic parameters of telmisartan 80 mg co-administered with ramipril 10 mg and telmisartan 80 mg administered alone

Telmisartan	**Adjusted gMean ratio (Test/reference) [%]**	**Two-sided 90% CI**		**Intra-individual gCV**
		Lower limit [%]	**Upper limit [%]**	
Telmisartan + ramipril vs Telmisartan alone				
$C_{max,ss}$	69.07	58.682	81.300	46.1
$AUC_{0-24,ss}$	83.89	77.508	90.802	21.5

ss: steady state

Table 5: Adjusted by-treatment geometric mean ratios of primary pharmacokinetic parameters of ramipril after ramipril 10 mg co-administered with telmisartan 80 mg and ramipril 10 mg administered alone

Telmisartan	**Adjusted gMean ratio (Test/reference) [%]**	**Two-sided 90% CI**		**Intra-individual gCV**
		Lower limit [%]	**Upper limit [%]**	
Ramipril + Telmisartan vs Ramipril alone				
$C_{max,ss}$	233.66	210.388	259.515	28.7
$AUC_{0-24,ss}$	206.03	195.290	217.367	14.4

Table 6: Adjusted by-treatment geometric mean ratios of primary pharmacokinetic parameters of ramiprilat after ramipril 10 mg co-administered with telmisartan 80 mg and ramipril 10 mg administered alone

Ramiprilat	**Adjusted gMean ratio (Test/reference) [%]**	**Two-sided 90% CI**		**Intra-individual gCV**
		Lower limit [%]	**Upper limit [%]**	
Ramipril + Telmisartan vs Ramipril alone				
$C_{max,ss}$	242.03	224.725	260.670	20.1
$AUC_{0-24,ss}$	146.63	140.520	153.012	11.4

Summary of Pharmacokinetics

Trial No. 1236.5 demonstrated bioequivalence for Altace and Delix when administered as a single dose concurrently with Micardis.

Trial No. 1236.6 demonstrated that at steady state co-administration on telmisartan and ramipril results in a decrease in telmisartan AUC of 16%, an increase in ramipril AUC of 100% and an increase in ramiprilat AUC of 47%. This would be expected to increase the effect of ramipril and decrease the effect of telmisartan during co-administration.

Pharmacodynamics

No new data in support of pharmacodynamics were included in the submission.

Efficacy

Pivotal study

Trial No. 502.373: **ON**going **T**elmisartan **A**lone and in Combination with **R**amipril **G**lobal **E**ndpoint **T**rial (ONTARGET) was a multinational, multicentre, randomised, double blind, double-dummy, parallel group, comparator controlled, non-inferiority efficacy and safety study (Table 7). The study was sponsored by Boehringer Ingelheim Pty Ltd and conducted at 732 centres. The objective of the trial was to determine if (a) the combination of telmisartan 80 mg and ramipril 10 mg was superior to ramipril 10 mg alone and if (b) telmisartan 80 mg was not inferior to ramipril 10 mg alone in reducing the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), stroke, or hospitalisation for congestive heart failure (CHF).

Table 7: Details of Trial No. 502.373 (ONTARGET)

No. of subjects with age and sex **Duration of Treatment**	**Diagnosis + criteria for inclusion/exclusion**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results** **(efficacy)**	**Adverse** **Reactions**
29019 subjects enrolled and entered the run-in period 25620 patients randomised: 8502 to telmisartan/ramipril; 8542 to telmisartan; 8576 to ramipril 25570 subjects completed the trial; 50 subjects did not complete There were 3068 deaths during the study 73.3% of patients were male, and 26.7% were female 57.1% were aged 65 years or more 3.5 to 5.5 years	Male or female patients, 55 years of age or older, and at high risk of developing a major CV event were eligible if they had any of the following: 1. Coronary arterial disease 2. Peripheral arterial disease 3. Previous stroke (stroke included definite or presumed cerebral infarction, intracerebral haemorrhage, stroke of uncertain subtype, but not subarachnoid haemorrhage) 4. TIA >7 days and <1 year prior to informed consent 5. High-risk diabetes (insulin-dependent or non-insulin-dependent) with evidence of end-organ damage	1. telmisartan 80 mg/ ramipril 5 mg for two weeks then telmisartan 80 mg/ ramipril 10 mg 2. telmisartan 80 mg (placebo also for first two weeks) Treatments administered once daily. Run-in period: ramipril 2.5 mg / telmisartan placebo for 3 days, telmisartan 40 mg/ ramipril 2.5 mg daily for 7 days, telmisartan 40 mg/ ramipril 5 mg daily for 11 to 18 days	3. ramipril 5 mg/ placebo daily for two weeks then ramipril 10 mg/ placebo daily	The primary efficacy outcome measures were: Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for CHF Composite of doubling of serum creatinine, progression to ESRD and all-cause mortality in the subgroup of diabetic nephropathy patients The secondary efficacy outcome measures included: Composite of CV death, non-fatal MI, and non-fatal stroke The individual components of the primary endpoints Occurrence of nephropathy Newly diagnosed CHF CV revascularisation procedures Newly diagnosed diabetes Cognitive impairment and cognitive decline New onset of atrial fibrillation	For the first primary efficacy outcome measure, the combination of telmisartan/ ramipril was not superior to ramipril: HR (95% CI) 0.99 (0.92 to 1.07) p=0.8462. Non-inferiority was demonstrated for telmisartan vs ramipril: HR (97.5% CI) 1.02 (0.93 to 1.12). There was no significant benefit for the telmisartan/ ramipril combination over telmisartan. There was no difference between treatments in the second primary efficacy outcome measure. The risk for newly diagnosed diabetes was greater in the telmisartan group than in the other two treatment groups Renal function appeared to deteriorate to a greater extent in the telmisartan treated groups,	The risk of discontinuing study medication was greater for telmisartan/ ramipril than ramipril RR (95% CI) 1.13 (1.04 to 1.22) and also compared with telmisartan 1.42 (1.30 to 1.56). The risk of discontinuing study medication due to AEs was less for telmisartan than for ramipril; RR (95% CI) 0.79 (0.72 to 0.87). Renal failure, hypotension, diarrhoea and hyperkalaemia were more common in the telmisartan/ ramipril group. Cough and angioedema were more common in the telmisartan/ ramipril and ramipril groups. Syncope leading to discontinuation was more common in the telmisartan/ ramipril group. Dizziness/ vertigo/light headedness, deteriorating renal function and hyperkalaemia were more frequent AEs leading to discontinuation in the telmisartan/ ramipril group

The inclusion criteria were:

Male or female patients, 55 years of age or older, and at high risk of developing a major CV event were eligible if they had any of the following:

1. Coronary arterial disease (CAD) defined as:

a) Previous MI: >2 days post uncomplicated MI prior to informed consent (as revascularisation procedures during the immediate MI period performed to reduce risk may result in a decreased overall risk for the patient, eligibility had to be considered on a case by case basis in these patients), or
b) Stable angina or unstable angina (> 30 days prior to informed consent) each with documented multi-vessel coronary disease, > 50% stenosis in at least two major coronary arteries on coronary angiography, or positive stress test (ST depression ≥2 mm or a positive nuclear perfusion scintigram), or
c) Multi-vessel percutaneous transluminal coronary angioplasty (PTCA) >30 days prior to informed consent, or
d) Multi-vessel coronary artery bypass graft (CABG) surgery without angina >4 years prior to informed consent, or with recurrent angina following surgery

2. Peripheral arterial disease (PAD) defined as:

a) Previous limb bypass surgery or percutaneous transluminal angioplasty, or
b) Previous limb or foot amputation, or
c) History of intermittent claudication with an ankle/arm blood pressure (BP) ratio ≤0.80 on at least one side, or
d) Significant peripheral artery stenosis (>50%) documented by angiography or noninvasive testing

3. Previous stroke (stroke included definite or presumed cerebral infarction, intracerebral haemorrhage, stroke of uncertain subtype, but not subarachnoid haemorrhage)

4. Transient ischaemic attack (TIA) >7 days and <1 year prior to informed consent (TIA was defined as acute loss of focal cerebral or monocular function with symptoms lasting <24 hours and which was thought to be due to inadequate cerebral or ocular blood supply as a result of arterial thrombosis or embolism)

5. High-risk diabetes (insulin-dependent or non-insulin-dependent) with evidence of end-organ damage, i.e. retinopathy, left ventricular hypertrophy (LVH), micro- or macroalbuminuria, or any evidence of previous cardiac or vascular disease

The exclusion criteria included:

- Inability to discontinue angiotensin converting enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs).
- Patients with known hypersensitivity or intolerance to ARBs or ACE-Is, (patients with known intolerance to ACE-I could be enrolled into the TRANSCEND study)
- Symptomatic congestive heart failure (CHF)
- Haemodynamically significant primary valvular or outflow tract obstruction (e.g. aortic or mitral valve stenosis, asymmetric septal hypertrophy, malfunctioning prosthetic valve)
- Constrictive pericarditis
- Complex congenital heart disease
- Syncopal episodes of unknown aetiology <3 months before informed consent
- Planned cardiac surgery or angioplasty within 3 months
- Uncontrolled hypertension on treatment (e.g. BP >160/100)
- Heart transplant recipient

- Strokes due to subarachnoid haemorrhage
- Significant renal disease defined as documented significant renal artery stenosis, creatinine clearance <36 mL/min or serum creatinine >265 μmol/L, or hyperkalaemia (potassium >5.5 mmol/L).
- Hepatic dysfunction as defined by the following laboratory parameters: serum alanine aminotransferase (ALT) or serum aspartate aminotransferase (AST) greater than four times the upper limit of normal (ULN), total bilirubin >20 μmol/L, or biliary obstructive disorders
- Uncorrected volume depletion or sodium depletion
- Primary aldosteronism
- Hereditary fructose intolerance
- Any other major non-cardiac illness expected to reduce life expectancy or interfere with study participation
- Patient had significant disability or other incapacity that precluded regular attendance at clinic for follow-up.

The treatment groups and details of the study treatments are described in Table 7.

The primary efficacy outcome measures were:

- Composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for CHF
- Composite of doubling of serum creatinine, progression to end-stage renal disease (ESRD) (as defined by initiation of dialysis, need for renal transplantation, or estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2), and all-cause mortality in the subgroup of diabetic nephropathy patients (that is, diabetic patients with macro- albuminuria assessed as a urinary albumin creatinine ratio (UACR) ≥300 mg/g creatinine at baseline)

The outcomes for the primary endpoint were centrally adjudicated, including all deaths. The secondary efficacy outcome measures were:

- Composite of CV death, non-fatal MI, and non-fatal stroke (in analogy to the Heart Outcomes Prevention Evaluation (HOPE) study)
- The individual components of the primary endpoints
- Occurrence of nephropathy based on the following six subcategories:
  - Doubling of serum creatinine
  - Progression to ESRD (i.e. initiation of dialysis, need for renal transplantation, or eGFR <15 mL/min/1.73 m^2)
  - New microalbuminuria (UACR ≥30 mg/g creatinine in patients with a UACR <30 mg/g creatinine at baseline)
  - New macroalbuminuria (UACR ≥300 mg/g creatinine in patients with a UACR <300 mg/g creatinine at baseline)
  - Combined endpoint of doubling of serum creatinine, progression to ESRD, new microalbuminuria, or new macroalbuminuria
  - Normalisation from micro- or macroalbuminuria to normoalbuminuria (UACR <30 mg/g creatinine in patients with a baseline UACR ≥30 mg/g creatinine)
- Newly diagnosed CHF
- CV revascularisation procedures
- Newly diagnosed diabetes
- Cognitive impairment and cognitive decline
- New onset of atrial fibrillation

Other efficacy endpoints were:

- All-cause mortality (non-CV mortality and CV mortality)

- Non-CV death
- Angina (unstable, new, and worsening)
- Transient ischaemic attack (TIA)
- Malignancy (fatal and non-fatal)
- Laser therapy for diabetic retinopathy

Additional measures included: changes from baseline in BP, ankle/arm BP ratio, mini mental status examination (MMSE), eGFR, serum creatinine, UACR, urinary potassium/ creatinine ratio, and urinary sodium/ creatinine ratio. The safety outcome measures were: serious adverse events (SAEs), adverse events (AEs) leading to discontinuation of trial medication, clinical laboratory evaluations; vital signs (BP and pulse rate (PR)), and electrocardiogram (ECG). Reporting of AEs was limited to AEs leading to permanent treatment discontinuation and SAEs.

Statistical Methods/Primary Analyses for the Pivotal Study:

There were two primary analyses: the comparison between the telmisartan/ramipril combination and ramipril; and the comparison between telmisartan and ramipril as monotherapies. Hypothesis tests were performed using time to event analysis (Kaplan Meier) and hazard ratios (HR) based on the intention-to-treat principle and using the proportional hazard model (Cox regression). Secondary analyses used both proportional hazard models and the chi-squared test for cognitive impairment and cognitive decline.

The comparison of telmisartan/ ramipril with ramipril was pre-specified as a superiority hypothesis test: that is if the two-sided 95% confidence interval (CI) around the hazard ratio of telmisartan/ ramipril vs ramipril excluded 1.

The comparison of telmisartan with ramipril was prespecified as a non-inferiority hypothesis test: that is, if the two-sided 95% CI around the hazard ratio of telmisartan vs. ramipril excluded the pre-specified margin of 1.13. Hence, the test of non-inferiority was a no more than 13% increase in risk with telmisartan compared with ramipril. The non-inferiority margin was based on the results of the HOPE study and upon the risk reduction observed in placebo controlled studies of ACE-I. The non-inferiority margin was not determined on the basis of clinical acceptability but instead it was determined upon the effect size observed in studies of ACE-I compared to placebo. However, a 13% increase in risk is a reasonable and plausible margin for non-inferiority.

Both primary analyses are stated to have been performed with the full analysis dataset, including the test of non-inferiority between telmisartan and ramipril. However, the results for the per-protocol data set were also calculated and presented in the study report. Hence, although the statistical analysis plan appears to diverge from ICH guidelines (as stated in CPMP/ICH/363/96) the analysis was conducted, and data were presented in accordance with the guidelines.

The sample size calculation was that based on a total sample size of at least 23,400 patients, a recruitment period of 2 years, and a maximum observation time of 5.5 years, and four sequential one-sided hypothesis tests with an α of 0.025, the study would have a power of approximately 93% for the superiority comparison of telmisartan/ramipril with ramipril; and for the non-inferiority comparison telmisartan with ramipril the power would have been approximately 89%. The data from the HOPE study were used for the sample size calculations. The sample size was not determined on the basis of any of the secondary endpoints or subgroup analyses.

Results for the Pivotal Study

A total of 29019 subjects were enrolled and entered the run-in period. Of the enrolled subjects, 25620 were randomised: 8502 to telmisartan/ramipril; 8542 to telmisartan; and 8576 to ramipril. A total of 25570 subjects completed the trial; and 50 subjects did not complete. There were 3068 deaths during the study. Of the full analysis set (FAS) dataset, 73.3% of patients were male, 26.7% were female, and 57.1% were aged 65 years or more. The treatment groups were similar in

demographic characteristics, comorbidity, HOPE risk scores, reason for inclusion, medical history, concomitant medications, and MMSE examinations. About half of the patients (47.6%) were enrolled by study centres in Europe, North America contributed 21.5%, Asia and the Middle East 14.7%, Latin America 9.1%, and Australia and New Zealand 7.2%. There were 41 centres in Australia and New Zealand, which randomized a total of 1825 subjects.

The results for the hypothesis tests were:

1. For the first primary efficacy outcome measure, the combination of telmisartan/ ramipril was not superior to ramipril: HR (95% CI) 0.99 (0.92 to 1.07) p=0.8462 (Table 8).

Table 8: Incidence and analysis of the primary composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalisation for CHF - first event / FAS

	T/R	**T**	**R**
Randomised, n (%)	8502 (100.0)	8542 (100.0)	8576 (100.0)
Primary endpoint, n (%)*	1386 (16.3)	1423 (16.7)	1412 (16.5)
CV death	385 (4.5)	367 (4.3)	373 (4.3)
Non-fatal MI	396 (4.7)	399 (4.7)	372 (4.3)
Non-fatal stroke	338 (4.0)	322 (3.8)	377 (4.4)
Hospitalisation for CHF	286 (3.4)	353 (4.1)	312 (3.6)
Total time to event/censoring (years)	36525	36742	36940
Events per 100 patient years	3.79	3.87	3.82
Hazard ratio vs ramipril**	0.99	1.01	
95% CI	(0.92, 1.07)	(0.94, 1.09)	
97.5% CI		(0.93, 1.10)	
p-value (conventional, two-sided)	0.8462	0.7248	
p-value (non-inferiority, one-sided)		0.0019	
Hazard ratio vs telmisartan*** (95% CI)	0.98 (0.91, 1.05)		
p-value	0.5859		

* The primary endpoint was defined as the time to first event. In case of simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcomes, ** Cox regression, *** Exploratory analysis

2. Non-inferiority was demonstrated for telmisartan vs ramipril:
   i. Per-protocol HR (97.5% CI) 1.02 (0.93 to 1.12)
   ii. Intention to treat HR (95% CI) 1.01 (0.93 to 1.10)

   Hence the upper limit of the 97.5% CI was below the pre-defined non-inferiority margin of 1.13 for both the per-protocol and the intention to treat analyses. The one-sided p-value for non-inferiority, per protocol, was 0.0078 (Table 9).
3. There was no significant benefit for the telmisartan/ ramipril combination over telmisartan, HR (95% CI) 0.98 (0.91 to 1.05) p=0.5859.

The Kaplan Meier plots for the three treatments were similar. Subgroup analysis of the comparison between telmisartan and ramipril suggested co-medication with beta-blockers did not favour telmisartan. There was no difference between treatments in the second primary efficacy outcome measure, the primary renal endpoint (Table 10).

Table 9: Incidence and analysis of the primary composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalisation for CHF - first event / PPS

	T/R	T	R
Randomised, n (%)	8502 (100.0)	8542 (100.0)	8576 (100.0)
Primary endpoint, n (%)*	1095 (12.9)	1214 (14.2)	1164 (13.6)
CV death	305 (3.6)	315 (3.7)	299 (3.5)
Non-fatal MI	307 (3.6)	347 (4.1)	312 (3.6)
Non-fatal stroke	277 (3.3)	282 (3.3)	321 (3.7)
Hospitalisation for CHF	224 (2.6)	286 (3.3)	254 (3.0)
Total time to event/censoring (years)	30431	33124	32500
Events per 100 patient years	3.60	3.66	3.58
Hazard ratio vs ramipril**	1.00	1.02	
95% CI	(0.93, 1.09)	(0.94, 1.11)	
97.5% CI		(0.93, 1.12)	
p-value (conventional, two-sided)	0.9093	0.5742	
p-value (non-inferiority, one-sided)		0.0078	
Hazard ratio vs telmisartan*** (95% CI)	0.98 (0.90, 1.07)		
p-value	0.6614		

* The primary endpoint was defined as the time to first event. In case of simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcomes, ** Cox regression, *** Exploratory analysis

Table 10: Incidence and analysis of the primary renal endpoint / FAS

	T/R	T	R
Diabetic nephropathy patients, randomised, n (%)	248 (100.0)	288 (100.0)	238 (100.0)
Primary endpoint, n (%)*	108 (43.5)	119 (41.3)	112 (47.1)
Death	63 (25.4)	82 (28.5)	71 (29.8)
Progression to ESRD	26 (10.5)	21 (7.3)	30 (12.6)
Total time to event/censoring (years)	973	1122	937
Events per 100 patient years	11.10	10.61	11.95
Hazard ratio vs ramipril** (95% CI)	0.92 (0.71, 1.20)	0.88 (0.68, 1.14)	
p-value (conventional, two-sided)	0.5461	0.3436	
Hazard ratio vs telmisartan*** (95% CI)	1.04 (0.80, 1.36)		
p-value	0.7446		

* The primary endpoint was defined as the time to first event. In case of simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcomes, ** Cox regression, *** Exploratory analysis

Table 11: Analysis of the composite of CV death, non-fatal MI, or non-fatal stroke in analogy to the HOPE study / FAS

	ONTARGET			HOPE	
	T/R	**T**	**R**	**R**	**Placebo**
Randomised, n (%)	8502 (100.0)	8542 (100.0)	8576 (100.0)	4645 (100.0)	4652 (100.0)
Three-fold endpoint, n (%)*	1200 (14.1)	1190 (13.9)	1210 (14.1)	651 (14.0)	826 (17.8)
CV death	454 (5.3)	438 (5.1)	448 (5.2)	282 (6.1)	377 (8.1)
Non-fatal MI	413 (4.9)	419 (4.9)	389 (5.2)	459 (9.9)	570 (12.3)
Non-fatal stroke	347 (4.1)	347 (4.1)	389 (4.5)	156 (3.4)	226 (4.9)
Total time to event/censoring (years)	37019	37390	37502		
Events per 100 patient years	3.24	3.18	3.23	3.51***	4.53***
Hazard ratio vs ramipril**	1.00	0.99			
95% CI	(0.93, 1.09)	(0.91, 1.07)			
97.5% CI		(0.90, 1.08)			
p-value (conventional, two-sided)	0.9086	0.7384			
p-value (non-inferiority, one-sided)		0.0004			
Hazard ratio vs telmisartan** (95% CI)	1.02 (0.94, 1.10)				
p-value	0.6544				
Hazard ratio vs placebo** (95% CI)				0.78 (0.70, 0.86)	
p-value				<0.001	

* The 3-fold endpoint was defined as the time to first event. In case of simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients counted for the 3-fold endpoint, ** Cox regression, *** personal communication from HOPE trial

With regard to the secondary efficacy outcome measures:

- There was no significant difference between treatments in the composite of CV death, non-fatal MI, and non-fatal stroke (in analogy to the HOPE study) (Table 11)
- There was no significant difference between treatments in the individual components of the primary endpoints (Table 12)
- There was a significant advantage for the telmisartan/ ramipril combination in comparison with ramipril for the occurrence of new microalbuminuria, and occurrence of new macroalbuminuria. There was also a significant advantage for the composite endpoint of doubling of serum creatinine, progression to ESRD, new microalbuminuria, or new macro-albuminuria. However, this result was heavily influenced by the results for new microalbuminuria and new macro-albuminuria because the findings for doubling of serum creatinine and progression to ESRD were actually in favour of ramipril, though not statistically significant.
- There was no significant difference between the groups in newly diagnosed CHF
- There was no significant difference between the groups in CV revascularisation procedures
- There was no significant difference between the groups in cognitive impairment and cognitive decline
- There was no significant difference between the groups in new onset of atrial fibrillation
- There was no significant difference between the groups in angina

- There was no significant difference between the groups in TIA
- The risk for newly diagnosed diabetes was greater in the telmisartan group than in the telmisartan/ramipril group (Table 13)
- There was no significant difference between the treatment groups in all-cause mortality. However the proportion of patients that died in the telmisartan group was lower.
- There was no significant difference between the groups in non-CV death. However the proportion of patients with non-CV death was lower in the telmisartan group.
- There was no significant difference between the groups in the rate of malignancy.
- There was no significant difference between the groups in the rate of laser therapy for diabetic retinopathy
- There was a greater fall in blood pressure in the combined treatment group than for the individual treatments. Supine ankle/arm SBP ratio was comparable in all treatment groups with no relevant changes over time. Changes in pulse rate were similar in all three treatment groups.

Table 12: Incidence and analyses of the individual components of the primary CV composite endpoint - first event in each category / FAS

	T/R	**T**	**R**
Randomised, n (%)	8502 (100.0)	8542 (100.0)	8576 (100.0)
CV death	620 (7.3)	598 (7.0)	603 (7.0)
Total time to event/censoring (years)	38493	38884	39048
Events per 100 patient years	1.61	1.54	1.54
Hazard ratio vs ramipril* (95% CI)	1.04 (0.93, 1.17)	1.00 (0.89, 1.12)	
Hazard ratio vs telmisartan* (95% CI)	1.05 (0.94, 1.17)		
Non-fatal MI	424 (5.0)	431 (5.0)	400 (4.7)
Total time to event/censoring (years)	37650	38065	38242
Events per 100 patient years	1.13	1.13	1.05
Hazard ratio vs ramipril* (95% CI)	1.08 (0.94, 1.23)	1.08 (0.94, 1.24)	
Hazard ratio vs telmisartan* (95% CI)	0.99 (0.87, 1.14)		
MI (non-fatal and fatal)**,***	435 (5.1)	438 (5.1)	409 (4.8)
Total time to event/censoring (years)	37650	38065	38242
Events per 100 patient years	1.16	1.15	1.07
Hazard ratio vs ramipril* (95% CI)	1.08 (0.94, 1.24)	1.08 (0.94, 1.23)	
Hazard ratio vs telmisartan* (95% CI)	1.00 (0.88, 1.15)		
Non-fatal stroke	364 (4.3)	364 (4.3)	402 (4.7)
Total time to event/censoring (years)	37829	38170	38242
Events per 100 patient years	0.96	0.95	1.05
Hazard ratio vs ramipril* (95% CI)	0.92 (0.79, 1.06)	0.91 (0.79, 1.05)	
Hazard ratio vs telmisartan* (95% CI)	1.01 (0.87, 1.17)		
Stroke (fatal and non-fatal)**, ***	372 (4.4)	369 (4.3)	405 (4.7)
Total time to event/censoring (years)	37829	38170	38274
Events per 100 patient years	0.98	0.97	1.06
Hazard ratio vs ramipril* (95% CI)	0.93 (0.81, 1.07)	0.91 (0.79, 1.05)	
Hazard ratio vs telmisartan* (95% CI)	1.02 (0.88, 1.17)		

	T/R	T	R
Randomised, n (%)	8502 (100.0)	8542 (100.0)	8576 (100.0)
Hospitalisation for CHF	332 (3.9)	394 (4.6)	354 (4.1)
Total time to event/censoring (years)	37898	38128	38381
Events per 100 patient years	0.88	1.03	0.92
Hazard ratio vs ramipril* (95% CI)	0.95 (0.82, 1.10)	1.12 (0.97, 1.29)	
Hazard ratio vs telmisartan* (95% CI)	0.85 (0.73, 0.98)		
Hospitalisation for CHF confirmed by X-ray	242 (2.8)	285 (3.3)	269 (3.1)
Total time to event/censoring (years)	38062	38327	38521
Events per 100 patient years	0.64	0.74	0.70
Hazard ratio vs ramipril* (95% CI)	0.91 (0.77, 1.08)	1.06 (0.90, 1.26)	
Hazard ratio vs telmisartan* (95% CI)	0.85 (0.72, 1.01)		

* Cox regression ** Only those fatal events which were not adjudicated as CV death *** These number are different to those published because new data has become available

Table 13: Incidence of newly diagnosed diabetes or impaired fasting glucose / FAS

	T/R	T	R
Randomised, n (%)	8502	8542	8576
Patients without diabetes at baseline	5037 (100.0)	4992 (100.0)	5123 (100.0)
Patients with newly diagnosed diabetes or impaired fasting glucose	785 (15.6)	880 (17.6)	860 (16.8)
Total time to event/censoring (years)	21691	21487	22095
Events per 100 patient years	3.62	4.10	3.89
Hazard ratio vs ramipril (95% CI)*	0.93 (0.85, 1.03)	1.05 (0.96, 1.15)	
Hazard ratio vs telmisartan (95% CI)*	0.89 (0.81, 0.98)		

* Cox regression

- There was no difference between the groups in the change in MMSE over time
- Renal function appeared to deteriorate to a greater extent in the telmisartan treated groups, with the combined telmisartan / ramipril group having the greatest deterioration in renal function over time (Table 14). This was reflected in a decrease in eGFR and an increase in serum creatinine. However eGFR is calculated using serum creatinine, therefore these measures reflect each other. This finding is reinforced by the result of the outcome measures: doubling of serum creatinine and progression to ESRD. The study did not determine whether these changes reversed when treatment was ceased.
- For the UACR the relationship was reversed (compared to that for creatinine) with the ramipril group having the greatest increase, indicating a beneficial effect for the combined treatment and telmisartan. There were no significant differences between the groups in urinary potassium/ creatinine ratio and urinary sodium/ creatinine ratio.

Table 14: Changes in the estimated glomerular filtration rate, serum creatinine and urinary albumin/creatinine ratio / FAS

	T/R n Mean (SD)*	T n Mean (SD)*	R n Mean (SD)*
eGFR (mL/min/1.73 m^2)			
Start of run-in (baseline)	8483 73.6 (19.6)	8525 73.9 (20.4)	8557 73.9 (19.9)
Final visit	6464 68.1 (22.1)	6570 69.7 (21.5)	6587 71.2 (20.8)
Change from baseline	-6.4 (19.9)	-4.8 (19.3)	-3.6 (19.3)
Mean adjusted change from baseline** (95% CI)	-6.4 (-6.8, -6.0)	-4.9 (-5.3, -4.4)	-3.5 (-3.9, -3.1)
Mean difference to ramipril (95% CI)	-2.9 (-3.5, -2.3)	-1.4 (-2.0, -0.7)	
Mean difference to telmisartan (95% CI)	-1.5 (-2.2, -0.9)		
Serum creatinine (mg/dL)			
Start of run-in (baseline)	8483 1.07 (0.28)	8525 1.06 (0.28)	8557 1.06 (0.27)
Final visit	6465 1.17 (0.46)	6570 1.14 (0.42)	6587 1.11 (0.42)
Change from baseline	0.12 (0.38)	0.09 (0.35)	0.06 (0.36)
Mean adjusted change from baseline**(95% CI)	0.12 (0.11, 0.13)	0.09 (0.08, 0.10)	0.06 (0.05, 0.07)
Mean difference to ramipril (95% CI)	0.06 (0.04, 0.07)	0.03 (0.01, 0.04)	
Mean difference to telmisartan (95% CI)	0.03 (0.02, 0.04)		
Urinary albumin/creatinine ratio (mg/g creat)			
Start of run-in (baseline)	7783 7.15 (6.90-7.40)	7817 7.34 (7.08-7.61)	7846 7.13 (6.89-7.39)
Final visit	6033 7.78 (7.48,8.10)	6111 7.96 (7.64,8.29)	6157 8.29 (7.96,8.63)
Ratio to baseline	1.22 (1.17, 1.26)	1.25 (1.20, 1.29)	1.32 (1.27, 1.37)
Adjusted gMean ratio to baseline*** (95% CI)	1.22 (1.18, 1.26)	1.25 (1.21, 1.29)	1.31 (1.27, 1.36)
Adjusted gMean ratio to ramipril***(95% CI)	0.93 (0.89, 0.97)	0.95 (0.91, 1.00)	
Adjusted gMean ratio to telmisartan*** (95% CI)	0.98 (0.93, 1.02)		

*SD: standard deviation but gMean and 95% CI for urinary albumin/creatinine ratio, ** adjusted for baseline, *** adjusted for baseline using ANCOVA

Supportive Studies

Trial No. 502.373 **T**elmisartan **R**andomized **A**ssessme**N**t **S**tudy in a**CE** i**N**tolerant subjects with cardiovascular **D**isease (TRANSCEND) was a multinational, multicentre, randomised, double blind, parallel group, placebo controlled trial of telmisartan in patients at high risk for cardiovascular events and intolerant of ACE-I (Table 15).

The inclusion criteria for the TRANSCEND trial were identical to the ONTARGET trial with the addition of: only patients with known intolerance to ACE-Is according to their medical history or as assessed during the run-in period of ONTARGET were included into this trial.

The exclusion criteria were similar to those of the ONTARGET trial except for the removal of two criteria which were not exclusion criteria for the TRANSCEND trial.

- Inability to discontinue ACE-Is
- Patients with known hypersensitivity or intolerance to ACE-Is

The study treatments and other treatment details are shown in Table 15.

Table 15: Details of Trial No. 502.373 (TRANSCEND)

Design	**Nr. Of subjects with age and sex** **Duration of Treatment**	**Diagnosis + criteria for inclusion/exclusion**	**Test Product** **Dosage Regimen** **Route of administration, Formulation** **Reference therapy** **Dose regimen**	**Criteria for evaluation**	**Results** **(efficacy)**	**Adverse Reactions**
Multinational, multicentre, randomised, double blind, parallel group, placebo controlled trial of telmisartan in patients at high risk for cardiovascular events and intolerant of ACE-I	6665 subjects enrolled into the run-in period, 5926 subjects randomised; 2954 to telmisartan and 2972 to placebo 57.0% male and 43.0% female Age range 55 to 84 years 3.5 to 8 years	Patients with known intolerance to ACE-Is Male or female patients, 55 years of age or older, and at high risk of developing a major CV event were eligible if they had any of the following: 1. Coronary arterial disease 2. Peripheral arterial disease 3. Previous stroke (stroke included definite or presumed cerebral infarction, intracerebral haemorrhage, stroke of uncertain subtype, but not subarachnoid haemorrhage) 4. TIA >7 days and <1 year prior to informed consent 5. High-risk diabetes (insulin-dependent or non-insulin-dependent) with evidence of end-organ damage	Telmisartan 80 mg Once daily oral administration Single blind run-in phase of placebo for one week, followed by telmisartan 80 mg daily for 2 to 3 weeks Randomised 1:1 Placebo	The primary efficacy outcome measure was the composite of CV death, MI, stroke, or hospitalisation for CHF. The secondary efficacy outcome measures were: Composite of CV death, non-fatal MI, and non-fatal stroke; The individual components of the primary endpoint; Occurrence of nephropathy Newly diagnosed CHF; CV revascularisation procedures Newly diagnosed diabetes Cognitive impairment and cognitive decline New onset of atrial fibrillation All-cause mortality	For the primary efficacy outcome measure there was no significant difference between telmisartan and placebo For the composite of CV death, non-fatal MI, and non-fatal stroke, there was a benefit for telmisartan which was of marginal statistical significance and of a lesser magnitude than the benefit of ramipril in the HOPE study There were lower rates of subjects with new microalbuminuria, new macroalbuminuria, and the combined endpoint of doubling of serum creatinine, progression to ESRD, new microalbuminuria, or new macroalbuminuria For subjects without malignancy at baseline, there was an increase in the rate of fatal and non-fatal malignancy in the telmisartan group In the telmisartan group there was an increase in serum creatinine with a corresponding decrease in eGFR, and also a decrease in UACR	The proportion of subjects that died; and discontinuation because of SAEs and AEs were slightly higher in the telmisartan group The percentage of patients who permanently stopped taking study medication was 17.7% in the telmisartan group and 19.4% in the placebo group: RR (95% CI) telmisartan vs. placebo was 0.91 (95% CI 0.82, 1.02 The there was an increased risk for hypotension, syncope, diarrhoea and renal dysfunction with telmisartan For AEs leading to discontinuation: hypotension, renal failure and hyperkalaemia were more common in the telmisartan group mean serum creatinine and potassium increased from baseline in the telmisartan group

The primary efficacy outcome measure was the composite of CV death, MI, stroke, or hospitalisation for CHF. The secondary efficacy outcome measures were:

- Composite of CV death, non-fatal MI, and non-fatal stroke
- The individual components of the primary endpoint (CV death, MI, stroke, and hospitalisation for CHF)
- Occurrence of nephropathy analysed based on the following 6 subcategories:
    - Doubling of serum creatinine
    - Progression to ESRD (i.e. initiation of dialysis, need for renal transplantation, or eGFR <15 mL/min/1.73m^2)

  - New microalbuminuria (UACR ≥30 mg/g creatinine in patients with a UACR <30 mg/g creatinine at baseline)
  - New macroalbuminuria (UACR ≥300 mg/g creatinine in patients with a UACR <300 mg/g creatinine at baseline)
  - Combined endpoint of doubling of serum creatinine, progression to ESRD, new microalbuminuria, or new macroalbuminuria
  - Normalisation from micro- or macroalbuminuria to normoalbuminuria (UACR <30 mg/g creatinine in patients with a UACR ≥30 mg/g creatinine at baseline)
- Newly diagnosed CHF
- CV revascularisation procedures
- Newly diagnosed diabetes
- Cognitive impairment and cognitive decline
- New onset of atrial fibrillation

Other outcome measures were:

- All-cause mortality (non-CV mortality and CV mortality)
- Non-CV death
- Angina (unstable, new, and worsening)
- TIA
- Malignancy (fatal and non-fatal)
- Laser therapy for diabetic retinopathy

In addition, changes from baseline in BP, ankle/arm BP ratio, MMSE, eGFR, serum creatinine, and UACR were determined. The safety outcome measures were: SAEs, AEs leading to discontinuation of trial medication, clinical laboratory evaluations; vital signs (BP and PR), and ECGs.

Statistical Methods/Primary Analysis for the TRANSCEND Study

The primary analysis was the time to the composite of CV death, MI, stroke, or hospitalisation for CHF for telmisartan compared with placebo. Hypothesis tests were for superiority and were performed using time-to-event analysis (Kaplan Meier) and HRs based on the intent-to-treat principle and using the proportional hazard model (Cox regression) and the chi-squared test. The analysis included all randomised patients on an intention to treat basis.

The sample size required to detect a HR (telmisartan vs placebo) of 0.81, assuming a total sample recruitment period of 2 years and a maximum observation time of 5.5 years, using an α of 0.05, and a power of 90% was 5,000 subjects. The actual intended sample size was 6000 subjects, in order to ensure "moderately high power" to detect an impact on CV death and MI if there was a 25% risk reduction, and "good power" for a 30% risk reduction in strokes. The sample size calculations were based on the results of the HOPE trial.

Results from the TRANSCEND Study

A total of 6665 subjects were enrolled into the run-in period, and of these 5926 subjects were randomised; 2954 to telmisartan and 2972 to placebo. The study population was 57.0% male and 43.0% female. The age range was 55 to 84 years. The treatment groups had similar demographic characteristics, alcohol use, tobacco use and physical activity, comorbidity status, inclusion diagnosis, and medical history. Previous and concomitant medication use was also similar for the two treatment groups. ECG findings were similar at baseline. For some categories of concomitant medications, the use after randomisation differed between treatment groups:

- The use of beta blockers decreased in the telmisartan group (from 59.3% at baseline to 56.6% at the final visit) while it increased in the placebo group (from 57.2% to 59.0%).

- The use of diuretics increased in the placebo group from 32.8% to 40.0%; no change over time was seen in the telmisartan group (33.2% to 33.7%).
- The use of calcium channel blockers (CCBs) excluding diltiazem/verapamil increased in the placebo group from 31.3% to 39.2%, while no change was seen with telmisartan (30.9% to 30.8%).
- The use of alpha blockers increased slightly in the telmisartan group (from 4.1% to 5.3%), while the increase was more pronounced in the placebo group (from 3.9% to 7.4%).

For the primary efficacy outcome measure there was no significant difference between telmisartan and placebo (Table 16). The study was not sufficiently powered to detect a significant difference between telmisartan and placebo because the hazard ratio determined by the study, 0.92, was not as favourable as that assumed in the sample size calculations: 0.81. It is also possible that the lack of a significant treatment effect could be explained by the telmisartan group "opting out" of co-medication (such as beta-blockers) and the placebo group "opting in". In the subgroups of patients that did not use dihydropyridines or that did not use any antihypertensives, there was a beneficial effect for telmisartan.

Table 16: Incidence and analysis of the primary composite endpoint of CV death, MI, stroke, and hospitalisation for CHF - first event/ FAS

	Telmisartan	**Placebo**
Randomised, n (%)	2954 (100.0)	2972 (100.0)
Primary endpoint, n (%)*	465 (15.7)	504 (17.0)
CV death	140 (4.7)	137 (4.6)
Non-fatal MI	106 (3.6)	136 (4.6)
Non-fatal stroke	106 (3.6)	127 (4.3)
Hospitalisation for CHF	123 (4.2)	112 (3.8)
Total time to event/censoring (years)	12994	13012
Events per 100 patient years	3.58	3.87
Hazard ratio vs placebo** (95% CI)	0.92 (0.81, 1.05)	
p-value	0.2192	

* The primary endpoint was defined as the time to first event. In case of simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcomes, ** Cox regression

For the secondary efficacy outcome measures the findings were:

- For the composite of CV death, non-fatal MI, and non-fatal stroke, there was a benefit for telmisartan which was of marginal statistical significance and of a lesser magnitude than the benefit of ramipril in the HOPE study (Table 17)
- For the individual components of the primary endpoint there was no significant difference between treatments.
- In the telmisartan group there were lower rates of subjects with new microalbuminuria, new macroalbuminuria, and the combined endpoint of doubling of serum creatinine, progression to ESRD, new microalbuminuria, or new macroalbuminuria. In addition, more subjects in the telmisartan group had normalisation from micro- or macroalbuminuria to normoalbuminuria. However, more subjects in the telmisartan group had a doubling of serum creatinine. There was no significant difference between the groups in progression to ESRD. Hence the composite endpoint of doubling of serum creatinine, progression to ESRD, new microalbuminuria, or new

macroalbuminuria is influenced primarily by the endpoints of new microalbuminuria and new macroalbuminuria.

- There was no significant difference between the treatment groups in the rate of newly diagnosed CHF or CV revascularisation procedures.

Table 17: Incidence and analysis of the composite endpoint of CV death, nonfatal MI, or non-fatal stroke in analogy to the HOPE study / FAS

	TRANSCEND		**HOPE**	
	Telmisartan	**Placebo**	**Ramipril**	**Placebo**
Randomised, n (%)	2954 (100.0)	2972 (100.0)	4645 (100.0)	4652 (100.0)
3-fold endpoint, n (%)	384 (13.0)	440 (14.8)	651 (14.0)	826 (17.8)
CV death	169 (5.7)	170 (5.7)	282 (6.1)	377 (8.1)
Non-fatal MI	111 (3.8)	138 (4.6)	459 (9.9)	570 (12.3)
Non-fatal stroke	111 (3.8)	136 (4.6)	156 (3.4)	226 (4.9)
Total time to event/censoring (years)	13241	13218		
Events per 100 patient years	2.90	3.33	3.51	4.53
Hazard ratio vs placebo	0.87		0.78	
95% CI	(0.76, 1.00)		(0.70, 0.86)	
p-value	0.0483		<0.001	

- There was no significant difference between the treatment groups in the rate of newly diagnosed diabetes.
- There was no significant difference between the treatment groups in cognitive impairment and cognitive decline.
- There was no significant difference between the groups in the occurrence of new onset of atrial fibrillation.
- There was no difference between the treatment groups in all-cause mortality or in non-CV death.
- There was no significant difference between the groups in the occurrence of angina.
- There was no significant difference between the groups in the occurrence of TIA.
- For subjects without malignancy at baseline, there was an increase in the rate of fatal and non-fatal malignancy combined in the telmisartan group.
- There was no significant difference between the groups in laser therapy for diabetic retinopathy.

Relative to placebo, there was a decrease in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the telmisartan group that persisted through the randomisation phase. Ankle/arm BP ratio and PR were similar for the two treatment groups throughout the trial. MMSE scores were similar in the two treatment groups.

Relative to placebo, in the telmisartan group there was an increased in serum creatinine with a corresponding decrease in eGFR, and also a decrease in UACR (Table 18). This finding is supported by the greater number of subjects in the telmisartan group with doubling of serum creatinine.

Table 18: Changes in the estimated glomerular filtration rate, serum creatinine, and urinary albumin/creatinine ratio / FAS

	Telmisartan n Mean (SD)	Placebo n Mean (SD)
eGFR (mL/min/1.73 m^2)		
Start of run-in (baseline)	2950 72.0 (20.2)	2965 71.9 (20.3)
Final visit	2247 69.0 (21.0)	2215 72.0 (20.6)
Change from baseline	-3.6 (20.4)	-0.7 (20.0)
Mean adjusted change from baseline (95% CI)	-3.6 (-4.4, -2.9)	-0.7 (-1.4, 0.1)
Mean difference to placebo (95% CI)	-3.0 (-4.0, -1.9)	
Serum creatinine (mg/dL)		
Start of run-in (baseline)	2950 1.04 (0.29)	2965 1.05 (0.28)
Final visit	2247 1.09 (0.39)	2215 1.05 (0.37)
Change from baseline	0.06 (0.36)	0.01 (0.33)
Mean adjusted change from baseline(95% CI)	0.06 (0.05, 0.07)	0.01 (0.00, 0.03)
Mean difference to placebo (95% CI)	0.05 (0.03, 0.06)	0.03 (0.01, 0.04)
Urinary albumin/creatinine ratio (mg/g creat)		
Start of run-in (baseline)	2691 6.03 (5.74, 6.35)	2721 5.86 (5.57, 6.16)
Final visit	1677 7.16 (6.69, 7.66)	1661 8.86 (8.21, 9.56)
Ratio to baseline	1.32 (1.23, 1.41)	1.63 (1.52, 1.76)
Adjusted gMean ratio to baseline (95% CI)	1.32 (1.23, 1.41)	1.64 (1.53, 1.75)
Mean difference to placebo (95% CI)	0.80 (0.73, 0.88)	

Trial No. 9.159: Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS) was a multinational, multicentre, randomised, double blind, double dummy, active and placebo controlled, parallel group, 2x2 factorial design clinical trial (Table 19). The study was sponsored by Boehringer Ingelheim Pty Ltd.

The inclusion criteria were:

- Patients of either gender who were at least 55 years of age and who had had an ischaemic stroke within 90 days of entry into the study; or
- Patients aged 50 to 54 years and/or those patients whose qualifying stroke had occurred 91 to 120 days prior to admission, provided the patient had at least two of the following additional risk factors: diabetes mellitus, hypertension (SBP ≥140 or DBP ≥90 mmHg), smoking at time of qualifying stroke, obesity (BMI ≥30 kg/m^2), previous vascular disease (stroke, MI, or PAD prior to the qualifying stroke), end-organ damage (retinopathy, LVH, or microalbuminurea), and/or hyperlipidaemia.
- Stroke, defined as a new focal neurologic deficit of vascular origin lasting more than 24 hours, or where there was evidence of a new brain infarct upon brain imaging (by computerised tomography [CT] or magnetic resonance imaging [MRI] scan), or retinal artery occlusion.
- Brain imaging that excluded haemorrhagic stroke.
- For patients whose symptoms lasted less than 24 hours, brain imaging that confirmed the presence of a new brain infarct consistent with the clinical syndrome.
- After the qualifying stroke, the patient's neurological and clinical condition had to have stabilised in the opinion of the investigator before the patient could be randomised to treatment.

For hospitalised patients, BP measurements taken over 24 hours were used to confirm that BP was stable and within the acceptable range for randomisation (SBP >120 mmHg but <180 mmHg; DBP <110 mmHg).

Table 19: Details of Trial No. 9.159 (PRoFESS)

Nr. Of subjects with age and sex **Duration of Treatment**	**Diagnosis + criteria for inclusion/exclusion**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen** **Route of administration**	**Criteria for evaluation**	**Results** **(efficacy)**	**Adverse** **Reactions**
20403 enrolled, 20332 randomised to treatment: 5086 to Telmisartan/Aggrenox; 5095 to placebo/Aggrenox; 5060 to telmisartan/clopidogrel; 5091 to placebo/clopidogrel 64.0% of patients were male and 36.0% of patients were female 19 months to 4 years 5 months	Patients of either gender who were at least 55 years of age and who had had an ischaemic stroke within 90 days of entry into the study; or Patients aged 50 to 54 years and/or those patients whose qualifying stroke had occurred 91 to 120 days prior to admission, provided the patient had at least two additional risk factors Stroke Brain imaging excluding haemorrhagic stroke. For patients whose symptoms lasted less than 24 hours, brain imaging that confirmed the presence of a new brain infarct consistent with the clinical syndrome. After the qualifying stroke, the patient's neurological and clinical condition had to have stabilised	Telmisartan 80 mg once daily/ Aggrenox (25 mg acetyl-salicylic acid (ASA) + 200 mg extended release dipyridamole (ER-DP) twice daily; Telmisartan 80 mg once daily /clopidogrel 75 mg once daily; All treatments were administered orally	placebo/ Aggrenox® (25 mg ASA + 200 mg ER-DP); twice daily placebo /clopidogrel 75 mg once daily	The primary efficacy outcome measure was the time to first recurrent stroke. Secondary efficacy outcome measures were: Composite outcome defined as time to the first of: recurrent stroke, MI, new or worsening CHF, or death due to vascular causes. Time to new onset of diabetes mellitus. Time to death (all-cause mortality) Time to other designated vascular events Time to first recurrent ischaemic stroke Cognitive decline measured by the Mini-Mental State Exam (MMSE)	For the primary efficacy outcome measure there was no significant difference between telmisartan and placebo. Over time there appeared to be some benefit for telmisartan, particularly after 2.5 years of treatment and there was a significant interaction between treatment and time on post-hoc analysis. There was no significant difference in the composite outcome of: time to the first of: recurrent stroke, MI, new or worsening CHF, or death due to vascular causes; first recurrent ischaemic stroke; death; new onset of diabetes mellitus; recurrent stroke or major haemorrhagic event; or MMSE	The death rate was similar for the two treatment groups: 738 (7.4%) subjects in the telmisartan group and 725 (7.2%) in the placebo There were more SAEs associated with hyperkalaemia in the telmisartan group: 15 (0.1%) subjects compared with 4 in the placebo. There were more SAEs associated with hypotension in the telmisartan group 161 (1.6%) subjects, compared with 127 (1.3%) in the placebo group. Acute renal failure was more common in the telmisartan group: 71 (0.7%) subjects, compared with 37 (0.4%) in the placebo group. There were more subjects with an AE leading to discontinuation in the telmisartan group: 1450 (14.5%) subjects, compared with 1127 (11.2%) in the placebo group. 4.1% of the telmisartan group, compared with 1.9% of the placebo, ceased medication because of AEs related to hypotension.

The exclusion criteria included:

- Primary haemorrhagic stroke (intracerebral haemorrhage or subarachnoid haemorrhage) confirmed by means of appropriate brain imaging (for example, CT scan, MRI). Patients with infarction with secondary haemorrhagic components at the time of presentation were eligible if, in the investigator's opinion, the risk of further haemorrhage had diminished by the time of randomisation.
- Patients who were unable to orally administer all required study medication.
- Known brain tumour.
- Current CHF.
- Patients with a pre-stroke history of dementia requiring institutional care.
- A modified Rankin scale score >4 at baseline.
- The patient was unlikely to be released from hospital following the qualifying stroke, or the presence of a severe disability after the qualifying stroke likely to lead to the patient being bedridden or demented, or a non-vascular disease or condition which made it unlikely that the patient would survive to the end of the trial.
- Patients whose qualifying stroke had been induced by a surgical or cardiovascular procedure such as carotid endarterectomy, angiogram, or cardiac surgery.
- Uncontrolled hypertension with DBP ≥110 mmHg or SBP ≥180 mmHg.
- Seated SBP ≤120 mmHg for patients who were still hospitalised following the qualifying stroke. If patient was not able to sit, supine BP was acceptable.
- Patients being treated with an ARB who were unable or unwilling to discontinue treatment with this class of drug.
- Treatment with antithrombotics or anticoagulants including heparin or warfarin, or non-study platelet inhibitors, or non-steroidal anti-inflammatory drugs (NSAIDs) unless they are selective cyclo-oxygenase type-2 selective (COX-2) inhibitors. Short-term co-administration (usually over a few days) of the following drugs along with study medication was allowed: low-dose unfractionated heparin, low-molecular weight heparin, heparinoids for deep vein thrombosis (DVT) prophylaxis during the acute post-stroke period.
- Known severe renal insufficiency, defined as renal artery stenosis, or creatinine clearance <0.6 mL/sec or serum creatinine >265 μmol/L.
- Known severe hepatic dysfunction as defined by: ALT or AST >4xULN, or total bilirubin >20 μmol/L.
- Hyperkalaemia, defined as potassium >5.5 mmol/L.
- Uncorrected volume depletion or sodium depletion.
- Known, active peptic ulcer disease.
- Patients with the syndrome of asthma, rhinitis and nasal polyps (all 3 present).
- Known severe CAD, including unstable angina pectoris or an MI within the previous 3 months.
- Known presence of, or history of, a haemostatic disorder or systemic bleeding
- History of thrombocytopenia (platelet count <100x109 cells/L) or neutropenia (neutrophil count <1.2x109 cells/L).
- Women who were breast-feeding, pregnant, or of childbearing potential who did not use a medically acceptable form of contraception
- Major surgery, carotid endarterectomy, or carotid angioplasty within 4 weeks prior to study entry.

The study treatments and other details of the trial are shown in Table 19. All treatments were administered orally. Patients were randomised to one of the four treatment arms using an interactive voice response system (IVRS). Patients were randomised at each site in blocks of eight. Treatment duration was 19 months to 4 years 5 months.

The primary efficacy outcome measure was the time to first recurrent stroke. The secondary efficacy outcome measures were:

For the telmisartan versus placebo comparison:

- Composite outcome defined as time to the first of: recurrent stroke, MI, new or first worsening CHF, or death due to vascular causes.
- Time to new onset of diabetes mellitus.
- Time to the individual components of the composite secondary endpoint (MI, new or first worsening of CHF, death due to vascular causes)
- Time to death (all-cause mortality)
- Time to other designated vascular events (ODVE), defined as time to the first of: pulmonary embolism, retinal vascular accident that is not a retinal arterial occlusion, deep vein thrombosis, cerebral venous thrombosis, peripheral arterial occlusion, or transient ischaemic attack
- Time to first recurrent ischaemic stroke
- Time to composite of recurrent stroke or major haemorrhagic event
- Cognitive decline measured by the MMSE

For the antiplatelet comparison:

- Composite outcome defined as time to the first of: recurrent stroke, MI, or death due to vascular causes.

Post hoc-defined efficacy outcome measures were:

For the telmisartan comparison:

- Time to composite of stroke, MI or death due to vascular causes

For the antiplatelet comparison:

- Time to haemorrhagic stroke
- Time to fatal or disabling stroke
- Time to composite of death or disabling stroke

Safety outcome measures included: deaths, SAEs, AEs leading to discontinuation of study medication, vital signs, laboratory analyses, waist circumference and ECG. Additional safety outcome measures were: time to major haemorrhagic events; time to intracranial haemorrhage; frequency of haemorrhagic events (major or minor); and frequency of thrombotic thrombocytopenic purpura (TTP) or neutropenia (for the antiplatelet comparison only).

Statistical Methods/Primary Analyses for the PRoFESS Study

The hypothesis test for the primary efficacy outcome measure (telmisartan compared with placebo) was performed as a test of superiority. The outcome measure was time to recurrent stroke and was tested using a Cox proportional hazard model. The analysis used an intention to treat approach and included all the randomized subjects.

The antiplatelet comparison (clopidogrel compared with Aggrenox [acetyl-salicylic acid 25 mg + dipyridamole ER 200 mg]) was performed as a non-inferiority comparison. The outcome measure was time to recurrent stroke and was tested using a Cox proportional hazard model. However, this comparison is not being presented in support of the present application.

Hypothesis tests for the secondary analyses (telmisartan compared with placebo) were preformed using Cox proportional hazard models or analysis of covariance (ANCOVA).

A sample size of 20,000 subjects was calculated as having 2280 subjects with recurrent stroke over a follow-up period of 4 years. This would result in a power of 94%, with an α of 0.05 to detect a 16% relative risk reduction for telmisartan in comparison with placebo for the primary analysis.

Results from the PRoFESS Study

There were a total of 20403 subjects enrolled in the study, of which 20332 were randomised to treatment: 5086 to Telmisartan/Aggrenox; 5095 to placebo/Aggrenox; 5060 to telmisartan/clopidogrel; 5091 to placebo/clopidogrel. Of these subjects, 64.0% were male and 36.0% were female. The telmisartan and placebo groups were similar in demographic composition, stroke related morbidity, medical history/ co-morbidity, and concomitant medications. The proportion of patients having concomitant antihypertensive medication (including ACE-I) decreased in the telmisartan group during the course of the study, but increased in the placebo group. This phenomenon might explain the absence of a significant difference between treatments, but was not explored in a post-hoc analysis.

For the primary efficacy outcome measure, the time to first recurrent stroke, there was no significant difference between telmisartan and placebo (Table 20). However, over time there appeared to be some benefit for telmisartan, particularly after 2.5 years of treatment (Figure 1). There was a significant interaction between treatment and time on post-hoc analysis (Table 21). There were no significant effects for the baseline covariates, including treatment with ACE-I.

Table 20: Cox proportional hazards analysis of recurrent stroke (telmisartan or placebo) / randomised patients

	Telmisartan	**Placebo**
Randomised, n	10146	101186
Patients with recurrent stroke, n (%)*	880 (8.7)	934 (9.2)
Hazard ratio vs placebo*	0.95	
95% CI	(0.86, 1.04)	
p-value	0.2312	

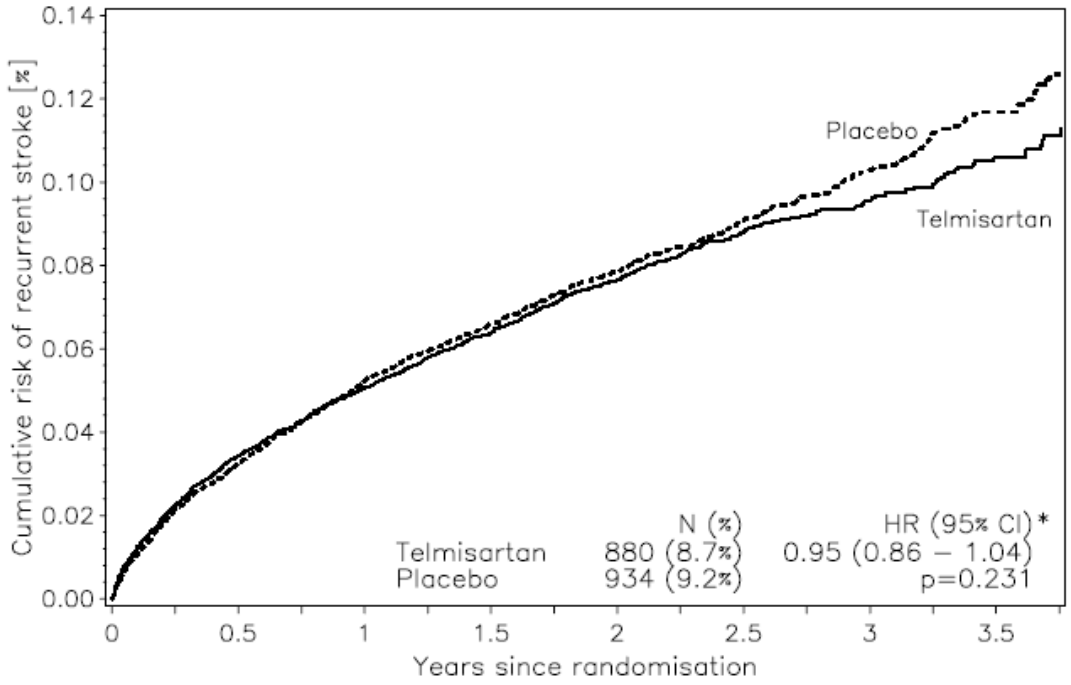
The analysis is based on adjudicated results. * Cox proportional hazards model with age, baseline diabetes status, baseline ACE-I use, and baseline modified Rankin score as covariates

Table 21: Post hoc analysis of recurrent stroke by time (telmisartan or placebo) / randomised patients

	Telmisartan	**Placebo**
Randomised, n	10146	101186
Patients with recurrent stroke ≤6 months after randomisation, n (%)*	347 (3.4)	326 (3.2)
Hazard ratio vs placebo*	1.07	
95% CI	(0.92, 1.25)	
Patients with recurrent stroke >6 months after randomisation, n (%)*	533 (5.3)	608 (6.0)
Hazard ratio vs placebo*	0.88	
95% CI	(0.78, 0.99)	
Time-period-by-treatment-interaction		
p-value	0.042	

* Cox proportional hazards model with age, baseline diabetes status, baseline ACE-I use, baseline modified Rankin score and time from randomisation as covariates

Figure 1: Kaplan-Meier estimates for the primary endpoint time to recurrent stroke (telmisartan comparison) / randomised patients



No. at risk:

Telmisartan	10146	9667	9400	9135	6947	4457	2337	1052
Placebo	10186	9725	9402	9148	6957	4404	2326	1045

NOTE: Figure displays Kaplan–Meier probability of having an event.

The results for the secondary efficacy outcome measures were:

- There was no significant difference in the composite outcome of: time to the first of: recurrent stroke, MI, new or worsening CHF, or death due to vascular causes.
- There was no significant difference for the time to the individual components of the composite secondary endpoint: MI, new or first worsening of CHF, death due to vascular causes.
- There was no significant difference in the time to first recurrent ischaemic stroke.
- There was no significant difference in time to death (all-cause mortality).
- There was no significant difference between treatments in the time to ODVE.
- There was no significant difference between treatment groups in time to new onset of diabetes mellitus.
- There was no significant difference between treatments in the time to recurrent stroke or major haemorrhagic event.
- There was no significant difference between treatments in MMSE (administered at 1 month, 2 years but not at baseline) in the adjusted mean change from 1 month to 2 years for telmisartan or placebo (0.07 vs. 0.09; 95% CI −0.10, 0.07).
- There was no significant difference between treatments for the post hoc-defined efficacy outcome measure of: time to composite of stroke, MI or death due to vascular causes.

For the outcome measures designed to test the antiplatelet comparison, there appeared to be no significant interaction effect for telmisartan. Haemorrhagic stroke was observed in 59 (6.7%) subjects on telmisartan and 69 (7.4%) on placebo. Data for the telmisartan versus placebo comparison were not presented for the remaining two post-hoc antiplatelet comparisons: time to fatal or disabling stroke; and time to composite of death or disabling stroke.

Efficacy data from combined analyses

Report U08-2024-01 was a combined analysis of the efficacy data from the randomised controlled trials conducted in support of the requested indication. The report included the tables of data from Trial No. 502.373, ONTARGET as discussed above. In addition there was a pooled analysis performed of data from Trial No. 502.373 TRANSCEND and Trial No. 9.159: PRoFESS, both of which compared telmisartan with placebo. This pooled analysis was a post-hoc analysis. The report mainly consisted of tabulations of data with an introductory section. The introductory section did not provide details of methods or discussion of the results. The report was intended to be a reference document for the applicant's Summary of Clinical Efficacy.

The pooled analysis included data from Trial No. 502.373 TRANSCEND and Trial No. 9.159: PRoFESS for subjects who did not take an ACE-I at baseline. There were 8587 subjects in the combined telmisartan group and 8290 in the combined placebo group. The primary efficacy outcome measures of the two studies were different. Hence, the combined analysis used a primary efficacy outcome measure of composite primary outcome of CV death, nonfatal MI, nonfatal stroke or hospitalisation for CHF. For this outcome measure in patients not treated with an ACE-I at baseline there was a clinically and statistically significant benefit for telmisartan, but also a study effect (Table 22). For the primary composite endpoint there was a significant benefit for males: HR (95% CI) 0.84 (0.76 to 0.93) but not for females: 1.01 (0.88 to 1.16).

Table 22: Incidence and analysis of the composite primary outcome of CV death, nonfatal MI, nonfatal stroke or hospitalisation for CHF for the patients not taking an ACE-I at baseline in the combined analysis of Trial No. 502.373 TRANSCEND and Trial No. 9.159: PRoFESS

	Telmisartan	**Placebo**
Randomised, N	8587	8290
Primary endpoint, n (%)*	1120 (13.0)	1196 (14.4)
CV death	265 (3.1)	291 (3.5)
Non-fatal MI	164 (1.9)	189 (2.3)
Non-fatal stroke	549 (6.4)	583 (7.0)
Hospitalisation for CHF	166 (1.9)	152 (1.8)
Total time to event/censoring (years)	26238	25314
Events per 100 patient years	4.27	4.72
Hazard ratio vs placebo** (95% CI)	0.90 (0.83, 0.98	
p-value	0.0107	
Study effect (Hazard ratio TRANSCEND vs PRoFESS) (95% CI)	0.75 (0.69, 0.83)	
p-value	<0.0001	
Interaction between treatment and study	0.4122	

In case of multiple events, all individual events are considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcome, ** Cox regression

In addition, the benefit was not as great when the treatment group as a whole was analysed (Table 23). There were similar findings for: incidence and analysis of the composite primary outcome of CV death, nonfatal MI or nonfatal stroke (HOPE endpoint) (Table 24). For the HOPE endpoint, there was significant benefit in the <65 years age category: HR (95% CI) 0.83 (0.72 to 0.96). There

was no significant benefit for the outcomes: CV death, all MIs (fatal and non-fatal), all strokes (fatal and non-fatal), hospitalisation for CHF, all-cause mortality, and non-CV death.

Table 23: Incidence and analysis of the composite primary outcome of CV death, nonfatal MI, nonfatal stroke or hospitalisation for CHF including all patients irrespective of ACE−I use, combined analysis of Trial No. 502.373 TRANSCEND and Trial No. 9.159: PRoFESS

	Telmisartan	**Placebo**
Randomised, N	13100	13158
Primary endpoint, n (%)*	1832 (14.0)	1967 (14.9)
CV death	383 (2.9)	418 (3.2)
Non-fatal MI	272 (2.1)	306 (2.3)
Non-fatal stroke	965 (7.4)	1042 (7.9)
Hospitalisation for CHF	254 (1.9)	238 (1.8)
Total time to event/censoring (years)	36878	36870
Events per 100 patient years	4.97	5.33
Hazard ratio vs placebo** (95% CI)	0.93 (0.87, 0.99)	
p-value	0.0297	
Study effect (Hazard ratio TRANSCEND vs PRoFESS) (95% CI)	0.67 (0.62, 0.73)	
p-value	<0.0001	
Interaction between treatment and study	0.8851	

* In case of multiple events, all individual events are considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcome, ** Cox regression

Table 24: Incidence and analysis of the composite primary outcome of CV death, nonfatal MI or nonfatal stroke (HOPE endpoint) including all patients irrespective of ACE−I use, combined analysis of Trial No. 502.373 TRANSCEND and Trial No. 9.159: PRoFESS

	Telmisartan	**Placebo**
Randomised, N	13100	13158
Incidence of HOPE outcome*, N (%)	1673 (12.8)	1817 (13.8)
CV death	383 (2.9)	418 (3.2)
Non-fatal MI	272 (2.1)	306 (2.3)
Non-fatal stroke	965 (7.4)	1042 (7.9)
Total time to event/censoring (years)	37242	37200
Events per 100 patient years	4.49	4.88
Hazard ratio vs placebo** (95% CI)	0.92 (0.86, 0.98)	
p-value	0.0148	
Study effect (Hazard ratio TRANSCEND vs PRoFESS) (95% CI)	0.59 (0.54, 0.64)	
p-value	<0.0001	
Interaction between treatment and study	0.3679	

*. ** as above

Summary of Efficacy

The results of **Trial No. 502.373: ONTARGET** demonstrated non-inferiority for telmisartan versus ramipril. This was demonstrated by both the per-protocol and intention to treat analysis. Non-inferiority was achieved with no more than a 13% increase in risk with telmisartan compared with ramipril. The 13% margin was a clinically meaningful difference. The patient group studied was relevant to the proposed indication: patients at high risk of developing a major CV event. The treatment duration was appropriate given the likely long-term nature of the treatment (treatment duration was for 3.5 to 5.5 years).

Trial No. 502.373: ONTARGET indicated no significant benefit for the telmisartan/ ramipril combination over telmisartan. The 16% drop in telmisartan AUC resulting from co-administration with ramipril is unlikely to have influenced this result.

In **Trial No. 502.373: ONTARGET** it is of some concern that:

- The risk for newly diagnosed diabetes was greater in the telmisartan group than in the telmisartan/ramipril group
- Renal function appeared to deteriorate to a greater extent in the telmisartan treated groups, with the combined telmisartan / ramipril group having the greatest deterioration in renal function over time.

However, for UACR there was a benefit for telmisartan, with the ramipril group having the greatest increase over time, indicating a beneficial effect for the combined treatment and telmisartan.

In **Trial No. 502.373: TRANSCEND** for the primary efficacy outcome measure there was no significant difference between telmisartan and placebo. Use of beta-blockers and diuretics increased in the placebo group relative to telmisartan and this could have obscured a beneficial effect for telmisartan. For the secondary endpoint: the composite of CV death, non-fatal MI, and non-fatal stroke, there was a benefit for telmisartan which was of marginal statistical significance and of a lesser magnitude than the benefit of ramipril in the HOPE study. In the telmisartan group there were lower rates of subjects with new microalbuminuria, new macroalbuminuria, and the combined endpoint of doubling of serum creatinine, progression to ESRD, new microalbuminuria, or new macroalbuminuria. However, for subjects without malignancy at baseline, there was an increase in the rate of fatal and non-fatal malignancy in the telmisartan group.

In **Trial No. 9.159: PRoFESS** for the primary efficacy outcome measure, the time to first recurrent stroke, there was no significant difference between telmisartan and placebo. There was no significant difference between telmisartan and placebo for the secondary efficacy outcome measures. The inability to detect a significant effect for telmisartan might be explained by more patients randomized to telmisartan "opting out" of concomitant antihypertensive medication (including ACE-I), whilst more patients in the placebo arm "opted in". However, **Trial No. 9.159: PRoFESS** does not provide evidence for efficacy of telmisartan in reducing stroke related morbidity or mortality.

The pooled analysis of data from **Trial No. 502.373 TRANSCEND** and **Trial No. 9.159: PRoFESS** was of limited utility because it appeared to be a post-hoc analysis of a selected sub-group of subjects. Although the analysis produced a statistically significant result for the post-hoc primary composite endpoint, this may relate to the post-hoc selection of the study population and of the primary composite endpoint. This analysis was rejected by the evaluator because of lack of validity.

Safety

The collection and reporting of safety data for the proposed indication was limited to SAEs and AEs leading to withdrawal. The studies did not collect or report all AEs or treatment emergent AEs. The sponsor justified this approach by stating that the safety profile had been established through

the safety data presented in support of the currently registered indications. The safety data presented in the present application was limited to:

Trial No. 502.373 ONTARGET: SAEs, AEs leading to discontinuation of trial medication, clinical laboratory evaluations; vital signs (BP and PR), and ECG. Reporting of AEs was limited to AEs leading to permanent treatment discontinuation and SAEs.

Trial No. 502.373 TRANSCEND: SAEs, AEs leading to discontinuation of trial medication, clinical laboratory evaluations; vital signs (BP and PR), and ECGs.

Trial No. 9.159 PRoFESS: deaths, SAEs, AEs leading to discontinuation of study medication, vital signs, laboratory analyses, waist circumference and ECG.

Safety data from efficacy studies

For ***Trial No. 502.373: ONTARGET***, exposure to treatment medication is summarized in Table 25. Observation time after ceasing treatment is presented in Table 26. The rate of SAEs was similar between the treatments, but the rate of discontinuations due to AEs and SAEs was higher in the telmisartan/ ramipril group than the other two treatment groups. The risk of discontinuing study medication was greater for telmisartan/ ramipril than ramipril RR (95% CI) 1.13 (1.04 to 1.22) and also compared with telmisartan 1.42 (1.30 to 1.56). The risk of discontinuing study medication due to AEs was less for telmisartan than for ramipril; RR (95% CI) 0.79 (0.72 to 0.87). Deaths during the study are discussed in later. Renal failure, hypotension, diarrhoea and hyperkalaemia were more common in the telmisartan/ ramipril group (Table 27). Cough and angioedema were more common in the telmisartan/ ramipril and ramipril groups. Syncope leading to discontinuation was more common in the telmisartan/ ramipril group.

Table 25: Observation time on treatment in the randomised period of the trial / FAS

	On treatment*		
	T/R	**T**	**R**
Number of patients randomised n (%)	8502 (100.0)	8542 (100.0)	8576 (100.0)
Observation time (days)			
Mean (SD)	1444.2 (564.9)	1507.2 (505.5)	1499.4 (516.2)
Median	1635.0	1641.0	1640.0
Observation categories			
≤1 year	158 (1.9)	140 (1.6)	125 (1.5)
1 to ≤2 years	215 (2.5)	214 (2.5)	199 (2.3)
2 to ≤3 years	234 (2.8)	198 (2.3)	239 (2.8)
3 to ≤4 years	271 (3.2)	253 (3.0)	261 (3.0)
4 to ≤5 years	5863 (69.0)	6019 (70.5)	5991 (69.9)
>5 years	1761 (20.7)	1718 (20.1)	1761 (20.5)
Overall patient years	33616	35249	35207

* the observation time on treatment was determined as the time difference between the date of the visit at which the permanent stop of the study medication was recorded and the date of randomisation + 1 day

Table 26: Observation time post-treatment in the randomised period of the trial / FAS

	Post-treatment*		
	T/R	**T**	**R**
Number of patients randomised n (%)	1730 (100.0)	1454 (100.0)	1468 (100.0)
Observation time (days)			
Mean (SD)	1034.9 (564.7)	917.4 (544.0)	960.9 (555.8)
Median	1115.5	898.0	1019.5
Observation categories			
≤1 year	19 (1.1)	14 (1.0)	14 (1.0)
1 to ≤2 years	56 (2.3)	39 (2.7)	48 (3.3)
2 to ≤3 years	60 (3.5)	51 (3.5)	62 (4.2)
3 to ≤4 years	85 (4.9)	64 (4.4)	74 (5.0)
4 to ≤5 years	1069 (61.8)	942 (64.8)	925 (63.0)
>5 years	441 (25.5)	344 (23.7)	345 (23.5)
Overall patient years	4902	3652	3862

* the observation time post-treatment was determined as the time between the date last seen (or vital status confirmed via telephone) and the date of the visit at which the permanent stop of the study medication was recorded + 1 day

The pattern of SAEs leading to death was similar for the three treatment groups (Table 28). In the subgroup of patients with diabetic nephropathy (comprised of 248 patients in the telmisartan/ ramipril group, 288 patients in the telmisartan group, and 238 patients in the ramipril group, a higher proportion of deaths occurred while on treatment (21.77%; 21.53%; 23.11% respectively) as well as post-treatment (30.43%; 35.71%; 40.00% respectively) compared to the overall study population. The overall pattern of SAEs was similar for the three treatment groups (Table 29). The listing of SAEs occurring post-treatment does not indicate differences between the treatment groups in withdrawal effects. In patients with diabetic nephropathy, the rate of SAEs was similar for the three treatment groups: 82.66% for telmisartan/ ramipril, 79.86% for telmisartan, and 78.57% for ramipril. Hypotension, cough, dizziness/vertigo/light headedness, deteriorating renal function and hyperkalaemia were more frequent AEs leading to discontinuation in the telmisartan/ ramipril group (Table 30). Cough was a less frequent AE leading to discontinuation in the telmisartan group.

Table 27: Frequencies of patients with selected SAEs (preferred terms [PTs]) on treatment and AEs for permanent treatment discontinuation during the randomized period / FAS

	T/R			T			R		
	n	**(%)**	**PY**	**n**	**(%)**	**PY**	**n**	**(%)**	**PY**
Randomised	8502	(100.00)		8542	(100.00)		8576	(100.00)	
Renal failure									
SAE on treatment	140	(1.65)	0.42	115	(1.35)	0.33	107	(1.25)	0.30
AEs leading to permanent treatment discontinuation	64	(0.75	0.19	52	(0.61)	0.15	50	(0.58)	0.14
Cough									
SAE on treatment	12	(0.14)	0.04	6	(0.07)	0.02	11	(0.13)	0.03
AEs leading to permanent treatment discontinuation	179	(2.11)	0.53	48	(0.56)	0.14	143	(1.67)	0.41
Angioedema									
SAE on treatment	8	(0.09)	0.02	5	(0.06)	0.01	16	(0.19)	0.05
AEs leading to permanent treatment discontinuation	14	(0.16)	0.04	6	(0.07)	0.02	20	(0.23)	0.06
Hypotension									
SAE on treatment	83	(0.98)	0.25	57	(0.67)	0.16	55	(0.64)	0.16
AEs leading to permanent treatment discontinuation	240	(2.82)	0.71	131	(1.53)	0.37	97	(1.13)	0.28
Syncope									
SAE on treatment	112	(1.32)	0.33	133	(1.56)	0.38	127	(1.48)	0.36
AEs leading to permanent treatment discontinuation	18	(0.21)	0.05	8	(0.09)	0.02	5	(0.06)	0.01
Diarrhoea									
SAE on treatment	45	(0.53)	0.13	39	(0.46)	0.11	32	(0.37)	0.09
AEs leading to permanent treatment discontinuation	30	(0.35)	0.09	16	(0.19)	0.05	9	(0.10)	0.03
Hyperkalaemia									
SAE on treatment	45	(0.53)	0.13	23	(0.27)	0.07	28	(0.33)	0.08
AEs leading to permanent treatment discontinuation	72	(0.85)	0.21	30	(0.35)	0.09	28	(0.33)	0.08

Mean creatinine and potassium levels increased in the telmisartan/ ramipril group compared with the telmisartan group, compared with the ramipril group. Plasma lipid profiles were similar between the three groups. Changes in weight and waist/hip ratios were similar between the three groups. ECG findings were similar for the three groups.

Table 28: Most common SAEs reported in association with death by system organ class (SOC) and PT categorised for patients on treatment during the randomised period (PT in at least 0.1% of patients in any treatment group) / FAS

	On treatment					
	T/R n=8502		**T n=8542**		**R n=8576**	
	%	PY	%	PY	%	PY
Patients with SAEs in association with death	9.17	2.32	8.78	2.13	8.85	2.16
General disorders and administrative site conditions	2.16	0.55	2.46	0.60	2.25	0.55
Sudden cardiac death	1.56	0.40	1.81	0.44	1.64	0.40
Death	0.34	0.09	0.36	0.09	0.33	0.08
Sudden death	0.12	0.03	0.15	0.04	0.13	0.03
Multi-organ failure	0.11	0.03	0.08	0.02	0.12	0.03
Cardiac disorders	2.29	0.58	2.11	0.51	2.18	0.53
Myocardial infarction	1.09	0.28	1.15	0.28	1.07	0.26
Cardiac failure	0.60	0.15	0.36	0.09	0.65	0.16
Ventricular tachyarrhythmia	0.22	0.06	0.22	0,.05	0.16	0.04
Cardiac arrest	0.09	0.02	0.07	0.02	0.02	0.01
Neoplasms benign, malignant and unspecified	1.85	0.47	1.57	0.38	1.59	0.39
Lung neoplasm malignant	0.62	0.01	0.50	0.12	0.56	0.14
Colon cancer	0.21	0.05	0.16	0.04	0.08	0.02
Hepatic neoplasm malignant	0.11	0.03	0.12	0.03	0.09	0.02
Pancreatic carcinoma	0.08	0.02	0.13	0.03	0.10	0.03
Nervous system disorders	0.86	0.22	0.75	0.18	0.83	0.20
Cerebrovascular accident	0.82	0.21	0.66	0.16	0.72	0.16
Infections and infestations	0.55	0.14	0.67	0.16	0.52	0.13
Pneumonia	0.15	0.04	0.26	0.06	0.12	0.03
Sepsis	0.21	0.05	0.16	0.04	0.12	0.03
Respiratory, thoracic and mediastinal disorders	0.45	0.11	0.36	0.09	0.54	0.13
Pulmonary embolism	0.14	0.04	0.09	0.02	0.14	0.03
Respiratory failure	0.11	0.03	0.08	0.02	0.09	0.02
Renal and urinary disorders	0.24	0.06	0.09	0.02	0.16	0.04
Renal failure	0.19	0.05	0.09	0.02	0.13	0.03

Table 29: Frequencies of patients with SAEs on treatment during the randomised period by SOC and PT (PT in at least 1% of patients in any treatment group) / FAS

	T/R n=8502		T n=8542		R n=8576	
	%	PY	%	PY	%	PY
Patients with SAEs	61.96	15.67	64.46	15.62	62.67	15.27
Surgical and medical procedures	26.88	6.80	28.38	6.88	27.66	6.74
Coronary angioplasty	7.13	1.80	7.55	1.83	7.19	1.75
Cataract operation	6.14	1.55	6.61	1.60	6.70	1.63
Angioplasty	4.07	1.03	3.90	0.94	3.70	0.90
Coronary artery bypass	2.82	0.71	3.04	0.74	3.16	0.77
Retinal laser coagulation	2.13	0.54	2.21	0.54	2.34	0.57
Knee arthroscopy	0.86	0.22	1.14	0.28	0.93	0.23
Hip arthroscopy	0.69	0.18	1.07	0.26	0.72	0.18
Cardiac disorders	24.58	6.22	26.75	6.48	25.45	6.20
Angina pectoris	14.18	3.59	15.17	3.68	14.51	3.53
Atrial fibrillation	5.28	1.34	5.84	1.42	5.94	1.45
Myocardial infarction	5.36	1.36	5.62	1.36	5.33	1.30
Cardiac failure	4.83	1.22	5.74	1.39	5.52	1.34
Vascular disorders	11.39	2.88	10.96	2.66	10.95	2.67
Intermittent claudication	8.10	2.05	8.03	1.95	7.66	1.87
Hypertension	1.14	0.29	0.98	0.24	1.10	0.27
Nervous system disorders	9.66	2.44	9.79	2.37	9.93	2.42
Cerebral infarction	2.99	0.76	3.03	0.73	3.16	0.77
Transient ischaemic attack	2.26	0.57	2.14	0.52	2.32	0.57
Cerebrovascular accident	1.69	0.43	1.65	0.40	1.89	0.46
Syncope	1.32	0.33	1.56	0.38	1.48	0.36
Neoplasms benign, malignant and unspecified	8.77	2.22	8.51	2.06	8.22	2.00
Prostate cancer	1.55	0.39	1.59	0.39	1.39	0.34
Lung neoplasm malignant	1.29	0.33	1.19	0.29	1.27	0.31
Skin cancer	1.08	0.27	1.17	0.28	1.19	0.29
Infections and infestations	8.14	2.06	8.10	1.96	8.52	2.08
Pneumonia	3.20	0.81	3.63	0.88	3.24	0.79
Metabolism and nutrition disorders	7.10	1.80	7.63	1.85	7.25	1.77
Diabetes mellitus	3.58	0.90	4.61	1.12	4.21	1.03
Hyperglycaemia	1.43	0.36	1.56	0.38	1.54	0.37
Renal and urinary disorders	5.45	1.38	4.89	1.19	4.63	1.13
Diabetic nephropathy	2.26	0.57	2.12	0.51	2.10	0.51
Renal failure	1.65	0.42	1.35	0.33	1.25	0.30
General disorders and administrative site conditions	5.00	1.26	4.95	1.20	4.71	1.15

Sudden cardiac death	1.58	0.40	1.81	0.44	1.64	0.40
Chest pain	1.38	0.35	1.12	0.27	1.20	0.29
Skin and subcutaneous tissue disorders	3.89	0.98	4.23	1.02	4.47	1.09
Skin ulcer	3.35	0.85	3.68	0.89	3.74	0.91
Diabetic ulcer	1.27	0.32	1.42	0.34	1.33	0.32
Investigations	4.02	1.02	4.49	1.02	3.71	0.90
Angiogram	1.00	0.25	0.92	0.22	0.84	0.20
Injury, poisoning and procedural complications	3.76	0.95	3.99	0.97	3.86	0.94
Fall	1.14	0.29	1.16	0.28	1.14	0.28
Blood and lymphatic system disorders	1.91	0.48	2.07	0.50	1.82	0.44
Anaemia	1.47	0.37	1.83	0.44	1.53	0.37

Table 30: Overview of AEs leading to permanent treatment discontinuation during the randomised period (in at least 0.1% of patients in any treatment group) / FAS

	T/R n=8502		**T n=8542**		**R n=8576**	
	%	PY	%	PY	%	PY
Patients with AEs leading to permanent treatment discontinuation	12.39	3.43	8.19	1.99	8.73	2.13
Hypotension/low blood pressure	2.82	0.71	1.53	0.37	1.13	0.28
Cough	2.11	0.53	0.56	0.14	1.67	0.41
Dizziness/vertigo/lightheadedness	1.59	0.40	0.73	0.18	0.50	0.12
Hospitalisation	0.56	0.14	0.76	0.18	0.69	0.17
Renal impairment/failure/artery stenosis/nephropathy/kidney disease/haemodialysis	0.75	0.19	0.61	0.15	0.58	0.14
Increase in K (potassium)/hyperkalaemia	0.85	0.21	0.35	0.09	0.33	0.08
Hypertension/higher blood pressure/uncontrolled high BP	0.42	0.11	0.59	0.14	0.48	0.12
Increase in creatinine	0.68	0.17	0.39	0.09	0.27	0.07
fatigue/weakness/lethargy/hypotonia	0.61	0.15	0.41	0.10	0.27	0.07
Cancer	0.45	0.11	0.26	0.06	0.48	0.12
Eczema/rash/itch/allergies/dermatitis	0.39	0.10	0.25	0.06	0.38	0.09
Other pain/myalgia/arthritis pain/back pain/joint pain	0.28	0.07	0.30	0.07	0.33	0.08
Unwell/malaise/discomfort/flu symptoms/cold	0.46	0.12	0.18	0.04	0.24	0.06
Stroke/TIA/cerebrovascular accident	0.18	0.04	0.25	0.06	0.27	0.07
Nausea/vomiting	0.27	0.07	0.20	0.05	0.20	0.05
Diarrhoea	0.35	0.09	0.19	0.05	0.10	0.03
Cephalgia/headache	0.39	0.10	0.08	0.02	0.13	0.03
CHF/heart failure/heart insufficiency/cardiac insufficiency	0.18	0.04	0.26	0.06	0.15	0.04
Abdominal discomfort, pain, upset/GI irritation/GI syndrome	0.27	0.07	0.13	0.03	0.14	0.03
MI	0.07	0.02	0.29	0.07	0.12	0.03
Dementia/cognitive impairment or decline/memory loss	0.13	0.03	0.19	0.05	0.16	0.04

Angioedema	0.16	0.04	0.07	0.02	0.23	0.06
Syncope/passed out	0.21	0.05	0.09	0.02	0.06	0.01
CABG	0.11	0.03	0.11	0.03	0.14	0.03
Surgery	0.08	0.02	0.13	0.03	0.12	0.03
Visual disturbance/blurred vision/problems with eye	0.16	0.04	0.07	0.02	0.05	0.01
Angina	0.11	0.03	0.08	0.02	0.07	0.02
Depression	0.06	0.01	0.12	0.03	0.03	0.01
Increase in laboratory values (general, not specified)	0.11	0.03	0.02	0.01	0.05	0.01

For ***Trial No. 502.373 TRANSCEND***, exposure to study treatment is summarised in Table 31. The overall exposure to telmisartan was 12349 patient years. A total of 2831 subjects were exposed to telmisartan for a duration of greater than 2 years. The proportion of subjects that died was slightly higher in the telmisartan group, as were the proportions of subjects that discontinued study medication because of SAEs and AEs. However, overall the percentage of patients who permanently stopped taking study medication was 17.7% in the telmisartan group and 19.4% in the placebo group: RR (95% CI) telmisartan vs. placebo was 0.91 (95% CI 0.82, 1.02). With regard to the AEs usually associated with ACE-I, there was a higher rate of renal failure, hypotension, syncope, diarrhoea and hyperkalaemia in the telmisartan group, but not of cough or angioedema (Table 32).

Table 31: Observation time on treatment in the randomised period of the trial / FAS

	On treatment	
	Telmisartan	**Placebo**
Number of patients randomised n (%)	2954 (100.0)	2972 (100.0)
Observation time (days)		
Mean (SD)	1526.9 (544.4)	1515.2 (548.2)
Median	1651.5	1644.0
≤1 year	57 (1.9)	58 (2.0)
1 to ≤2 years	66 (2.2)	64 (2.2)
2 to ≤3 years	85 (2.9)	84 (2.8)
3 to ≤4 years	246 (8.3)	263 (8.8)
4 to ≤5 years	1239 (41.9)	1211 (40.7)
5 to ≤6 years	1224 (41.4)	1252 (42.1)
>6 years	37 (1.3)	40 (1.3)
Overall patient years	12349	12329

The increased risk was statistically significant for hypotension, syncope, diarrhoea and renal dysfunction. The pattern of SAEs leading to death appears to be similar for the two treatment groups (Table 33). The pattern of SAEs was similar for the two groups, but the rate of blood and lymphatic disorders appears to be higher in the telmisartan group (Table 34). The rate of malignancy was higher in the telmisartan group. With regard to AEs leading to discontinuation: hypotension, renal failure and hyperkalaemia were more common in the telmisartan group; whilst hypertension was more common in the placebo (Table 35). There was an increase in mean serum

creatinine and potassium from baseline in the telmisartan group. There were 42 (1.4%) subjects in the telmisartan group and 35 (1.2%) in the placebo with serum creatinine ≥2.0 x ULN at some stage during the randomization or post-treatment phases. Serum lipids were similar for the two groups over time. There were no changes in waist-hip ratios during the study for either treatment group. The proportion of subjects developing ECG evidence of LVH during the study was greater in the placebo group than the telmisartan.

Table 32: Frequencies of patients with selected SAEs (PTs) on treatment and AEs leading to permanent treatment discontinuation during the randomised period /FAS

	Telmisartan			**Placebo**		
	n	**%**	**PY**	**n**	**%**	**PY**
Randomised	2954	100.00		2972	100.00	
Renal failure						
SAE on treatment	23	0.78	0.19	19	0.64	0.15
AEs leading to permanent treatment discontinuation	19	0.64	0.15	11	0.37	0.09
Cough						
SAE on treatment	1	0.03	0.01	4	0.13	0.03
AEs leading to permanent treatment discontinuation	13	0.44	0.11	12	0.13	0.03
Angioedema						
SAE on treatment	1	0.03	0.01	1	0.03	0.01
AEs leading to permanent treatment discontinuation	2	0.07	0.02	3	0.10	0.02
Hypotension						
SAE on treatment	15	0.51	0.12	13	0.44	0.11
AEs leading to permanent treatment discontinuation	21	0.71	0.17	11	0.37	0.09
Syncope						
SAE on treatment	31	1.05	0.25	19	0.64	0.15
AEs leading to permanent treatment discontinuation	1	0.03	0.01	0	0.0	0
Diarrhoea						
SAE on treatment	12	0.41	0.10	3	0.10	0.02
AEs leading to permanent treatment discontinuation	7	0.24	0.06	2	0.07	0.02
Hyperkalaemia						
SAE on treatment	7	0.24	0.06	3	0.10	0.02
AEs leading to permanent treatment discontinuation	10	0.34	0.08	0	0.0	0

Table 33: Most common SAEs reported in association with death by SOC and PT for patients on treatment during the randomised period (PT in at least 3 patients [0.1%] in either treatment group) / FAS

	On treatment			
	Telmisartan n=2954		**Placebo n=2972**	
	%	PY	%	PY
Patients with SAEs in association with death	9.61	2.30	8.95	2.16
General disorders and administrative site conditions	2.84	0.68	2.73	0.66
Sudden cardiac death	2.34	0.56	2.25	0.54
Death	0.37	0.09	0.27	0.06
Sudden death	0.03	0.01	0.10	0.02
Cardiac disorders	2.47	0.59	2.19	0.53
Myocardial infarction	1.18	0.28	1.18	0.28
Cardiac failure	0.91	0.22	0.64	0.15
Ventricular tachyarrhythmia	0.20	0.05	0.03	0.01
Cardiac arrest	0.10	0.02	0.10	0.02
Neoplasms benign, malignant and unspecified	1.59	0.38	1.58	0.38
Lung neoplasm malignant	0.58	0.14	0.44	0.11
Pancreatic carcinoma	0.14	0.03	0.17	0.04
Breast cancer	0.07	0.02	0.17	0.04
Colon cancer	0.14	0.03	0.10	0.02
Hepatic neoplasm malignant	0.14	0.03	0.10	0.02
Prostate cancer	0.10	0.02	0.00	0.00
Nervous system disorders	0.64	0.15	0.64	0.15
Cerebrovascular accident	0.58	0.14	0.61	0.15
Infections and infestations	0.71	0.17	0.54	0.13
Pneumonia	0.27	0.06	0.17	0.04
Sepsis	0.24	0.06	0.10	0.02
Septic shock	0.10	0.02	0.07	0.02
Respiratory, thoracic and mediastinal disorders	0.44	0.11	0.50	0.12
Respiratory failure	0.14	0.03	0.10	0.02
Pulmonary embolism	0.14	0.03	0.07	0.02
Psychiatric disorders	0.14	0.03	0.0	0.00
Renal failure	0.14	0.03	0.0	0.00

Table 34: Frequencies of patients with SAEs on treatment during the randomised period by SOC and PT (PT in at least 30 patients [1%] in either treatment group) / FAS

	Telmisartan n=2954		**Placebo n=2972**	
	%	PY	%	PY
Patients with SAEs	60.29	14.42	61.57	14.84
Cardiac disorders	24.51	5.86	26.62	6.42
Angina pectoris	14.15	3.38	15.31	3.69
Cardiac failure	5.96	1.43	5.82	1.40
Myocardial infarction	4.67	1.12	5.42	1.31
Atrial fibrillation	4.94	1.18	5.01	1.21
Surgical and medical procedures	22.27	5.33	24.09	5.81
Coronary angioplasty	6.70	1.60	7.10	1.71
Cataract operation	4.91	1.17	5.32	1.28
Coronary artery bypass	2.67	0.64	2.79	0.67
Angioplasty	2.40	0.57	2.29	0.55
Retinal laser coagulation	1.32	0.32	1.21	0.29
Knee arthroscopy	0.95	0.23	1.01	0.24
Metabolism and nutrition disorders	9.34	2.24	10.46	2.52
Diabetes mellitus	6.60	1.58	8.04	1.94
Hyperglycaemia	1.35	0.32	1.58	0.38
Vascular disorders	9.68	2.32	8.65	2.08
Intermittent claudication	6.70	1.60	5.65	1.36
Hypertension	1.12	0.27	1.41	0.34
Nervous system disorders	8.97	2.15	8.95	2.16
Cerebral infarction	2.78	0.66	3.13	0.75
Transient ischaemic attack	1.93	0.46	2.02	0.49
Cerebrovascular accident	1.73	0.41	1.78	0.43
Syncope	1.05	0.25	0.64	0.15
Infections and infestations	8.97	2.15	7.97	1.92
Pneumonia	3.35	0.80	3.26	0.79
Urinary tract infection	1.05	0.25	0.87	0.21
Neoplasms benign, malignant and unspecified	7.41	1.77	6.43	1.55
Prostate cancer	1.15	0.28	0.81	0.19
Lung neoplasm malignant	1.02	0.24	0.77	0.19
General disorders and administrative site conditions	5.08	1.21	4.74	1.14
Sudden cardiac death	2.34	0.56	2.29	0.55
Chest pain	1.29	0.56	0.87	0.21

Table 35: Overview of AEs leading to permanent treatment discontinuation during the randomised period (in at least 6 patients [0.2%] in either treatment group) / FAS

	Telmisartan n=2954		**Placebo n=2972**	
	%	PY	%	PY
Patients with AEs leading to permanent treatment discontinuation	12.39	3.43	8.19	1.99
Hypotension/low blood pressure	2.82	0.71	1.53	0.37
Cough	2.11	0.53	0.56	0.14
Dizziness/vertigo/lightheadedness	1.59	0.40	0.73	0.18
Hospitalisation	0.56	0.14	0.76	0.18
Renal impairment/failure/artery stenosis/nephropathy/kidney disease/haemodialysis	0.75	0.19	0.61	0.15
Increase in K (potassium)/hyperkalaemia	0.85	0.21	0.35	0.09
Hypertension/higher blood pressure/uncontrolled high BP	0.42	0.11	0.59	0.14
Increase in creatinine	0.68	0.17	0.39	0.09
fatigue/weakness/lethargy/hypotonia	0.61	0.15	0.41	0.10
Cancer	0.45	0.11	0.26	0.06
Eczema/rash/itch/allergies/dermatitis	0.39	0.10	0.25	0.06
Other pain/myalgia/arthritis pain/back pain/joint pain	0.28	0.07	0.30	0.07
Unwell/malaise/discomfort/flu symptoms/cold	0.46	0.12	0.18	0.04
Stroke/TIA/cerebrovascular accident	0.18	0.04	0.25	0.06
Nausea/vomiting	0.27	0.07	0.20	0.05
Diarrhoea	0.35	0.09	0.19	0.05
Cephalgia/headache	0.39	0.10	0.08	0.02
CHF/heart failure/heart insufficiency/cardiac insufficiency	0.18	0.04	0.26	0.06
Abdominal discomfort, pain, upset/GI irritation/GI syndrome	0.27	0.07	0.13	0.03
MI	0.07	0.02	0.29	0.07
Dementia/cognitive impairment or decline/memory loss	0.13	0.03	0.19	0.05
Angioedema	0.16	0.04	0.07	0.02
Syncope/passed out	0.21	0.05	0.09	0.02
CABG	0.11	0.03	0.11	0.03
Surgery	0.08	0.02	0.13	0.03
Visual disturbance/blurred vision/problems with eye	0.16	0.04	0.07	0.02
Angina	0.11	0.03	0.08	0.02
Depression	0.06	0.01	0.12	0.03
Increase in laboratory values (general, not specified)	0.11	0.03	0.02	0.01

For ***Trial No. 9.159: PRoFESS***, exposure to telmisartan is summarised in Table 36. There was a slightly higher rate of SAEs and AEs leading to discontinuation in the telmisartan group. The death rate was similar for the two treatment groups: 738 (7.4%) subjects in the telmisartan group and 725 (7.2%) in the placebo. Although the proportion of subjects with SAEs was higher in the telmisartan group, the pattern of SAEs was similar for the two treatment groups (Table 37). There were more SAEs associated with hyperkalaemia in the telmisartan group: 15 (0.1%) subjects compared with four in the placebo. There were more SAEs associated with hypotension in the telmisartan group 161 (1.6%) subjects, compared with 127 (1.3%) in the placebo group. Acute renal failure was more common in the telmisartan group: 71 (0.7%) subjects, compared with 37 (0.4%) in the placebo group. There were four subjects with SAEs associated with angioedema in the telmisartan group, and two in the placebo. The number of subjects with haemorrhagic events was similar for the two treatment groups: 385 (3.8%) for telmisartan and 399 (3.9%).

There were more subjects with an AE leading to discontinuation in the telmisartan group: 1450 (14.5%) subjects, compared with 1127 (11.2%) in the placebo group (Table 38). Hypotension, dizziness, syncope and orthostatic hypotension were reported more commonly in the telmisartan group as AEs leading to discontinuation. Altogether, 4.1% of the telmisartan group, compared with 1.9% of the placebo, ceased medication because of AEs related to hypotension. Acute renal failure leading to discontinuation was more common in the telmisartan group.

Table 36: Exposure to study medication (telmisartan or placebo), for Trial No. 9.159: PRoFESS

	Telmisartan	**Placebo**
Number of patients exposed	10019	10053
Duration of treatment exposure (days)		
Mean (±SD)	714.4 (±402.0)	738 (±388.7)
Median (minimum, maximum)	766 (1, 1554)	783 (1, 1542)
Time categories, n (%)		
<3 months	1328 (13.3)	1120 (11.1)
3 to 6 months	404 (4.0)	359 (3.6)
>6 months to <1 year	553 (5.5)	538 (5.4)
1 to ≤2 years	2387 (23.8)	2426 (24.1)
>2 to ≤3 years	3686 (36.8)	3888 (38.7)
>3 to ≤4 years	1581 (15.8)	1637 (16.3)
>4 years	80 (0.8)	85 (0.8)
Overall patient years	19596	20312

Table 37: Incidence of the most frequent SAEs during the treatment period with a frequency ≥1% in any treatment group, by SOC and PT, sorted by frequency in the telmisartan treatment arm (telmisartan or placebo)

	Telmisartan n (%)	**Placebo n (%)**
Number of patients treated	10019 (100.0)	10053 (100.0)
Patients with SAEs	2474 (24.7)	2374 (23.6)
Infections and infestations	479 (4.8)	443 (4.4)
Pneumonia	141 (1.4)	142 (1.4)
Cardiac disorders	438 (4.4)	402 (4.0)
Atrial fibrillation	104 (1.0)	90 (0.9)
Nervous system disorders	433 (4.3)	397 (3.9)
Injury, poisoning and procedural complications	313 (3.1)	303 (3.0)
Fall	83 (0.8)	111 (1.1)
Gastrointestinal disorders	293 (2.9)	285 (2.8)
General disorders and administrative site conditions	276 (2.8)	250 (2.5)
Neoplasms benign, malignant and unspecified	273 (2.7)	297 (3.0)
Musculoskeletal and connective tissue disorders	197 (2.0)	186 (1.9)
Metabolism and nutrition disorders	178 (1.8)	153 (1.5)
Respiratory, thoracic and mediastinal disorders	164 (1.6)	158 (1.6)
Vascular disorders	163 (1.6)	152 (1.5)
Renal and urinary disorders	157 (1.6)	130 (1.3)
Psychiatric disorders	100 (1.0)	95 (0.9)

There was an increase in mean serum potassium, but not in mean creatinine, in the telmisartan group compared with placebo. Mean SBP and DBP decreased in both treatment groups during the study, but to a slightly greater extent in the telmisartan group. ECG findings were similar for the two treatment groups. Mean (SD) change from baseline in waist circumference was 0.9 (9.3) cm in the telmisartan group, compared with 0.7 (9.4) cm in the placebo.

Table 38: Overview of adverse events leading to permanent discontinuation of telmisartan (or placebo) study medication with an overall incidence of ≥1% in any treatment group during the treatment period, by SOC and PT, sorted by frequency in the telmisartan treatment arm (telmisartan comparison)

	Telmisartan n (%)	**Placebo n (%)**
Number of patients treated	10019 (100.0)	10053 (100.0)
Patients with an AE leading to permanent discontinuation	1450 (14.5)	1127 (11.2)
Nervous system disorders	399 (4.0)	309 (3.1)
Headache	231 (2.3)	203 (2.0)
Dizziness	132 (1.3)	89 (0.9)
Gastrointestinal disorders	310 (3.1)	249 (2.5)
Nausea	104 (1.0)	72 (0.7)
Vascular disorders	304 (3.0)	120 (1.2)
Hypotension	250 (2.5)	85 (0.9)
Cardiac disorders	150 (1.5)	137 (1.4)
General disorders and administrative site conditions	101 (1.0)	79 (0.8)

Safety data from bioequivalence studies

For ***Trial No. 1236.5***, 55 (65.5%) subjects reported at least one AE (Table 39). The most frequently reported AEs were headache (32.1%), fatigue (28.6%), dizziness (21.4%), nausea (9.5%), diarrhoea (8.3%), and somnolence (6.0%). There were no deaths or SAEs. One subject had elevated creatinine, none had elevated potassium. Blood pressure and pulse rate decreased with all three treatments.

In ***Trial No. 1236.6***, 33 (78.6%) subjects experienced at least one AE during the study. Twenty (47.6%) subjects experienced AEs during telmisartan alone, nine (22.0%) during ramipril alone, and 16 (39.0%) during combination. The commonest AEs were headache, dizziness and postural dizziness (Table 40). There were no SAEs or deaths reported. One subject discontinued because of an AE during the first run-in period with ramipril: flushing. Two subjects in the co-administration group had elevated serum potassium: 6.20 mmol/L and 5.54 mmol/L. There were no other clinically significant laboratory abnormalities. All three treatments resulted in clinically significant decreases in SBP and DBP.

Table 39: Adverse events occurring in at least 2 subjects, by primary system organ class and preferred term, sorted by overall incidence

System Organ Class	**FDC**	**Mic + Alt**	**Mic + Del**	**Total treated**
Preferred term	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Number of subjects	83 (100.0)	84 (100.0)	82 (100.0)	84 (100.0)
Total with AEs	26 (31.3)	37 (44.0)	31 (37.8)	55 (65.5)
Nervous system disorders	17 (20.5)	23 (27.4)	22 (26.8)	40 (47.6)
Headache	14 (16.9)	15 (17.9)	14 (17.1)	27 (32.1)
Dizziness	3 (3.6)	10 (11.9)	9 (11.0)	18 (21.4)
Somnolence	0	4 (4.8)	1 (1.2)	5 (6.0)
Paraesthesia	1 (1.2)	0	1 (1.2)	2 (2.4)
General disorders and administrative site conditions	9 (10.8)	11 (13.1)	8 (9.8)	25 (29.8)
Fatigue	8 (9.6)	10 (11.9)	8 (9.8)	24 (28.6)
Peripheral coldness	1 (1.2)	1 (1.2)	0	2 (2.4)
Gastrointestinal disorders	4 (4.8)	9 (10.7)	7 (8.5)	14 (16.7)
Nausea	0	4 (4.8)	6 (7.3)	8 (9.5)
Diarrhoea	3 (3.6)	4 (4.8)	3 (3.7)	7 (8.3)
Stomach discomfort	1 (1.2)	1 (1.2)	0	2 (2.4)
Vomiting	0	1 (1.2)	2 (2.4)	2 (2.4)
Infections and infestations	2 (2.4)	2 (2.4)	2 (2.4)	6 (7.1)
Nasopharyngitis	1 (1.2)	1 (1.2)	1 (1.2)	3 (3.6)
Rhinitis	1 (1.2)	1 (1.2)	0	2 (2.4)
Respiratory, thoracic and mediastinal disorders	1 (1.2)	0	3 (3.7)	4 (4.8)
Pharyngolaryhgeal pain	1 (1.2)	0	3 (3.7)	4 (4.8)
Skin and subcutaneous tissue disorders	1 (1.2)	1 (1.2)	0	2 (2.4)
Psychiatric disorders	1 (1.2)	1 (1.2)	0	2 (2.4)
Vascular disorders	0	1 (1.2)	1 (1.2)	2 (2.4)
Phlebitis	0	1 (1.2)	1 (1.2)	2 (2.4)

Mic = telmisartan, Del = ramipril, Mic + Del = temisartan + ramipril

Table 40: Summary of the most frequently reported AEs by treatment at onset and MedDRA preferred term (only AEs experienced by more than 5% of all subjects are listed)

AE by preferred term	Mic N (%)	Del N (%)	Mic+Del N (%)	r-i Del N (%)	r-i Mic+Del N (%)	w-o Mic N (%)	w-o Del N (%)	w-o Mic+Del N (%)	Total N (%)
No. of subjects treated (=100%)	42	41	41	41	42	42	41	41	42
Subjects with any AEs	20 (47.6)	9 (22.0)	16 (39.0)	4 (9.8)	8 (19.0)	8 (19.0)	3 (7.3)	4 (9.8)	33 (78.6)
Headache	9 (21.4)	3 (7.3)	2 (4.9)	3 (7.3)	4 (9.5)	4 (9.5)	1 (2.4)	0	18 (42.9)
Dizziness	3 (7.1)	2 (4.9)	4 (9.8)	0	0	0	0	0	9 (21.4)
Dizziness postural	0	1 (2.4)	2 (4.9)	0	1 (2.4)	0	0	0	4 (9.5)
Cough	1 (2.4)	2 (4.9)	3 (7.3)	0	1 (2.4)	1 (2.4)	0	0	5 (11.9)
Nasopharyngitis	1 (2.4)	0	0	0	0	1 (2.4)	0	2 (4.9)	4 (9.5)
Nausea	2 (4.8)	0	1 (2.4)	1 (2.4)	0	0	0	0	3 (7.1)
Fatigue	3 (7.1)	0	0	0	0	0	0	0	3 (7.1)

Mic = telmisartan, Del = ramipril, Mic + Del = temisartan + ramipril, r-I = run-in phase, w-o = wash-out phase

Safety data from pooled analyses

Report No. U08-2025-01 was a summary of safety data from all studies, other than the ONTARGET and TRANSCEND studies, conducted in support of the indication: the reduction of risk for major cardiovascular events such as cardiovascular death, myocardial infarction, stroke, and hospitalisation for congestive heart failure. The data included the data from those patients in the PRoFESS study who received at least one dose of telmisartan or matching placebo. The report did not appear to cover any additional studies. The analyses mirrored those in Report No. U08-3667-01 and did not appear to include any additional data.

The sponsor's Integrated Summary of Safety did not report any pooled analyses. The data from the clinical studies were presented in the same format as the study reports and, as would be expected, with less detail.

It is stated in the Integrated Summary of Safety that: "In ONTARGET, TRANSCEND study drug discontinuations of less than 5 days were not recorded, in the PRoFESS study discontinuations of less than 28 days were not recorded. The 6-monthly visit frequency did not allow an assessment of withdrawal and rebound phenomena."

Summary of Safety

For **Trial No. 502.373: ONTARGET** the rate of discontinuations due to AEs and SAEs was higher in the telmisartan/ ramipril group than the other two treatment groups; and renal failure, hypotension, diarrhoea and hyperkalaemia were more common in the telmisartan/ ramipril group. Syncope leading to discontinuation was more common in the telmisartan/ ramipril group. Mean creatinine and potassium levels increased to in the telmisartan/ ramipril group compared with the telmisartan group, compared with the ramipril group. It is not clear whether these findings indicate a pharmacodynamic interaction between telmisartan and ramipril, or result from the pharmacokinetic interaction. The pharmacokinetic interaction has been demonstrated in Trial No. 1236.6 to lead to around 50% greater exposure to ramiprilat.

However, **Trial No. 502.373: ONTARGET** indicates a lower rate of cough and angioedema with telmisartan compared with ramipril.

In **Trial No. 502.373 TRANSCEND**, compared to placebo the proportion of subjects that died, and the proportions of subjects that discontinued study medication because of SAEs and AEs, were slightly higher in the telmisartan group. With telmisartan there was a higher rate of renal failure, hypotension, syncope, diarrhoea and hyperkalaemia in the telmisartan group, but not of cough or angioedema. The rate of malignancy was higher in the telmisartan group. There was an increase in mean serum creatinine and potassium from baseline in the telmisartan group.

In **Trial No. 9.159: PRoFESS**, compared to placebo there was also a slightly higher rate of SAEs and AEs leading to discontinuation in the telmisartan group. SAEs associated with hyperkalaemia, hypotension and acute renal failure were more common in the telmisartan group. Hypotension, dizziness, syncope, orthostatic hypotension and acute renal failure were reported more commonly in the telmisartan group as AEs leading to discontinuation.

No additional safety data or analyses were presented in the pooled analysis of safety data.

Clinical Summary and Conclusions

There are sufficient data contained in the submission to demonstrate that telmisartan is no worse than ramipril for prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes. Ramipril has previously been demonstrated (in the HOPE Study) to be superior to placebo for this indication in this patient group. In patients that tolerate ACE-I it would have been difficult, if not unethical, to have conducted a long term placebo controlled trial of telmisartan for this indication.

However the wording used in the proposed indication "*high risk for cardiovascular disease"* is vague and does not adequately describe the population included in the efficacy studies of telmisartan. It would be more appropriate to describe this population as *"patients 55 years and older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes"*. The data presented in the submission are sufficient to demonstrate efficacy for the alternative indication of: *prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes*.

The results of **Trial No. 502.373: ONTARGET** demonstrated non-inferiority for telmisartan versus ramipril. The margin for non-inferiority was clinically significant: a no more than 13% increase in risk with telmisartan compared with ramipril. The patient group studied was relevant to the proposed indication: patients at high risk of developing a major CV event. The treatment duration was appropriate given the likely long-term nature of the treatment (treatment duration was for 3.5 to 5.5 years). For UACR there was a benefit for telmisartan, with the ramipril group having the greatest increase over time, indicating a beneficial effect for the combined treatment and telmisartan.

Telmisartan was not demonstrated to be superior to placebo for the requested indication in patients intolerant of ACE-Is. In **Trial No. 502.373: TRANSCEND** for the primary efficacy outcome measure there was no significant difference between telmisartan and placebo. Use of beta-blockers and diuretics increased in the placebo group relative to telmisartan and this could have obscured a beneficial effect for telmisartan. For the composite of CV death, non-fatal MI, and non-fatal stroke, there was a benefit for telmisartan which was of marginal statistical significance and of a lesser magnitude than the benefit of ramipril in the HOPE study. In the telmisartan group there were lower rates of subjects with new microalbuminuria, new macroalbuminuria, and the combined endpoint of doubling of serum creatinine, progression to ESRD, new microalbuminuria, or new

macroalbuminuria. However, for subjects without malignancy at baseline, there was an increase in the rate of fatal and non-fatal malignancy in the telmisartan group.

In **Trial No. 9.159: PRoFESS** for the primary efficacy outcome measure, the time to first recurrent stroke, there was no significant difference between telmisartan and placebo. There was no significant difference between telmisartan and placebo for the secondary efficacy outcome measures. The inability to detect a significant effect for telmisartan might be explained by more patients randomized to telmisartan "opting out" of concomitant antihypertensive medication (including ACE-I), whilst more patients in the placebo arm "opted in". However, **Trial No. 9.159: PRoFESS** does not provide evidence for efficacy of telmisartan in reducing stroke related morbidity or mortality.

The safety profile of telmisartan was similar to that for ramipril except that in **Trial No. 502.373: ONTARGET** there was a lower rate of cough and angioedema with telmisartan. However, renal function appeared to deteriorate to a greater extent in the telmisartan treated groups.

In **Trial No. 502.373 TRANSCEND**, compared to placebo the proportion of subjects that died, and the proportions of subjects that discontinued study medication because of SAEs and AEs, were slightly higher in the telmisartan group. With telmisartan there was a higher rate of renal failure, hypotension, syncope, diarrhoea and hyperkalaemia in the telmisartan group, but not of cough or angioedema. The rate of malignancy was higher in the telmisartan group. There was an increase in mean serum creatinine and potassium from baseline in the telmisartan group.

In **Trial No. 9.159: PRoFESS**, compared to placebo there was also a slightly higher rate of SAEs and AEs leading to discontinuation in the telmisartan group. SAEs associated with hyperkalaemia, hypotension and acute renal failure were more common in the telmisartan group. Hypotension, dizziness, syncope, orthostatic hypotension and acute renal failure were reported more commonly in the telmisartan group as AEs leading to discontinuation.

Co-administration of telmisartan and ramipril should be discouraged. **Trial No. 502.373: ONTARGET** indicated no significant benefit for the telmisartan/ ramipril combination over telmisartan. The 16% drop in telmisartan AUC resulting from co-administration with ramipril is unlikely to have influenced this result. However, there was an increase in SAEs and AEs leading to discontinuation when telmisartan was co-administered with ramipril. The rate of discontinuations due to AEs and SAEs was higher in the telmisartan/ ramipril group than the other two treatment groups; and renal failure, hypotension, diarrhoea and hyperkalaemia were more common in the telmisartan/ ramipril group. Syncope leading to discontinuation was more common in the telmisartan/ ramipril group. Mean creatinine and potassium levels increased to in the telmisartan/ ramipril group compared with the telmisartan group, compared with the ramipril group. The combined telmisartan / ramipril group had the greatest deterioration in renal function over time compared with telmisartan and ramipril alone. It is not clear whether these findings indicate a pharmacodynamic interaction between telmisartan and ramipril, or result from the pharmacokinetic interaction. The pharmacokinetic interaction has been demonstrated in ***Trial No. 1236.6*** to lead to around 50% greater exposure to ramiprilat. Co-administration of ramipril should be listed as a contraindication to telmisartan.

Trial No. 1236.5 demonstrated bioequivalence for Altace and Delix when administered as a single dose concurrently with Micardis. **Trial No. 1236.6** demonstrated that at steady state co-administration on telmisartan and ramipril results in a decrease in telmisartan AUC of 16%, an increase in ramipril AUC of 100% and an increase in ramiprilat AUC of 47%. This would be expected to increase the effect of ramipril and decrease the effect of telmisartan during co-administration.

Deficiencies in the Submission

The safety data did not present all AEs but instead only presented SAEs, AEs leading to discontinuation and AEs of special interest. This means that the safety data for the indication applied for in the submission is incomplete. The justification for not reporting all AEs in the clinical trials was that the adverse event profile for telmisartan is well known.

However, the AE profile of telmisartan is not well described in the population of patients for which the proposed indication applies. This patient group might be susceptible to higher rates of AEs, or alternatively might have a different AE profile for telmisartan. The sponsor should provide a listing of all AEs (or alternatively all treatment emergent AEs) and all SAEs (or alternatively all treatment emergent SAEs) for ***Trial No. 502.373 ONTARGET***, ***Trial No. 502.373 TRANSCEND*** and ***Trial No. 9.159 PRoFESS***.

Neither the sponsor's Integrated Summary of Safety nor ***Report No. U08-2025-01*** presented pooled analyses of all the safety data collected in support of the present application. This represents a missed opportunity to detect signals of rarer AEs. The sponsor should provide a pooled analysis of the safety data from all the studies performed in support of the present application.

It is stated in the Integrated Summary of Safety that: "In ONTARGET, TRANSCEND study drug discontinuations of less than 5 days were not recorded, in the PRoFESS study discontinuations of less than 28 days were not recorded. The 6-monthly visit frequency did not allow an assessment of withdrawal and rebound phenomena."

Recommendations

The evaluator recommended that the present application should be rejected because of insufficient data to demonstrate the safety profile of telmisartan for the proposed indication. However, there are sufficient data contained in the submission to demonstrate that telmisartan is no worse than ramipril for prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes.

The proposed indication, as presently worded, is too vague in identifying the target patient group. Hence, the evaluator recommended rejecting the indication:

Prevention of cardiovascular morbidity and mortality in patients 55 years or older at high risk for cardiovascular disease.

However, if the sponsor provides adequate safety data, the efficacy data presented in the submission are sufficient to demonstrate efficacy for the alternative indication of: *prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes*.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There is no requirement for a quality evaluation in an application of this type.

Nonclinical

There is no requirement for a nonclinical evaluation in an application of this type.

Clinical

The clinical evaluator has recommended rejection of the application because of insufficient data to demonstrate the safety profile of telmisartan for the proposed indication. However, the evaluator was of the opinion that there were sufficient data to demonstrate that telmisartan is no worse than ramipril for prevention of cardiovascular mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes. The clinical evaluator was also of the opinion that the indication, as presently worded, was too vague in identifying the target patient group. The clinical evaluator further recommended that, if the sponsor were able to submit adequate safety data, then alternative suitable wording for the proposed indication would be:

Prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes.

Pharmacokinetics

Trial No. 1236.5 was an open-label, randomised, single-dose, three way crossover bioequivalence study whose aim was to demonstrate bioequivalence between the fixed-dose combination of telmisartan 80 mg/ramipril 10 mg with Micardis (telmisartan 80 mg) and Altace (the US-registered formulation of ramipril 10 mg) given separately and Micardis (telmisartan 80 mg) and Delix (the commercially available formulation of ramipril 10 mg in Europe) also given separately. A total of 84 subjects, all healthy volunteers, were enrolled and 82 completed. Bioequivalence was demonstrated for Altace and Delix when administered as single doses concurrently with Micardis.

Trial No. 1236.6 was an open-label, randomised, multiple dose (steady state), three way crossover, PK interaction study involving the following study treatments, (i) telmisartan 80 mg (Micardis), (ii) ramipril 10 mg (Delix) and (iii) telmisartan 80 mg (Micardis) and ramipril 10 mg (Delix). This study demonstrated that at steady state co-administration of telmisartan and ramipril results in a decrease in telmisartan AUC of 16%, an increase in ramipril AUC of 100% and an increase in ramiprilat AUC of 47%. The clinical evaluator indicated that this would be expected to increase the effect of ramipril and decrease the effect of telmisartan during co-administration.

Efficacy

Trial 502.373, ONTARGET, the pivotal study, was a multinational, multicentre, randomised, double-blind, double-dummy, parallel-group, comparator-controlled, non-inferiority efficacy and safety study. The objective of the trial was to determine if (a) the combination of telmisartan 80 mg and ramipril 10 mg was superior to ramipril alone and if (b) telmisartan 80 mg was not inferior to ramipril 10 mg alone in reducing the composite endpoint of cardiovascular death, myocardial infarction (MI), stroke or hospitalization for congestive cardiac failure (CHF).

The primary efficacy outcome measures were:

- composite of CV death, non-fatal MI, non-fatal stroke or hospitalization for CHF
- composite of doubling of serum creatinine, progression to ESRD (as defined by initiation of dialysis, need for renal transplantation or eGFR < 15 mL/min/1.73m^2) and all-cause mortality in the sub-group of diabetic nephropathy patients (i.e. diabetic patients with macro-albuminuria assessed as a UACR ≥ 300 mg/g creatinine at baseline).

There were a number of secondary efficacy outcome measures, the first of which was the composite of CV death, non-fatal MI and non-fatal stroke (analogous to the HOPE study).

There were two primary analyses, the comparison between the telmisartan/ramipril combination and ramipril and the comparison between telmisartan and ramipril as monotherapies. Hypothesis tests were performed using time-to-event analyses (Kaplan-Meier) and hazard ratios. The comparison of

the combination telmisartan/ramipril with ramipril was pre-specified as a superiority hypothesis test, that is, the two-sided 95% CI around the hazard ratio of telmisartan/ramipril versus. Ramipril was to exclude 1. The comparison of telmisartan with ramipril was pre-specified as a non-inferiority hypothesis test, that is, the upper limit of the two-sided 95% CI around the hazard ratio of telmisartan vs. ramipril was to be less than 1.13. Thus the test of non-inferiority was that there should be no more than a 13% increase in risk with telmisartan compared with ramipril.

A total of 29019 subjects were enrolled and 25620 randomised with around 8500 in each of the 3 groups. A total of 25570 subjects completed the trial with 50 not completing. There were 3068 deaths during the study. Of the full analysis set, 73.3% of patients were male, 26.7% female and 57.1% were aged 65 years or more. The treatment groups were balanced with regard to demographic characteristics, co-morbidities, HOPE risk scores, reason for inclusion, medical history, concomitant medications and MMSE examination results.

For the first primary efficacy outcome measure, the combination of telmisartan/ramipril was not superior to ramipril (Table 8).

There were similar results in the per-protocol population (Table 9).

Nor was there any difference between treatments in the second primary outcome measure, the primary renal endpoint (Table 10).

Non-inferiority was demonstrated for telmisartan vs. ramipril with a hazard ratio of 1.02, 97.5% CI [0.93, 1.12], p = 0.0078, in the per-protocol analysis and a hazard ratio of 1.01, 97.5% CI [0.93, 1.10] in the ITT analysis. For each analysis, the upper limit of the 97.5% CI was below the pre-defined value of 1.13. There was no significant difference between any of the three treatments in the composite outcome of CV death, non-fatal MI and non-fatal stroke (first secondary endpoint analogous to the primary outcome of the HOPE study).

Renal function appeared to deteriorate to a greater extent in the telmisartan-treated groups, with the combined telmisartan/ramipril group having the greatest deterioration in renal function over time (decreased eGFR and increased serum creatinine). For the UACR the relationship was reversed, with the ramipril group having the greatest increase, indicating a potential benefit of the combined treatment and of telmisartan.

Trial 502.373, TRANSCEND, was a multinational, multicentre, randomized, double-blind, parallel-group, placebo-controlled trial of telmisartan in patients at high risk for cardiovascular events and intolerant of ACE-inhibitors. The study treatments were either telmisartan 80 mg or placebo once daily. The primary efficacy outcome measure was the composite of CV death, MI, stroke or hospitalization for CHF. The primary analysis was the time to this latter endpoint, with telmisartan compared to placebo (time-to-event analysis by Kaplan-Meier & hazard ratio using the Cox proportional hazard model). A total of 6665 subjects were enrolled of whom 5926 were randomized, 2954 to telmisartan and 2972 to placebo. The study population was 57.0% male and 43.0% female and the age range 55-84 years. The treatment groups had similar demographic and baseline characteristics.

For the primary efficacy outcome measure, there was no significant difference between telmisartan and placebo (Table 16).

As noted by the clinical evaluator, possible explanations for this finding are that the study was underpowered and that in the telmisartan group there was a tendency for subjects to "opt out" of co-medication while in the placebo group there was the opposite tendency to "opt in".

For the first secondary endpoint, the composite of CV death, non-fatal MI and non-fatal stroke, the clinical evaluator has noted a benefit for telmisartan which was of marginal statistical significance and of a lesser magnitude than the benefit of ramipril in the HOPE study (Table 17). It should be noted that despite the p-value of 0.0483, the upper limit of the 95% CI is actually 1.00. The

comparable result in the HOPE trial was highly significant with an upper limit of the 95% CI which was well less than unity.

Relative to placebo in the telmisartan group, there was an increase in serum creatinine with a corresponding decrease in eGFR and at the same time a decrease in UACR. These findings mirrored the corresponding findings in the previous study, ONTARGET.

Trial 9.159, PRoFESS, was a multinational, multicentre, randomized, double-blind, double-dummy, active- and placebo-controlled, parallel-group, 2 x 2 factorial design clinical trial. There were four (4) treatment groups:

- telmisartan 80 mg once daily/Aggrenox twice daily
- telmisartan 80 mg once daily/clopidogrel 75 mg once daily
- placebo/ Aggrenox twice daily
- placebo/clopidogrel 75 mg once daily

The primary efficacy outcome measure was the time to first recurrence of stroke (by Cox proportional hazards model) and there were two pairs of treatments compared, the first being telmisartan vs. placebo and the second being a comparison of the anti-platelet therapies, that is, Aggrenox (ASA 25 mg + dipyridamole ER 200 mg) twice daily versus clopidogrel 75 mg once daily. The hypothesis test for the primary efficacy outcome measure for the comparison of telmisartan vs. placebo was performed as a test of superiority. It involved pooling the results for treatment arms 1 & 2 and comparing them with the results from the pooling of treatment arms 3 & 4. The comparison of the anti-platelet therapies was tested by means of a non-inferiority strategy but it is not relevant to the current submission. There were a total of 20403 subjects enrolled of whom 20332 were randomized to one of the four treatments – with a little over 5000 subjects in each group. This then gave an enrolment of just over 10000 in each of the combined telmisartan and placebo groups. Of the subjects, 64.0% were male and 36.0% were female. The telmisartan and placebo groups were similar in baseline and demographic characteristics.

For the primary efficacy outcome measure, the time to first recurrence of stroke, there was no significant difference between telmisartan and placebo (Table 20).

There was also a *post-hoc* pooled analysis from the TRANSCEND and PRoFESS trials of data from subjects who did not take an ACE inhibitor at baseline. There were 8587 subjects in the combined telmisartan group and 8290 in the combined placebo group. Since the primary efficacy outcome measures of the two studies were different, this combined analysis used a composite primary efficacy outcome measure of CV death, non-fatal MI, non-fatal stroke or hospitalization for CHF. For this outcome measure in patients not treated with an ACE inhibitor at baseline, there was a clinically and statistically significant benefit for telmisartan but also a study effect.

Safety

The collection and reporting of safety data for the proposed indication was limited to SAEs and AEs leading to withdrawal. The studies did not collect or report all AEs or treatment emergent AEs.

For the ONTARGET trial the rates of discontinuations due to AEs and SAEs were higher in the telmisartan/ramipril group than in the other two treatment groups. Renal failure, hypotension, diarrhoea and hyperkalaemia were more common in the telmisartan/ramipril group. Syncope leading to discontinuation was more common in the telmisartan/ramipril group. Mean creatinine and potassium levels increased in all three groups with the levels of increase being highest in the telmisartan/ramipril group, next highest in the telmisartan group and lowest in the ramipril group. The cause of these latter findings is not clear. There was a lower rate of cough and angioedema with telmisartan compared with ramipril.

In the TRANSCEND study, the proportions of subjects that died and of those that discontinued study medication because of SAEs and AEs were slightly higher in the telmisartan group compared with the placebo group. With telmisartan there were higher rates of renal failure, hypotension, syncope, diarrhoea and hyperkalaemia but not of cough or angioedema compared with the placebo group. The rate of malignancy was higher in the telmisartan group. There were increases in mean serum creatinine and potassium from baseline in the telmisartan group.

In the PRoFESS study compared to placebo there were also slightly higher rates of SAEs and AEs leading to discontinuation in the telmisartan group. SAEs associated with hyperkalaemia, hypotension and acute renal failure were more common in the telmisartan group. Hypotension, dizziness, syncope, orthostatic hypotension and acute renal failure were reported more commonly in the telmisartan group as AEs leading to discontinuation.

No additional safety data or analyses were presented in the pooled analysis of safety data.

No post-marketing data were included in the submission. The clinical evaluator noted that the Integrated Summary of Safety stated that no post-marketing data are available for telmisartan in the proposed indication.

Summary of the clinical evaluator's recommendation

The evaluator was of the opinion that there are sufficient data contained in the submission to demonstrate that telmisartan is no worse than ramipril for prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes. Ramipril has previously been demonstrated in the HOPE study to be superior to placebo for this indication in this patient group. The clinical evaluator noted that in patients who tolerate ACE inhibitors, it would have been difficult, if not unethical, to have conducted a long-term placebo-controlled trial of telmisartan for this indication. The clinical evaluator was also of the opinion that the description of the target population as of "*high risk for cardiovascular disease*" was too vague and ought to be replaced as those "*patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes*".

The clinical evaluator expressed concerns that the safety data did not present all AEs but instead only presented SAEs, AEs leading to discontinuation and AEs of special interest with the result that, in the opinion of the clinical evaluator, the safety data for the indication applied for was incomplete. Nor did the clinical evaluator think that the AE profile of telmisartan was well known in the population of patients described in the indications. The clinical evaluator's decision to reject the application was therefore because what was perceived to be insufficient data to demonstrate the safety profile of telmisartan for the proposed indication.

Risk-Benefit Analysis

Efficacy

The pivotal trial of this submission, named ONTARGET, involved 25620 randomized patients of whom 25570 completed the trial with a mean treatment duration of 4.6 years. There were 3 treatment groups, the combination of telmisartan and ramipril, telmisartan monotherapy and ramipril monotherapy, with each group having a little over 8500 subjects. The study failed to demonstrate superiority of the combination of telmisartan and ramipril over ramipril with respect to the composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke or hospitalization for congestive heart failure. The statistical test involved the construction of the 95% CI for the hazard ratio of the primary event rate per 100 patient years for the comparison of the combination telmisartan/ramipril vs. the monotherapy ramipril. There were two analyses, the first on the full analysis set (FAS) and the second on the per-protocol population (PP). The results for the hazard ratio and the corresponding 95% CI were as follows: 0.99 [0.92. 1.07], FAS and 1.00 [0.93, 1.09],

PP. Because the 95% CI contained unity in each case, this is a very robust demonstration of the lack of superiority of the combination treatment over the monotherapy. One notes also the tightness of the confidence intervals. A superiority trial is designed to detect a difference between treatments. The result of this trial shows that there is no significant difference between the two treatments.

The other major objective of this study was the comparison of telmisartan monotherapy with ramipril monotherapy. Once again the statistical test involved the construction of the 95% CI for the hazard ratio of the primary event rate per 100 patient years for the comparison. It was pre-specified as a non-inferiority comparison with non-inferiority established if the upper limit of the 95% CI was less than 1.13. Thus the aim was to show that telmisartan is at least as good as ramipril in preventing or lowering the rate of the composite event. The maximum clinically acceptable between-treatment difference of 13% was defined in advance. As stated by the evaluator, the test of non-inferiority was that there should no more than a 13% increase in risk of the primary event with telmisartan compared to ramipril. The results for the hazard ratio and the corresponding 95% CI were as follows: 1.01 [0.94, 1.09], FAS and 1.02 [0.94, 1.11], PP, while the results for the hazard ratio and the corresponding 97.5% CI were as follows: 1.01 [0.93, 1.10], FAS and 1.02 [0.93, 1.12], PP. In all cases, the upper limit of the confidence interval was less than the pre-specified 1.13 and so non-inferiority was established. It is not clear from the CER which analysis set and which level of confidence were pre-specified as the primary statistical tests. The sponsor was asked to clarify this issue.

It should also be noted that, for a non-inferiority study, both the PP and FAS analysis sets have equal weight. In fact there is an argument that the PP analysis provides the more conservative assessment and thus greater reliance can be placed upon it. In the PP analysis the upper limit of the 97.5% CI was 1.12 and of the 95% CI was 1.11. The question is – is a 12% difference still acceptable? Furthermore, 12% is nudging close to 13%. How comfortably assured can be one that non-inferiority has truly been demonstrated?

The Delegate expressed concerns over the choice of 13% as the pre-specified maximum clinically acceptable between-treatment difference. Firstly, the clinical evaluator states that the latter was not determined on the basis of clinical acceptability. As we shall see, the sponsor goes to great lengths, in justifying its modified safety data collection, to show that both ACE inhibitors and A-II receptor antagonists (in particular telmisartan) have a well characterised and long established clinical profile – some 20 years or more for the former and 10 years for the latter. The delta value is defined as a maximum clinically acceptable between treatment difference. The Delegate would find it unacceptable if the well known clinical profiles had not been taken into account in determining the delta value. The clinical evaluator goes on to state that the non-inferiority margin was based on the results of the HOPE study and upon the risk reduction observed in placebo-controlled studies of ACE inhibitors.

The HOPE study was a superiority study comparing the effects of ramipril monotherapy vs. placebo with respect to a composite primary outcome of cardiovascular death, MI or stroke. The statistical test involved the construction of the 95% CI for the hazard ratio of the primary event rate per 100 patient years for the comparison of ramipril vs. placebo. The results for the hazard ratio and the corresponding 95% CI were: 0.78 [0.70, 0.86], p-value < 0.001, FAS. Thus there was a mean reduction in the hazard ratio of 22%. However, the level of this reduction was just as likely to be as low as 14% (1.00 – 0.86). The pre-defined maximum clinically acceptable between-treatment difference (i.e. between telmisartan and ramipril) in the ONTARGET trial is 13% which, in the view of the delegate, is unacceptably close to this possible value of 14% for the treatment difference between ramipril and placebo.

In its pre-ADEC response, the sponsor was requested to give a full account and justification of the choice of the delta value.

The TRANSCEND study had as its objective the proof of the superiority of telmisartan over placebo with regard to a primary composite endpoint of cardiovascular death, MI, stroke or hospitalization for congestive heart failure. This was perhaps a somewhat more exacting aim than that in the HOPE study whose primary endpoint did not include hospitalization for congestive cardiac failure. There were 6665 patients enrolled, 5926 randomized, with 2954 in the telmisartan group and 2972 in the placebo group. For the primary efficacy outcome measure, there was no significant difference between telmisartan and placebo. The results for the hazard ratio vs. placebo and the corresponding 95% CI were as follows: 0.92 [0.81, 1.05], p-value = 0.2192. Telmisartan was not shown to be superior to placebo with regard to the composite endpoint. Sample size calculations had assumed a hazard ratio of 0.81 which turned out to be the value of the lower end of the 95% CI. This may suggest that the study was in fact underpowered. The clinical evaluator also noted the existence of a significant treatment effect with subjects in the telmisartan group opting out of co-medication and their counterparts in the placebo group opting in. Treatment duration was described as "greater than 2 years" which is of course well short of the 4.5 years in the HOPE study. Despite all of these factors, the study was designed to test the superiority of telmisartan over placebo for an endpoint similar to that tested in the HOPE study but it failed to demonstrate such superiority.

Also in terms of the indication sought, namely the prevention of cardiovascular morbidity and mortality, one can see that there is no consistency in terms of the components of the primary endpoint. For two of those four endpoints, namely non-fatal MI and hospitalization for CHF, the rates in the telmisartan group were greater than those in the ramipril group. Is this evidence of the prevention of cardiovascular morbidity?

The PRoFESS study also involved a comparison of telmisartan vs. placebo for a primary efficacy outcome measure of time to the first recurrence of stroke. It was a large trial with 20403 subjects enrolled of whom 20332 were randomised to treatment with 10146 in the telmisartan groups and 10186 in the placebo groups. Approximately half of the telmisartan and placebo populations were each taking either concomitant Aggrenox or clopidogrel – there was also an anti-platelet comparison being tested. For the primary efficacy outcome measure, the time to first recurrent stroke, there was no significant difference between telmisartan and placebo. Given that this was a trial against placebo, this raises doubts that telmisartan prevents stroke, in other words, that it prevents cardiovascular morbidity. The hazard ratio vs. placebo and the associated 95% CI was 0.95 [0.86, 1.04]. The clinical evaluator noted that the proportion of patients taking concomitant anti-hypertensive medications, including ACE inhibitors decreased in the telmisartan group during the course of the study but increased in the placebo group. The clinical evaluator also pointed out that there appeared to be some benefit for telmisartan after 2.5 years of treatment. However, one must be very cautious in asserting any such benefit. After 2.5 years, the numbers in each group had dropped by more than 50% from just over 10000 in each group to less than 4500. After another 6 months, that is, after 3 years, the numbers in each had dropped again, this time by slightly less than 50%, to approximately 2300. Finally, after another 6 months, that is after 3.5 years, the numbers in each group had dropped further, this time by more than 50 %, to just over 1000. A *post hoc* analysis showed that there was a significant interaction between treatment and time. For patients with recurrence of stroke less than 6 months after randomization, there appeared to be no difference between telmisartan and placebo while for patients with recurrence of stroke more than 6 months after randomization, there appeared to be a slight benefit for telmisartan. However, this was a *post hoc* analysis. Nor was there any significant difference between treatments in the composite outcome of time to first recurrent stroke, MI, new or worsening congestive heart failure or death due to vascular causes (the first secondary endpoint and akin to the HOPE study endpoint). Thus, like the TRANSCEND study, the PRoFESS study failed in its attempt to demonstrate any significant difference between telmisartan and placebo for the primary endpoint.

The pooled analysis included selected data from both the TRANSCEND and PRoFESS trials for subjects who did not take an ACE inhibitor at baseline. There were 8587 subjects in the combined telmisartan group and 8290 in the combined placebo group. For the composite measure in patients not treated with an ACE inhibitor at baseline, there was a statistically significant benefit of telmisartan over placebo. However, as noted by the clinical evaluator, this analysis was *post hoc* and as such its findings could not be accepted as robust evidence.

Thus there are two clinical trials, TRANSCEND and PRoFESS, which have failed to demonstrate any statistically significant benefit of telmisartan over placebo for the pre-specified endpoints tested. These findings are indirectly supported by the finding from the ONTARGET study that there was no statistically significant difference between the combination treatment of telmisartan and ramipril and the monotherapy ramipril. Despite the positive demonstration of the non-inferiority of telmisartan monotherapy to ramipril monotherapy, there are three significantly negative findings which call into question the performance of telmisartan over placebo. The HOPE study provided robust evidence of a significant benefit of ramipril treatment over placebo. Acceptance of the finding of non-inferiority to telmisartan with respect to ramipril has to imply that telmisartan treatment also confers a benefit over placebo. If one cannot be totally sure of the latter, then the validity of the finding of non-inferiority has to be called into question. The point about a non-inferiority finding between two treatments is that the test treatment is thereby endorsed as an alternative treatment to the comparator. If there are in fact doubts about the ability of the test treatment to confer a benefit over placebo, one could not logically endorse it as an alternative to the comparator. A non-inferiority study must always be subject to special scrutiny in terms of the study's external validity.

In summary, there is considerable doubt that telmisartan is more effective than placebo over a range of endpoints – a doubt arising from more than one study. While the studies which aimed to test the superiority of telmisartan over placebo may have had flaws of one type or another, they were double-blind, randomized trials which have not achieved what they set out to achieve. While noting the clinical evaluator's point that, in patients able to tolerate an ACE inhibitor, it would have been difficult, if not unethical, to have conducted a long-term placebo-controlled trial of telmisartan, that is, out to 4.5 years, one is still left with doubts as to any real benefit of telmisartan over placebo. This creates problems for the non-inferiority portion of the ONTARGET trial. As is well known, in contrast to a superiority trial, a non-inferiority trial without a placebo arm suffers from an implicit lack of any measure of internal validity. The result is that external validation is crucial for a non-inferiority study. The failure of the two trials, TRANSCEND and PRoFESS and to a lesser extent the failure of the ONTARGET trial to demonstrate superiority of telmisartan/ramipril over ramipril, casts considerable doubt over that external validity. As well, the concerns expressed by the delegate over the value of 13% assigned to the maximum clinically acceptable treatment difference between telmisartan and ramipril also calls into question the external validity of the ONTARGET trial.

The Delegate was therefore of the opinion that there are sufficient doubts about the proof of efficacy of telmisartan for the indication sought which make it impossible for him at this stage to recommend approval.

Safety

As noted by the sponsor in its response to the clinical evaluation report, the safety data from the ONTARGET study demonstrated that the overall safety profiles of telmisartan and ramipril were similar. As well there were no new signals detected in the proposed population of patients at high risk of cardiovascular disease. Overall mortality, the rates of treatment-emergent serious AEs and the rates of AEs resulting in permanent treatment discontinuation were comparable by and large between telmisartan and ramipril groups in the whole population as well as in a number of specific sub-groups. The analysis of AEs leading to permanent treatment discontinuation and of serious

AEs showed that cough and angioedema were less frequently reported in the telmisartan group than in the ramipril group. On the other hand hypotension was reported more frequently with telmisartan than with ramipril.

Also the established safety profile of telmisartan compared to placebo was confirmed in both the TRANSCEND and PRoFESS studies. Overall mortality and the rate of serious AEs on treatment were comparable between the telmisartan and the placebo groups. Adverse events leading to permanent treatment discontinuation were somewhat more frequently reported with telmisartan than with placebo. In the telmisartan group, hypotensive and gastrointestinal symptoms, renal dysfunction and increases in the concentrations of creatinine or potassium led more frequently to permanent treatment discontinuation than in the placebo group.

In its response to the clinical evaluation report, the sponsor submitted the latest PSUR, no. 9 for the period 12 April 2008 to 11 April 2009. A total of 1388 health care professional confirmed cases reporting 2112 ADRs were received during the update period. Of the 1388 cases, 232 (16.7%) were serious and 1156 (83.3%) were non-serious. The patient exposure to marketed product during this update period was estimated at 4.49 million patient years, representing approximately 20.10% of the estimated overall exposure to marketed telmisartan (22.34 million patient years). The company core data sheet (CCDS) was amended to include new information on pregnancy and lactation based on class labelling decisions by the EMEA for ARBs and a warning and precautionary statement on dual renin angiotensin aldosterone system (RAAS) blockade in susceptible patients. Finally, 'sepsis including fatal outcome' was added as a side effect of telmisartan. There had been a dedicated risk-benefit report devoted to hepatic-related events in Japanese patients. As there was no difference in the frequency of hepatic-related events in Japanese patients compared with non-Japanese patients, it was judged that the listed hepatic side effects remain adequate. Therefore no changes were made to the CCDS for these events. The sponsor will continue to monitor the following events: sepsis, fetotoxicity, hepatic-related events in Japanese patients, renal dysfunction secondary to dual RAAS blockade (hypotension, hyperkalaemia and renal impairment), hypoglycaemia, rhabdomyolysis, arrhythmias, atrial fibrillation, myocardial infarction, hypotension-related events (dizziness, somnolence and falls) and cerebrovascular events. The Delegate requested that the sponsor in the pre-ADEC response please provide comment on the new information on pregnancy and lactation and on the warning and precautionary statement on dual RAAS blockade in susceptible patients

It should be remembered that the amount of safety-related data collected in these large, clinical outcome trials is vast (randomized populations, ONTARGET n = 25620, TRANSCEND n = 5926 and PRoFESS n = 20332) and also obtained over lengthy periods of time. Both of these features stand in marked contrast to the smaller, shorter-term trials which would have been in the initial registration dossier for telmisartan. The Delegate agreed that the exposure to telmisartan in previous clinical trials and in the post-marketing arena has been substantial enough for the safety profile of the drug to be well known. Also large proportions of the study populations in all three of the trials in the dossier had a history of hypertension or were hypertensive at baseline and so there would have been a reasonable degree of concordance and overlap between the populations in the three trials and those patients for whom anti-hypertensive therapy with telmisartan is already indicated.

As noted by the sponsor, the modified collection of safety data employed in the ONTARGET, TRANSCEND and PRoFESS trials was carefully evaluated in the planning phases of these three large trials. The same modified approach to the collection of safety data had previously been used in the HOPE trial which was the reference trial for both the ONTARGET and TRANSCEND trials. The sponsor argues that in prior communications and/or protocol review processes with ethics committees and regulatory authorities, no objections had been raised to the planned methodology of safety data collection. These are all valid arguments.

Finally, as pointed out by the sponsor, this modified approach to the collection of safety data has previously been accepted by the relevant regulatory authorities worldwide, including the TGA, in relation to the demonstration of the safety profile of ramipril in the population of patients at high risk of cardiovascular disease. Thus a valid precedent has been established in the evaluation of safety data such as was collected in the HOPE study.

The Delegate was satisfied that there is sufficient safety data, both in terms of quantity and quality, in the submission to be able to conclude that there is no evidence of a significant change in the safety profile of the drug when used in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes.

Response to the TGA Clinical Evaluation Report by the Sponsor

The sponsor submitted a detailed response to the clinical evaluation report. The sponsor lodged its strong disagreement with the clinical evaluator's recommended rejection of the application on the basis of "*insufficient data to demonstrate the safety profile of telmisartan for the proposed indication*". To support its position, the sponsor first highlighted that the pivotal study in the submission, namely the ONTARGET study, had a design based on that of the HOPE study. This latter study demonstrated the efficacy and safety of ramipril in reducing the incidence of MI, stroke and cardiovascular death in comparison with placebo in patients at high risk. In particular, the modified approach to safety data collection in the ONTARGET study was similar to that employed in the HOPE study. Based on the HOPE study outcomes, health authorities around the world, including the TGA, approved the extension of indications of ramipril to include cardiovascular protection. In other words, the TGA has previously accepted such a modified safety data collection. The sponsor added that the safety profile of telmisartan is well known from previous clinical trials conducted for registration and also from extensive post-marketing experience world-wide.

Summary

Overall, the Delegate was of the opinion that there is insufficient evidence of efficacy but sufficient evidence of safety to support the registration of telmisartan (Micardis and Pritor) for the revised indication, "*Prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes*".

The Delegate proposed to reject the submission based on the premise that the efficacy of the product has not been satisfactorily established for the above indication.

The Delegate also requested the sponsor to address a number of issues in their pre-ADEC response including:

- which analysis set and which level of confidence were pre-specified as the primary statistical tests in the ONTARGET trial.
- A full account and justification of the choice of the delta value (i.e. the maximum clinically acceptable between-treatment difference) in the ONTARGET study and whether any of the regulatory agencies mentioned in a) above have requested any further clarification, explanation, discussion or argument concerning the delta value chosen. If any of the latter have been requested, then the sponsor is requested to give full details of the exchange(s) of information.
- Whether any of the regulatory agencies mentioned in a) above have requested any further clarification, explanation, discussion or argument concerning the possible impact of the major negative efficacy findings of the three trials, ONTARGET, TRANSCEND and PRoFESS, on the validity of the non-inferiority result for the comparison of telmisartan and

ramipril from the ONTARGET trial. If any of the latter have been requested, then the sponsor is requested to give full details of the exchange(s) of information.

- a commitment to the provision of a detailed cumulative review of the rates of malignancy observed in people on telmisartan in the next available PSUR.
- comment from the sponsor on the situation of people with mild to moderate hepatic impairment in the context of this new indication and whether this needs special attention in the Dosage and Administration section

These issues were satisfactorily addressed by the sponsor.

The Delegate also requested that the Australian Drug Evaluation Committee (ADEC) consider the following questions:

- the validity of the sponsor's choice of 13% as the pre-defined maximum clinically acceptable between-treatment difference in the ONTARGET study
- the impact of the major negative efficacy findings of the three trials, ONTARGET, TRANSCEND and PRoFESS, on the validity of the non-inferiority result for the comparison of telmisartan and ramipril from the ONTARGET trial
- the Delegate's acceptance of the sponsor's arguments concerning the validity of the modified approach to the collection of safety data in the three trials, ONTARGET, TRANSCEND and PRoFESS
- whether the concomitant or concurrent prescription of telmisartan and ramipril should be specifically contraindicated in the PI; if not, the Committee's advice was sought on the adequacy of the adverse event reporting and precautionary statements concerning the combination of telmisartan and ramipril.
- the sponsor's proposals for the reporting of the adverse effect profile of telmisartan based on adverse drug reactions and the clinical evaluator's and delegate's recommendations against this proposal

The ADEC, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, disagreed with the Delegate's proposal.

ADEC recommended approval of the submission for the indication:

Prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes with evidence of end organ damage

In making this resolution, the ADEC agreed with the clinical evaluator that there are sufficient data contained in the submission to demonstrate that telmisartan is not inferior to ramipril for prevention of cardiovascular morbidity in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes. Subjects with diabetes who participated in the pivotal study had evidence of organ damage; therefore the Committee considered that proposed indication should accurately reflect this study population.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Micardis and Pritor tablets containing telmisartan 40 mg and 80 mg for the new indication:

Prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes with evidence of end organ damage (see Clinical Trials).

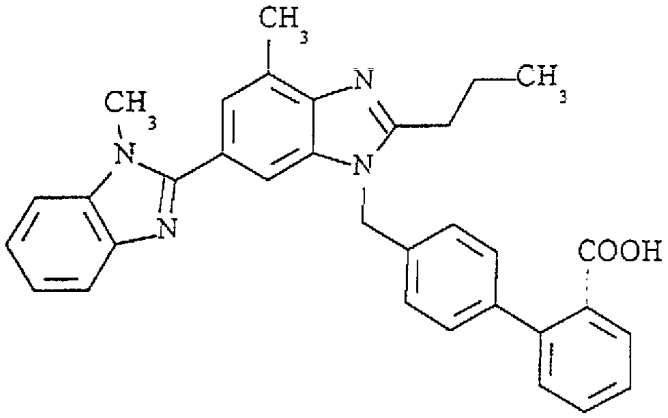
Attachment 1. Product Information

MICARDIS® Tablets (telmisartan)

NAME OF THE MEDICINE

MICARDIS® contains the active ingredient telmisartan.

Telmisartan has the following structural formula:



DESCRIPTION

Telmisartan is a specific angiotensin II receptor (type AT_1) antagonist. The chemical name for telmisartan is 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)-methyl]-[1,1'-biphenyl]-2-carboxylic acid (IUPAC nomenclature). The molecular formula is $C_{33}H_{30}N_4O_2$ and the molecular weight is 514.6. The CAS number is 144701-48-4.

Telmisartan is an off-white to yellowish crystalline powder. It is practically insoluble in water, very slightly soluble in ethanol, slightly soluble in methanol and soluble in a mixture of chloroform and methanol (1:1).

MICARDIS® is available as tablets for oral administration. Tablets containing 40 mg and 80 mg of telmisartan are available. The excipients are povidone K25, meglumine, sodium hydroxide, sorbitol and magnesium stearate.

PHARMACOLOGY

Pharmacodynamics

Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan binds selectively with the AT_1 receptor and does not reveal relevant affinity for other receptors nor does it inhibit human plasma renin or block ion channels. The clinically relevant effect of AT_1 receptor blockade is to lower blood pressure by inhibition of angiotensin II mediated vasoconstriction leading to reduction of systemic vascular resistance. During administration with telmisartan, removal of angiotensin II negative feedback on renin secretion results in increased plasma renin activity, which in turn leads to increases in angiotensin II in plasma. Despite these increases, antihypertensive

activity and suppressed aldosterone levels indicate effective angiotensin II receptor blockade. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse effects or cause oedema.

In humans, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked increase in blood pressure. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

After administration of the first dose of MICARDIS®, onset of antihypertensive activity occurs gradually within 3 hours. The maximal reduction in blood pressure is generally attained 4-8 weeks after the start of treatment.

With ambulatory blood pressure monitoring and conventional blood pressure measurements, the 24 hour trough to peak ratio for 40-80 mg doses of telmisartan was >70% for both systolic and diastolic blood pressure.

In patients with hypertension, telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The antihypertensive efficacy of telmisartan is independent of gender or age, and has been compared to antihypertensive drugs including amlodipine, atenolol, enalapril, ramipril, hydrochlorothiazide, lisinopril and valsartan. Telmisartan (40-120 mg once daily) is at least as effective as amlodipine (5-10 mg) and atenolol (50-100 mg once daily). Telmisartan (20-80 mg once daily) is equivalent to enalapril (5-20 mg once daily), and telmisartan (40-160 mg once daily) is comparable to lisinopril (10-40 mg once daily) (see also CLINICAL TRIALS).

After the first dose of telmisartan, the incidence of symptomatic orthostatic hypotension with symptoms severe enough to be reported as an adverse event in 3445 patients was 0.4% (14/3445).

Upon abrupt cessation of treatment, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

Pharmacokinetics

Absorption

Following oral administration of telmisartan, absorption is rapid (t_{max} ranges from 0.5 to 2 hours) although the amount absorbed varies. Absolute bioavailability of telmisartan was shown to be dose dependent. The mean absolute bioavailability of 40 mg telmisartan was 40%, whereas the mean absolute bioavailability of the 160 mg dose amounted to about 60%.

The maximum plasma concentration (C_{max}) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. In a Phase II clinical trial, 40, 80 and 120 mg of telmisartan were administered (in capsules) for 28 days to hypertensive subjects. Maximum plasma concentrations at steady state, $C_{max,ss}$, and AUC_{ss} were determined in 37–39 subjects per dose group.

In this trial, the mean C_{max} showed a more-than-proportional increase with dose, increasing 4.4 fold for a two-fold increase in dose from 40 to 80 mg, and increasing 2.4 fold with a 1.5 fold increase in dose from 80 to 120 mg. The mean AUC_{ss} were nearly proportional with increasing dose, increasing 2.3 fold for a two-fold increase in

dose from 40 to 80 mg, and increasing 1.5 fold with a 1.5 fold increase in dose from 80 to 120 mg.

There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose.

When MICARDIS® is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). The small reduction in AUC should not cause a reduction in the therapeutic efficacy. Therefore, MICARDIS® may be taken with or without food.

Distribution

Telmisartan is highly bound to plasma protein (>99.5%), mainly albumin and alpha-1-acid glycoprotein. The mean steady state apparent volume of distribution (V_{dss}) is approximately 6.6 L/kg.

Metabolism

Telmisartan undergoes substantial first-pass metabolism by conjugation to the acylglucuronide. No pharmacological activity has been shown for the conjugate. Telmisartan is not metabolised by the cytochrome P450 system.

Elimination

Telmisartan is characterised by bi-exponential decay pharmacokinetics with a terminal elimination half-life of 18.3-23.0 hours.

After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1% of dose. Total plasma clearance (CL_{tot}) is high (approximately 1000 mL/min) when compared with hepatic blood flow (about 1500 mL/min).

Special populations

Elderly patients: The pharmacokinetics of telmisartan do not differ between younger and elderly patients (i.e., patients older than 65 years of age).

Patients with renal impairment: Lower plasma concentrations were observed in patients with renal insufficiency (creatinine clearance 30-80 mL/min) undergoing dialysis, however, this has proved not to be of clinical significance. Telmisartan is highly bound to plasma proteins in renal-insufficient subjects and cannot be removed by dialysis.

Patients with hepatic impairment: Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100%.

Gender: Plasma concentrations are generally 2-3 times higher in females than in males. In clinical trials, however, no clinically significant increases in blood pressure response or incidences of orthostatic hypotension were found in females. No dosage adjustment is necessary.

Children: There are limited data on the pharmacokinetics of telmisartan in patients less than 18 years of age.

CLINICAL TRIALS

Treatment of hypertension:

The antihypertensive effects of MICARDIS® were examined in three pivotal short-term (8-12 weeks) placebo-controlled clinical trials, studying a range of 40-160 mg daily. The studies involved a total of 908 patients with hypertension (diastolic blood pressure of 95-114 mmHg), 483 of whom were randomised to receive telmisartan. One of the studies was a 12 week, fixed-dose study comparing telmisartan (40-160 mg), enalapril 20 mg, and placebo. The other two were dose titration studies; one comparing telmisartan (40 to 80 mg and 80 to 120 mg), atenolol (50 to 100 mg), and placebo over an 8 week period, the other comparing telmisartan (40 to 80 to 120 mg), amlodipine (5 to 10 mg), and placebo over a 12 week period. Once daily doses of 40-160 mg provided statistically and clinically significant decreases in both systolic and diastolic blood pressure.

Last trough readings of mean decreases in placebo-subtracted systolic/diastolic blood pressure in the fixed-dose study were 12.4 ± 2.2 / 7.5 ± 1.3 mmHg (40 mg dose) and 12.6 ± 2.2 / 7.9 ± 1.3 mmHg (80 mg dose). Dose titration regimens attained mean decreases in placebo-subtracted systolic/diastolic blood pressure of 9.2 ± 3.0 / 5.7 ± 1.5 mmHg (40 to 80 mg titrated regimen), 13.1 ± 3.1 / 6.4 ± 1.5 mmHg (80 to 120 mg titrated regimen), and 13.2 ± 2.3 / 7.1 ± 1.4 mmHg (40 to 80 to 120 mg optional titration regimen).

In long term open-label dose-titration studies of telmisartan (with optional hydrochlorothiazide add-on and addition of calcium channel blocker or beta-blocker), 1425 patients were analysed after 46-58 weeks treatment for hypertension. Mean reductions from baseline in last trough systolic/diastolic blood pressure ranged from 17.9 to 25.8 / 14.1 to 16.1 mmHg.

By combining all clinical trials involving angiotensin converting enzyme inhibitors, the incidence of cough was significantly less in patients treated with telmisartan than in those treated with angiotensin converting enzyme (ACE) inhibitors. Additionally, the incidence of cough occurring with telmisartan in six placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In a study in 378 patients with stable congestive heart failure (NYHA class II to III), telmisartan (10 to 80 mg) replaced former enalapril treatment. No difference was observed between telmisartan and enalapril with respect to ejection fraction, functional capacity, signs of heart failure or body weight.

Another study of 533 patients found no significant differences after treatment between both the telmisartan and atenolol treatment groups in a subgroup of hypertensive patients (78 of 533 patients) with respect to left atrium and ventricular or aortic diameters, or in left ventricular wall thickness or muscle mass, when compared to baseline results. In a small substudy involving 33 patients (21 on telmisartan, 11 on atenolol) with left ventricular hypertrophy (defined as LVM index ≥125 g/m^2 at baseline) at baseline, telmisartan and atenolol reduced left ventricular mass index to a similar degree (14-19 g/m^2) after 4 months of treatment.

In a study in 30 patients receiving telmisartan with or without hydrochlorothiazide, no significant effects were found on renal plasma flow, glomerular filtration rate or creatinine clearance after 8 weeks treatment, when both systolic and diastolic blood pressure were lowered significantly. In another study in 71 patients with moderate renal failure

(creatinine clearance 30-80 mL/min), blood pressure was lowered significantly without changes in creatinine clearance or other renal function parameters. In both trials urinary albumin and protein secretion was reduced, while no changes in sodium or potassium elimination were detected. Plasma electrolytes remained unaffected. Treatment with telmisartan showed no uricosuric effect.

No effect on plasma glucose, C-peptide or insulin levels was found after telmisartan administration. There is no evidence that telmisartan adversely affects patients who have stabilised diabetes.

Prevention of cardiovascular morbidity and mortality:

The ONTARGET study evaluated prevention of cardiovascular morbidity and mortality in patients with known high risk for its occurrence either due to prior documented disease or the presence of risk factors, such as diabetes with documented end organ damage. The TRANSCEND and PRoFESS studies included different populations, ACE-I intolerant patients and those with a recent stroke (< 120 days), respectively; and evaluated prevention of cardiovascular morbidity and mortality and secondary stroke prevention, respectively as the primary endpoint.

ONTARGET (pivotal study)

ONTARGET (**ON**going **T**elmisartan **A**lone and in Combination with **R**amipril **G**lobal **E**ndpoint **T**rial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, transient ischaemic attack, peripheral vascular disease, or diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which represents a broad cross-section of patients at high risk of cardiovascular events.

The co-primary objectives of the ONTARGET trial were to determine if (a) the combination of telmisartan 80 mg and ramipril 10 mg is superior to ramipril 10 mg alone and if (b) telmisartan 80 mg is not inferior to ramipril 10 mg alone in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure. Hypothesis tests were performed using hazard ratios and time-to-event analyses (Kaplan-Meier).

The principal patient exclusion criteria included: symptomatic heart failure or other specific cardiac diseases, syncopal episodes of unknown aetiology or planned cardiac surgery within 3 months of the start of study, uncontrolled hypertension or haemorrhagic stroke.

Patients were randomised to one of the three following treatment groups: telmisartan 80 mg (n=8542), ramipril 10 mg (n=8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n=8502), and followed for a mean observation time of 4.5 years. The population studied was 73% male, 74% Caucasian, 14% Asian and 43% were 65 years of age or older. Hypertension was present in nearly 83% of randomised patients: 69% of patients had a history of hypertension at randomisation and an additional 14% had actual blood pressure readings ≥140/90 mmHg. At baseline, the total percentage of patients with a medical history of diabetes was 38% and an additional 3% presented with elevated fasting plasma glucose levels. Baseline therapy included acetylsalicylic acid (76%), statins (62%), beta-blockers (57%), calcium channel blockers (34%), nitrates (29%) and diuretics (28%).

Adherence to treatment was better for telmisartan than for ramipril or the combination of telmisartan and ramipril, although the study population had been pre-screened for tolerance to treatment with an ACE-inhibitor. During the study, significantly less telmisartan patients (22.0%) discontinued treatment, compared to ramipril patients (24.4%) and telmisartan/ramipril patients (25.3%). The analysis of adverse events leading to permanent treatment discontinuation and of serious adverse events showed that cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Comparison of telmisartan versus ramipril: The choice of the non-inferiority margin of 1.13 was solely based on the results of the HOPE (**H**eart **O**utcomes **P**revention **E**valuation) study. Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7%) and ramipril (16.5%) groups. In the intention-to-treat (ITT) analysis, the hazard ratio for telmisartan versus ramipril was 1.01 (97.5% CI 0.93-1.10, p(non-inferiority)=0.0019). The non-inferiority result was confirmed in the per-protocol (PP) analysis, where the hazard ratio was 1.02 (97.5% CI 0.93-1.12, p(non-inferiority)=0.0078). Since the upper limit of the 97.5% CI was below the pre-defined non-inferiority margin of 1.13 and the p-value for non-inferiority was below 0.0125 in both the ITT and PP analyses, the trial succeeded in demonstrating the non-inferiority of telmisartan versus ramipril in the prevention of the composite primary endpoint. The non-inferiority conclusion was found to persist following corrections for differences in systolic blood pressure at baseline and over time. There was no difference in the primary endpoint in subgroups based on age, gender, race, baseline concomitant therapies or underlying diseases.

Telmisartan was also found to be similarly effective to ramipril in several pre-specified secondary endpoints, including a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, the primary endpoint in the reference study HOPE, which had investigated the effect of ramipril versus placebo. The ITT hazard ratio of telmisartan versus ramipril for this endpoint in ONTARGET was 0.99 (97.5% CI 0.90-1.08, p(non-inferiority)=0.0004), and confirmed by the PP hazard ratio of 1.00 (97.5% CI 0.91-1.11, p(non-inferiority)=0.0041.

Comparison of telmisartan plus ramipril combination versus ramipril monotherapy alone: Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone, thus superiority of the combination could not be demonstrated. The incidence of the primary endpoint was 16.3% in the telmisartan plus ramipril combination group, compared to the telmisartan (16.7%) and ramipril (16.5%) groups. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination group. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

<u>TRANSCEND</u>

TRANSCEND (**T**elmisartan **R**andomised **A**ssessme**N**t **S**tudy in a**CE** i**N**tolerant subjects with cardiovascular **D**isease) randomised a total of 5926 ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to telmisartan 80 mg (n=2954) or placebo (n=2972), both given on top of standard care. The exclusion criteria of TRANSCEND were similar to those of ONTARGET, with the additional exclusion of patients with proteinuria.

The primary objective of the TRANSCEND trial was to determine if telmisartan 80 mg is superior to placebo given on top of standard care in reducing the composite endpoint of cardiovascular death, myocardial infarction, stroke and hospitalisation for congestive heart failure in patients who are intolerant to ACE-inhibitors. Hypothesis test was performed using hazard ratios and time-to-event analyses (Kaplan-Meier).

The mean duration of follow-up was 4 years and 8 months. The population studied was 57% male, 62% Caucasian, 21% Asian, and 60% were 65 years of age or older. Baseline therapy included acetylsalicylic acid (75%), lipid lowering agents (58%), beta-blockers (58%), calcium channel blockers (41%), nitrates (34%) and diuretics (33%). Mean baseline blood pressure at baseline was 140/82 mmHg. During the study, 17.7% of telmisartan patients discontinued treatment, compared to 19.4% of placebo patients.

No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure) was found [15.7% in the telmisartan and 17.0% in the placebo groups; the event rates per 100 patient years were 3.58 and 3.87, respectively, with a hazard ratio of 0.92 (95% CI 0.81-1.05, p=0.22)]. Thus the trial was not able to demonstrate superiority of telmisartan over placebo given on top of standard care. Analysis of the secondary and other endpoints are therefore considered exploratory in nature. For the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (the primary endpoint in HOPE), a lower incidence was found in the telmisartan group (13.0%) compared to the placebo group (14.8%); the event rates per 100 patient years were 2.90 and 3.33, respectively.

The observed yearly event rates observed in TRANSCEND were lower than expected, most likely due to improved medical care, including more frequent use of cardioprotective medications (e.g. statins and beta blockers). This caused the study to be underpowered to detect between group differences. Additionally, in more patients in the placebo group, cardioprotective medications (e.g. blood pressure-lowering drugs such as beta blockers and diuretics) were added during the course of the trial than in the telmisartan group, which could have further confounded the detection of a treatment difference.

PRoFESS

The **PRoFESS** (**PR**eventi**o**n Regimen **F**or **E**ffectively avoiding **S**econd **S**trokes) study was a randomised, parallel group, international, double-blind, double-dummy, active and placebo controlled, 2x2 factorial study to compare aspirin plus extended-release dipyridamole with clopidogrel, and simultaneously telmisartan with placebo in the prevention of stroke in patients who had previously experienced an ischaemic stroke, mainly of non-cardioembolic origin. The study specifically enrolled only patients soon after their stroke (< 120 days) and there were no blood pressure related inclusion criteria.

Of the 20332 patients randomised, 10146 received telmisartan 80 mg and 10186 received placebo, both given on a background of standard treatment. The mean blood pressure at baseline was 144.1/83.8 mmHg.

The primary efficacy outcome measure was the time to first recurrent stroke of any type. For the telmisartan versus placebo comparison, hypothesis test of the primary efficacy outcome measure was performed as a test of superiority using hazard ratios and time-to-event analyses (Kaplan-Meier).

The mean duration of follow-up in PRoFESS was short (2.5 years) and more patients in the placebo group received concomitant blood-pressure lowering medications, which

may have confounded the results. Additionally, the adherence to the telmisartan regimen was much lower than in ONTARGET, due in part to the factorial nature of the trial and patient population studied (early post stroke).

The incidence of the primary endpoint of recurrent stroke were 8.7% for telmisartan and 9.2% for placebo (hazard ratio 0.95; 95% CI 0.86-1.04, p=0.23). Thus the trial was not able to demonstrate superiority of telmisartan over placebo given on top of standard care. Analysis of the secondary, tertiary and other endpoints are therefore considered exploratory in nature. The incidence of the pre-defined secondary composite endpoint of recurrent stroke, myocardial infarction, death due to vascular causes, and new or worsening congestive heart failure were 13.5% for telmisartan and 14.4% for placebo.

INDICATIONS

MICARDIS® is indicated for:

- Treatment of hypertension
- Prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes with evidence of end organ damage (see CLINICAL TRIALS)

CONTRAINDICATIONS

- Hypersensitivity to any of the components of the product
- Pregnancy
- Lactation
- Biliary obstructive disorders
- Severe hepatic impairment

In case of rare hereditary conditions that may be incompatible with an excipient of the product, the use of the product is contraindicated (see PRECAUTIONS).

PRECAUTIONS

Renal artery stenosis and kidney transplant

There are no data available on the use of MICARDIS® in patients who have had a kidney transplant.

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Increases in serum creatinine have been observed in studies with ACE-inhibitors in patients with single or bilateral renal artery stenosis. An effect similar to that observed with ACE inhibitors should be anticipated with MICARDIS®.

Impaired renal function

When MICARDIS® is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists has been associated with acute hypotension, oliguria and/or progressive uraemia and rarely with acute renal failure and/or death.

Dual blockade of the renin-angiotensin-aldosterone system

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should therefore be limited to individually defined cases with close monitoring of renal function.

In the ONTARGET trial, patients receiving the combination of MICARDIS® and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of hyperkalaemia, renal failure, hypotension and syncope compared with groups receiving telmisartan alone or ramipril alone (see also CLINICAL TRIALS). Concomitant use of MICARDIS® and ramipril is therefore not recommended in patients with already controlled blood pressure.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE-inhibitor or angiotensin receptor antagonist, an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

Aortic and mitral valve stenosis, and obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Hyperkalaemia

During treatment with medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium levels in patients at risk is recommended.

Based on experience with the use of medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase the potassium level (e.g., heparin, etc.) may lead to an increase in serum potassium and should, therefore, be co-administered cautiously with MICARDIS®.

Hepatic impairment

The majority of telmisartan is eliminated in the bile. Patients with biliary obstructive disorders or severe hepatic insufficiency can be expected to have reduced clearance. MICARDIS® is, therefore, contraindicated for use in these patients.

MICARDIS® should only be used with caution in patients with mild to moderate hepatic impairment (see DOSAGE AND ADMINISTRATION).

Sorbitol

MICARDIS® contains approximately 338 mg of sorbitol per maximum recommended daily dose. Patients with rare hereditary condition of fructose intolerance should not take this product.

Sodium- and/or volume-depleted patients

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions, especially volume and/or sodium depletion, should be corrected before the administration of MICARDIS®.

Use in cardiac failure

Telmisartan may be used in patients with congestive heart failure. However patients should be carefully observed for hypotension when initiating therapy.

Other

As observed for angiotensin converting enzyme inhibitors, angiotensin receptor antagonists including MICARDIS® are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

<u>Effects on Fertility</u>

Fertility of male and female rats was unaffected at oral telmisartan doses up to 100 mg/kg/day.

Use in Pregnancy (Category D)

Angiotensin II receptor antagonists should not be initiated during pregnancy. The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy.

Although there is no clinical experience with telmisartan in pregnant women, *in utero* exposure to drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and even death. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. Therefore, when pregnancy is detected, MICARDIS® should be discontinued as soon as possible.

Preclinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

Angiotensin II receptor antagonists 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, hyperkalaemia). Oligohydramnios reported in this setting, presumably resulting from decreased fetal renal function, has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to occur when drug exposure has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Women of child-bearing age should be warned of the potential hazards to their fetus should they become pregnant.

Unless continued angiotensin II receptor antagonist 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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension, oliguria and hyperkalaemia.

Telmisartan has been shown to cross the placenta in rats. There were no teratogenic effects when telmisartan was administered orally to rats and rabbits during the period of organogenesis at doses up to 50 and 45 mg/kg/day, respectively. However, fetal resorptions were observed at the highest dose level in rabbits. Administration of 50 mg/kg/day telmisartan to rats during pregnancy and lactation caused a decrease in birth weight and suppression of postnatal growth and development of the offspring.

The no-effect dose level in rabbits was 15 mg/kg/day, and corresponded to a plasma AUC value that was about 9 times higher than that anticipated in women at the highest recommended dose. Plasma drug levels were not measured at the high dose level in

rats, but data from other studies suggest that they would have been similar to those in women at the maximum recommended dose.

Use in Lactation

MICARDIS® is contraindicated during lactation since it is not known whether it is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk. No clinical trials have been carried out in lactating women. Therefore, lactating women should either not be prescribed MICARDIS® or should discontinue breastfeeding, if MICARDIS® is administered.

Telmisartan is excreted in the milk of lactating rats. When administered orally to lactating rats at 50 mg/kg/day, telmisartan suppressed postnatal growth and development of the offspring.

Use in Children

MICARDIS® is not recommended for use in children below 18 years due to limited data on safety and efficacy.

Effects on ability to drive and use machines

There are no data to suggest that MICARDIS® affects the ability to drive and use machines. However, when driving or operating machinery it should be taken into account that with antihypertensive therapy, occasionally dizziness or drowsiness may occur.

Carcinogenicity

Two-year studies in mice and rats did not show any increases in tumour incidences when telmisartan was administered in the diet at doses up to 1000 and 100 mg/kg/day, respectively. Plasma AUC values at the highest dose levels were approximately 60 and 15 times greater, respectively, than those anticipated in humans at the maximum recommended dose.

Genotoxicity

Telmisartan was not genotoxic in a battery of tests for gene mutations and clastogenicity.

Interactions with Other Medicines

MICARDIS® may increase the hypotensive effect of other antihypertensive agents.

Other interactions of clinical significance have not been identified. Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine.

When telmisartan was co-administered with digoxin, an increase in digoxin AUC (22%), C_{max} (50%), and C_{min} (13%) values was observed. It is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under- digitalisation.

In one study, the co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1 fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16% respectively. The clinical relevance of this observation is not fully known. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamics effects of the combined drugs and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Combining telmisartan with ramipril in the ONTARGET trial resulted in a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope compared to telmisartan alone or ramipril alone (see also CLINICAL TRIALS). Concomitant use of MICARDIS® and ramipril is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function (see also PRECAUTIONS).

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Cases have also been reported with angiotensin II receptor antagonists including MICARDIS®. Careful monitoring of serum lithium levels is recommended during concomitant use.

Treatment with NSAIDs (ie. aspirin at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the renin-angiotensin system like telmisartan may have synergistic effects. Patients receiving NSAIDs and MICARDIS® should be adequately hydrated and be monitored for renal function at the beginning of combined treatment. A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

Telmisartan is not metabolised by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit, or are metabolised by, cytochrome P450 enzymes.

ADVERSE EFFECTS

Adverse reactions have usually been mild and transient in nature and have only infrequently required discontinuation of therapy. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients.

Treatment of Hypertension:

The overall incidence of adverse reactions reported with MICARDIS® was comparable to placebo in placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20-160 mg) for up to 12 weeks. Therefore, the following information refers to adverse events irrespective of their causal relationship.

Adverse events with an incidence of 1% or more in telmisartan-treated patients and greater than placebo are shown in Table 1. The frequency of these adverse events was not significantly different between the telmisartan-treated and placebo patients.

Table 1 Frequency of adverse events (%) in placebo-controlled trials.

	Telmisartan monotherapy (n = 1041)	Placebo (n = 380)
General		
Pain	3.5	4.7
Fatigue	3.0	3.7
Influenza like illness	2.1	1.8
Chest pain	1.3	1.3
Nervous System		
Headache	9.7	17.4
Dizziness	4.2	6.3
Gastrointestinal		
Diarrhoea	2.8	1.6
Dyspepsia	1.9	1.6
Nausea	1.1	1.6
Abdominal pain	1.0	0.8
Respiratory		
Coughing	1.4	1.6
Musculoskeletal / Connective tissue / Bone	3.2	1.1
Back pain	1.4	1.1
Myalgia		
Infections / Infestations		
Upper respiratory tract infections	6.9	6.1
Sinusitis	2.2	2.4
Pharyngitis	1.1	0.0
Urinary tract infections (including cystitis)	1.2	1.1

In addition, the following adverse events occurred in more than 1% of the 3455 patients treated in all trials with telmisartan although causal association of these events with telmisartan could not be established: bronchitis, insomnia, arthralgia, anxiety, depression, palpitation, muscle spasms (cramps in legs) and rash.

In addition to those listed above, adverse events that occurred in less than 1% but more than 0.3% of 3500 patients treated with MICARDIS® monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to MICARDIS® tablets:

Infections and infestations: upper respiratory tract infections (including rhinitis), bronchitis, urinary tract infections (including cystitis), infection, fungal infection, abscess, otitis media

Immune system disorders: allergy

Metabolism and nutrition disorders: gout, hypercholesterolaemia, diabetes mellitus

Psychiatric disorders: anxiety, insomnia, depression, nervousness

Nervous system disorders: somnolence, migraine, paraesthesia, hypoaesthesia

Eye disorders: visual disturbance, conjunctivitis

Ear and labyrinth disorders: vertigo, tinnitus, earache

Cardiac disorders: tachycardia, palpitation, angina pectoris

Vascular disorders: flushing, cerebrovascular disorder

Respiratory disorders: dyspnoea, asthma, epistaxis

Gastrointestinal disorders: dry mouth, flatulence, stomach discomfort, vomiting, constipation, gastritis, haemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache

Skin and subcutaneous tissue disorders: eczema, pruritus, hyperhidrosis, rash, dermatitis

Musculoskeletal, connective tissue and bone disorders: arthralgia, involuntary muscle contractions or muscle spasms (cramps in legs) or pain in extremity (leg pain), arthritis

Renal and urinary tract disorders: micturition frequency

Reproductive system and breast disorders: impotence

General disorders and administration site conditions: malaise, fever, leg oedema, dependent oedema

Investigations: abnormal ECG

Laboratory findings

No significant differences in changes in laboratory test parameters were observed in clinical studies with telmisartan.

Haemoglobin decreased: A greater than 2 g/dL decrease in haemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anaemia.

Blood creatinine increased: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Hepatic enzymes increased: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Prevention of cardiovascular morbidity and mortality:

Because common adverse reactions were well characterised in studies of MICARDIS® in hypertension, only adverse events leading to discontinuation and serious adverse events were recorded in subsequent studies of MICARDIS® in the prevention of cardiovascular morbidity and mortality.

The safety profile of MICARDIS® in patients treated for the prevention of cardiovascular morbidity and mortality was consistent with that obtained in hypertensive patients.

In ONTARGET (N=25620, 4.5 years mean duration of follow up), discontinuations due to adverse events were 8.7% on telmisartan, 11.0% on ramipril and 12.4% on combination of telmisartan and ramipril.

In TRANSCEND (N=5926, 4 years and 8 months of follow up), discontinuations due to adverse events were 8.4% on telmisartan and 7.6% on placebo.

In PRoFESS (N=20332, 2.5 years follow up), discontinuations due to adverse events were 14.5% on telmisartan and 11.2% on placebo. Because of the factorial design of the

PRoFESS trial, the discontinuation rates observed in the telmisartan and placebo groups could also be due in part to the concomitant administration of either antiplatelet study medication (clopidogrel or aspirin + dipyridamole).

Adverse events in TRANSCEND occurring at least 1% more common in telmisartan-treated patients than in placebo-treated patients are shown in Table 2. Additionally for these events the incidences from ONTARGET are also presented. The data is derived from all serious adverse events reported during the study.

Table 2 TRANSCEND adverse events (%) occurring at least 1% or more common in patients treated with telmisartan than in patients treated with placebo, including ONTARGET incidences

	TRANSCEND*		ONTARGET*		
	Telmisartan (*n*=2954)	Placebo (*n*=2972)	Telmisartan (*n*=8542)	Ramipril (*n*=8576)	Telmisartan /Ramipril (*n*=8502)
Intermittent claudication	7	6	8	8	8
Skin ulcer	3	2	4	4	3

*Based on serious adverse events collected during the trial.

Combining telmisartan with ramipril in the ONTARGET study resulted in a higher incidence of hyperkalemia, renal failure, hypotension and syncope compared to telmisartan or ramipril alone.

In clinical studies with patients at high risk of developing major cardiovascular events, cases of sepsis, including some with fatal outcomes, have been reported. In the PRoFESS trial, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70 % versus 0.49 %; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33 %) versus patients taking placebo (0.16 %). The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known.

Post-Marketing Experience

In addition, the following have also been reported since the introduction of telmisartan in the market:

Blood and lymphatic system disorders: anaemia, eosinophilia, thrombocytopenia

Immune system disorders: anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders: hyperkalaemia

*Nervous system disorders: s*yncope (faint)

Cardiac disorders: bradycardia

Vascular disorders: hypotension, orthostatic hypotension

Hepatobiliary disorders: hepatic function abnormal / liver disorder

Skin and subcutaneous tissue disorders: angioedema, erythema, urticaria, drug eruption, toxic skin eruption

Musculoskeletal, connective tissue and bone disorders: tendon pain (tendinitis like symptoms)

Renal and urinary tract disorders: renal impairment including acute renal failure (see PRECAUTIONS)

General disorders and administration site conditions: asthenia (weakness)

Investigations: blood uric acid increased, blood creatine phosphokinase (CPK) increased

DOSAGE AND ADMINISTRATION

Treatment of hypertension:

Adults: The recommended dose is 40 mg once daily. In cases where the target blood pressure is not achieved, telmisartan dose can be increased to 80 mg once daily. Telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide which has been shown to have an additive blood pressure lowering effect with telmisartan. When considering raising the dose, it must be borne in mind that, while reduction in blood pressure is achieved after the first dose, the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment.

Prevention of cardiovascular morbidity and mortality:

The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of telmisartan are effective in preventing cardiovascular morbidity and mortality.

When initiating telmisartan therapy for the prevention of cardiovascular morbidity and mortality, monitoring of blood pressure is recommended, and if appropriate, adjustment of medications that lower blood pressure may be necessary.

MICARDIS® may be administered with or without food.

Elderly: No dosing adjustment is necessary.

Renal impairment: No dose adjustment is required for patients with renal impairment, including those on haemodialysis. Telmisartan is not removed from blood by haemofiltration.

Hepatic impairment: In patients with mild to moderate hepatic impairment, the dosage should not exceed 40 mg once daily (see PRECAUTIONS).

OVERDOSAGE

In case of overdose, advice can be obtained from the Poisons Information Centre (telephone 13 11 26).

Limited information is available with regard to overdose in humans. The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia also occurred. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by haemodialysis.

PRESENTATION AND STORAGE CONDITIONS

MICARDIS® tablets are white to off-white, oblong tablets. Tablets containing 40 mg and 80 mg of telmisartan are available. MICARDIS® 40 mg tablets have one face marked with 51H and the other with the Boehringer Ingelheim company symbol. MICARDIS®

80 mg tablets have one face marked with 52H and the other with the Boehringer Ingelheim company symbol.

MICARDIS® tablets are available in blister packs containing 7, 28, 56 and 98 tablets.

Store MICARDIS® tablets below 30°C. Protect from light and moisture.

MICARDIS® tablets should not be removed from their foil pack until required for administration.

NAME AND ADDRESS OF THE SPONSOR

BOEHRINGER INGELHEIM PTY LIMITED
ABN 52 000 452 308
78 WATERLOO ROAD
NORTH RYDE NSW 2113

POISON SCHEDULE

Schedule 4

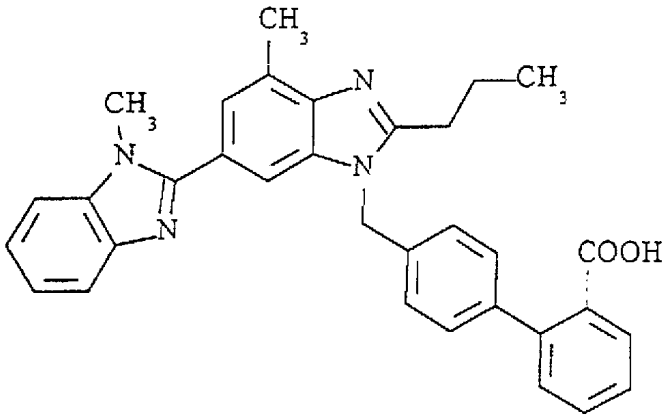
Text approved by the Therapeutic Goods Administration on 18 February 2010

PRITOR® Tablets
(telmisartan)

NAME OF THE MEDICINE

PRITOR® contains the active ingredient telmisartan.

Telmisartan has the following structural formula:



DESCRIPTION

Telmisartan is a specific angiotensin II receptor (type AT_1) antagonist. The chemical name for telmisartan is 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)-methyl]-[1,1'-biphenyl]-2-carboxylic acid (IUPAC nomenclature). The molecular formula is $C_{33}H_{30}N_4O_2$ and the molecular weight is 514.6. The CAS number is 144701-48-4.

Telmisartan is an off-white to yellowish crystalline powder. It is practically insoluble in water, very slightly soluble in ethanol, slightly soluble in methanol and soluble in a mixture of chloroform and methanol (1:1).

PRITOR® is available as tablets for oral administration. Tablets containing 40 mg and 80 mg of telmisartan are available. The excipients are povidone K25, meglumine, sodium hydroxide, sorbitol and magnesium stearate.

PHARMACOLOGY

Pharmacodynamics

Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan binds selectively with the AT_1 receptor and does not reveal relevant affinity for other receptors nor does it inhibit human plasma renin or block ion channels. The clinically relevant effect of AT_1 receptor blockade is to lower blood pressure by inhibition of angiotensin II mediated vasoconstriction leading to reduction of systemic vascular resistance. During administration with telmisartan, removal of angiotensin II negative feedback on renin secretion results in increased plasma renin activity, which in turn leads

to increases in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppressed aldosterone levels indicate effective angiotensin II receptor blockade. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse effects or cause oedema.

In humans, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked increase in blood pressure. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

After administration of the first dose of PRITOR®, onset of antihypertensive activity occurs gradually within 3 hours. The maximal reduction in blood pressure is generally attained 4-8 weeks after the start of treatment.

With ambulatory blood pressure monitoring and conventional blood pressure measurements, the 24 hour trough to peak ratio for 40-80 mg doses of telmisartan was >70% for both systolic and diastolic blood pressure.

In patients with hypertension, telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The antihypertensive efficacy of telmisartan is independent of gender or age, and has been compared to antihypertensive drugs including amlodipine, atenolol, enalapril, ramipril, hydrochlorothiazide, lisinopril and valsartan. Telmisartan (40-120 mg once daily) is at least as effective as amlodipine (5-10 mg) and atenolol (50-100 mg once daily). Telmisartan (20-80 mg once daily) is equivalent to enalapril (5-20 mg once daily), and telmisartan (40-160 mg once daily) is comparable to lisinopril (10-40 mg once daily) (see also CLINICAL TRIALS).

After the first dose of telmisartan, the incidence of symptomatic orthostatic hypotension with symptoms severe enough to be reported as an adverse event in 3445 patients was 0.4% (14/3445).

Upon abrupt cessation of treatment, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

Pharmacokinetics

Absorption

Following oral administration of telmisartan, absorption is rapid (t_{max} ranges from 0.5 to 2 hours) although the amount absorbed varies. Absolute bioavailability of telmisartan was shown to be dose dependent. The mean absolute bioavailability of 40 mg telmisartan was 40%, whereas the mean absolute bioavailability of the 160 mg dose amounted to about 60%.

The maximum plasma concentration (C_{max}) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. In a Phase II clinical trial, 40, 80 and 120 mg of telmisartan were administered (in capsules) for 28 days to hypertensive subjects. Maximum plasma concentrations at steady state, $C_{max,ss}$, and AUC_{ss} were determined in 37–39 subjects per dose group.

In this trial, the mean C_{max} showed a more-than-proportional increase with dose, increasing 4.4 fold for a two-fold increase in dose from 40 to 80 mg, and increasing 2.4 fold with a 1.5 fold increase in dose from 80 to 120 mg. The mean AUC_{ss} were nearly proportional with increasing dose, increasing 2.3 fold for a two-fold increase in

dose from 40 to 80 mg, and increasing 1.5 fold with a 1.5 fold increase in dose from 80 to 120 mg.

There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose.

When PRITOR® is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). The small reduction in AUC should not cause a reduction in the therapeutic efficacy. Therefore, PRITOR® may be taken with or without food.

Distribution

Telmisartan is highly bound to plasma protein (>99.5%), mainly albumin and alpha-1-acid glycoprotein. The mean steady state apparent volume of distribution (V_{dss}) is approximately 6.6 L/kg.

Metabolism

Telmisartan undergoes substantial first-pass metabolism by conjugation to the acylglucuronide. No pharmacological activity has been shown for the conjugate. Telmisartan is not metabolised by the cytochrome P450 system.

Elimination

Telmisartan is characterised by bi-exponential decay pharmacokinetics with a terminal elimination half-life of 18.3-23.0 hours.

After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1% of dose. Total plasma clearance (CL_{tot}) is high (approximately 1000 mL/min) when compared with hepatic blood flow (about 1500 mL/min).

Special populations

Elderly patients: The pharmacokinetics of telmisartan do not differ between younger and elderly patients (i.e., patients older than 65 years of age).

Patients with renal impairment: Lower plasma concentrations were observed in patients with renal insufficiency (creatinine clearance 30-80 mL/min) undergoing dialysis, however, this has proved not to be of clinical significance. Telmisartan is highly bound to plasma proteins in renal-insufficient subjects and cannot be removed by dialysis.

Patients with hepatic impairment: Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100%.

Gender: Plasma concentrations are generally 2-3 times higher in females than in males. In clinical trials, however, no clinically significant increases in blood pressure response or incidences of orthostatic hypotension were found in females. No dosage adjustment is necessary.

Children: There are limited data on the pharmacokinetics of telmisartan in patients less than 18 years of age.

CLINICAL TRIALS

Treatment of hypertension:

The antihypertensive effects of PRITOR® were examined in three pivotal short-term (8-12 weeks) placebo-controlled clinical trials, studying a range of 40-160 mg daily. The studies involved a total of 908 patients with hypertension (diastolic blood pressure of 95-114 mmHg), 483 of whom were randomised to receive telmisartan. One of the studies was a 12 week, fixed-dose study comparing telmisartan (40-160 mg), enalapril 20 mg, and placebo. The other two were dose titration studies; one comparing telmisartan (40 to 80 mg and 80 to 120 mg), atenolol (50 to 100 mg), and placebo over an 8 week period, the other comparing telmisartan (40 to 80 to 120 mg), amlodipine (5 to 10 mg), and placebo over a 12 week period. Once daily doses of 40-160 mg provided statistically and clinically significant decreases in both systolic and diastolic blood pressure.

Last trough readings of mean decreases in placebo-subtracted systolic/diastolic blood pressure in the fixed-dose study were 12.4 ± 2.2 / 7.5 ± 1.3 mmHg (40 mg dose) and 12.6 ± 2.2 / 7.9 ± 1.3 mmHg (80 mg dose). Dose titration regimens attained mean decreases in placebo-subtracted systolic/diastolic blood pressure of 9.2 ± 3.0 / 5.7 ± 1.5 mmHg (40 to 80 mg titrated regimen), 13.1 ± 3.1 / 6.4 ± 1.5 mmHg (80 to 120 mg titrated regimen), and 13.2 ± 2.3 / 7.1 ± 1.4 mmHg (40 to 80 to 120 mg optional titration regimen).

In long term open-label dose-titration studies of telmisartan (with optional hydrochlorothiazide add-on and addition of calcium channel blocker or beta-blocker), 1425 patients were analysed after 46-58 weeks treatment for hypertension. Mean reductions from baseline in last trough systolic/diastolic blood pressure ranged from 17.9 to 25.8 / 14.1 to 16.1 mmHg.

By combining all clinical trials involving angiotensin converting enzyme inhibitors, the incidence of cough was significantly less in patients treated with telmisartan than in those treated with angiotensin converting enzyme (ACE) inhibitors. Additionally, the incidence of cough occurring with telmisartan in six placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In a study in 378 patients with stable congestive heart failure (NYHA class II to III), telmisartan (10 to 80 mg) replaced former enalapril treatment. No difference was observed between telmisartan and enalapril with respect to ejection fraction, functional capacity, signs of heart failure or body weight.

Another study of 533 patients found no significant differences after treatment between both the telmisartan and atenolol treatment groups in a subgroup of hypertensive patients (78 of 533 patients) with respect to left atrium and ventricular or aortic diameters, or in left ventricular wall thickness or muscle mass, when compared to baseline results. In a small substudy involving 33 patients (21 on telmisartan, 11 on atenolol) with left ventricular hypertrophy (defined as LVM index $\geq$125 g/m^2 at baseline) at baseline, telmisartan and atenolol reduced left ventricular mass index to a similar degree (14-19 g/m^2) after 4 months of treatment.

In a study in 30 patients receiving telmisartan with or without hydrochlorothiazide, no significant effects were found on renal plasma flow, glomerular filtration rate or creatinine clearance after 8 weeks treatment, when both systolic and diastolic blood pressure were lowered significantly. In another study in 71 patients with moderate renal failure

(creatinine clearance 30-80 mL/min), blood pressure was lowered significantly without changes in creatinine clearance or other renal function parameters. In both trials urinary albumin and protein secretion was reduced, while no changes in sodium or potassium elimination were detected. Plasma electrolytes remained unaffected. Treatment with telmisartan showed no uricosuric effect.

No effect on plasma glucose, C-peptide or insulin levels was found after telmisartan administration. There is no evidence that telmisartan adversely affects patients who have stabilised diabetes.

Prevention of cardiovascular morbidity and mortality:

The ONTARGET study evaluated prevention of cardiovascular morbidity and mortality in patients with known high risk for its occurrence either due to prior documented disease or the presence of risk factors, such as diabetes with documented end organ damage. The TRANSCEND and PRoFESS studies included different populations, ACE-I intolerant patients and those with a recent stroke (< 120 days), respectively; and evaluated prevention of cardiovascular morbidity and mortality and secondary stroke prevention, respectively as the primary endpoint.

ONTARGET (pivotal study)

ONTARGET (**ON**going **T**elmisartan **A**lone and in Combination with **R**amipril **G**lobal **E**ndpoint **T**rial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, transient ischaemic attack, peripheral vascular disease, or diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which represents a broad cross-section of patients at high risk of cardiovascular events.

The co-primary objectives of the ONTARGET trial were to determine if (a) the combination of telmisartan 80 mg and ramipril 10 mg is superior to ramipril 10 mg alone and if (b) telmisartan 80 mg is not inferior to ramipril 10 mg alone in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure. Hypothesis tests were performed using hazard ratios and time-to-event analyses (Kaplan-Meier).

The principal patient exclusion criteria included: symptomatic heart failure or other specific cardiac diseases, syncopal episodes of unknown aetiology or planned cardiac surgery within 3 months of the start of study, uncontrolled hypertension or haemorrhagic stroke.

Patients were randomised to one of the three following treatment groups: telmisartan 80 mg (n=8542), ramipril 10 mg (n=8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n=8502), and followed for a mean observation time of 4.5 years. The population studied was 73% male, 74% Caucasian, 14% Asian and 43% were 65 years of age or older. Hypertension was present in nearly 83% of randomised patients: 69% of patients had a history of hypertension at randomisation and an additional 14% had actual blood pressure readings $\geq$140/90 mmHg. At baseline, the total percentage of patients with a medical history of diabetes was 38% and an additional 3% presented with elevated fasting plasma glucose levels. Baseline therapy included acetylsalicylic acid (76%), statins (62%), beta-blockers (57%), calcium channel blockers (34%), nitrates (29%) and diuretics (28%).

Adherence to treatment was better for telmisartan than for ramipril or the combination of telmisartan and ramipril, although the study population had been pre-screened for tolerance to treatment with an ACE-inhibitor. During the study, significantly less telmisartan patients (22.0%) discontinued treatment, compared to ramipril patients (24.4%) and telmisartan/ramipril patients (25.3%). The analysis of adverse events leading to permanent treatment discontinuation and of serious adverse events showed that cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Comparison of telmisartan versus ramipril: The choice of the non-inferiority margin of 1.13 was solely based on the results of the HOPE (**H**eart **O**utcomes **P**revention **E**valuation) study. Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7%) and ramipril (16.5%) groups. In the intention-to-treat (ITT) analysis, the hazard ratio for telmisartan versus ramipril was 1.01 (97.5% CI 0.93-1.10, p(non-inferiority)=0.0019). The non-inferiority result was confirmed in the per-protocol (PP) analysis, where the hazard ratio was 1.02 (97.5% CI 0.93-1.12, p(non-inferiority)=0.0078). Since the upper limit of the 97.5% CI was below the pre-defined non-inferiority margin of 1.13 and the p-value for non-inferiority was below 0.0125 in both the ITT and PP analyses, the trial succeeded in demonstrating the non-inferiority of telmisartan versus ramipril in the prevention of the composite primary endpoint. The non-inferiority conclusion was found to persist following corrections for differences in systolic blood pressure at baseline and over time. There was no difference in the primary endpoint in subgroups based on age, gender, race, baseline concomitant therapies or underlying diseases.

Telmisartan was also found to be similarly effective to ramipril in several pre-specified secondary endpoints, including a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, the primary endpoint in the reference study HOPE, which had investigated the effect of ramipril versus placebo. The ITT hazard ratio of telmisartan versus ramipril for this endpoint in ONTARGET was 0.99 (97.5% CI 0.90-1.08, p(non-inferiority)=0.0004), and confirmed by the PP hazard ratio of 1.00 (97.5% CI 0.91-1.11, p(non-inferiority)=0.0041.

Comparison of telmisartan plus ramipril combination versus ramipril monotherapy alone: Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone, thus superiority of the combination could not be demonstrated. The incidence of the primary endpoint was 16.3% in the telmisartan plus ramipril combination group, compared to the telmisartan (16.7%) and ramipril (16.5%) groups. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination group. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

<u>TRANSCEND</u>

TRANSCEND (**T**elmisartan **R**andomised **A**ssessme**N**t **S**tudy in a**CE** i**N**tolerant subjects with cardiovascular **D**isease) randomised a total of 5926 ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to telmisartan 80 mg (n=2954) or placebo (n=2972), both given on top of standard care. The exclusion criteria of TRANSCEND were similar to those of ONTARGET, with the additional exclusion of patients with proteinuria.

The primary objective of the TRANSCEND trial was to determine if telmisartan 80 mg is superior to placebo given on top of standard care in reducing the composite endpoint of cardiovascular death, myocardial infarction, stroke and hospitalisation for congestive heart failure in patients who are intolerant to ACE-inhibitors. Hypothesis test was performed using hazard ratios and time-to-event analyses (Kaplan-Meier).

The mean duration of follow-up was 4 years and 8 months. The population studied was 57% male, 62% Caucasian, 21% Asian, and 60% were 65 years of age or older. Baseline therapy included acetylsalicylic acid (75%), lipid lowering agents (58%), beta-blockers (58%), calcium channel blockers (41%), nitrates (34%) and diuretics (33%). Mean baseline blood pressure at baseline was 140/82 mmHg. During the study, 17.7% of telmisartan patients discontinued treatment, compared to 19.4% of placebo patients.

No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure) was found [15.7% in the telmisartan and 17.0% in the placebo groups; the event rates per 100 patient years were 3.58 and 3.87, respectively, with a hazard ratio of 0.92 (95% CI 0.81-1.05, p=0.22)]. Thus the trial was not able to demonstrate superiority of telmisartan over placebo given on top of standard care. Analysis of the secondary and other endpoints are therefore considered exploratory in nature. For the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (the primary endpoint in HOPE), a lower incidence was found in the telmisartan group (13.0%) compared to the placebo group (14.8%); the event rates per 100 patient years were 2.90 and 3.33, respectively.

The observed yearly event rates observed in TRANSCEND were lower than expected, most likely due to improved medical care, including more frequent use of cardioprotective medications (e.g. statins and beta blockers). This caused the study to be underpowered to detect between group differences. Additionally, in more patients in the placebo group, cardioprotective medications (e.g. blood pressure-lowering drugs such as beta blockers and diuretics) were added during the course of the trial than in the telmisartan group, which could have further confounded the detection of a treatment difference.

PRoFESS

The **PRoFESS** (**PR**eventi**o**n Regimen **F**or **E**ffectively avoiding **S**econd **S**trokes) study was a randomised, parallel group, international, double-blind, double-dummy, active and placebo controlled, 2x2 factorial study to compare aspirin plus extended-release dipyridamole with clopidogrel, and simultaneously telmisartan with placebo in the prevention of stroke in patients who had previously experienced an ischaemic stroke, mainly of non-cardioembolic origin. The study specifically enrolled only patients soon after their stroke (< 120 days) and there were no blood pressure related inclusion criteria.

Of the 20332 patients randomised, 10146 received telmisartan 80 mg and 10186 received placebo, both given on a background of standard treatment. The mean blood pressure at baseline was 144.1/83.8 mmHg.

The primary efficacy outcome measure was the time to first recurrent stroke of any type. For the telmisartan versus placebo comparison, hypothesis test of the primary efficacy outcome measure was performed as a test of superiority using hazard ratios and time-to-event analyses (Kaplan-Meier).

The mean duration of follow-up in PRoFESS was short (2.5 years) and more patients in the placebo group received concomitant blood-pressure lowering medications, which

may have confounded the results. Additionally, the adherence to the telmisartan regimen was much lower than in ONTARGET, due in part to the factorial nature of the trial and patient population studied (early post stroke).

The incidence of the primary endpoint of recurrent stroke were 8.7% for telmisartan and 9.2% for placebo (hazard ratio 0.95; 95% CI 0.86-1.04, p=0.23). Thus the trial was not able to demonstrate superiority of telmisartan over placebo given on top of standard care. Analysis of the secondary, tertiary and other endpoints are therefore considered exploratory in nature. The incidence of the pre-defined secondary composite endpoint of recurrent stroke, myocardial infarction, death due to vascular causes, and new or worsening congestive heart failure were 13.5% for telmisartan and 14.4% for placebo.

INDICATIONS

PRITOR® is indicated for:

- Treatment of hypertension
- Prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack or high risk diabetes with evidence of end organ damage (see CLINICAL TRIALS)

CONTRAINDICATIONS

- Hypersensitivity to any of the components of the product
- Pregnancy
- Lactation
- Biliary obstructive disorders
- Severe hepatic impairment

In case of rare hereditary conditions that may be incompatible with an excipient of the product, the use of the product is contraindicated (see PRECAUTIONS).

PRECAUTIONS

Renal artery stenosis and kidney transplant

There are no data available on the use of PRITOR® in patients who have had a kidney transplant.

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Increases in serum creatinine have been observed in studies with ACE-inhibitors in patients with single or bilateral renal artery stenosis. An effect similar to that observed with ACE inhibitors should be anticipated with PRITOR®.

Impaired renal function

When PRITOR® is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists has been associated with acute hypotension, oliguria and/or progressive uraemia and rarely with acute renal failure and/or death.

Dual blockade of the renin-angiotensin-aldosterone system

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should therefore be limited to individually defined cases with close monitoring of renal function.

In the ONTARGET trial, patients receiving the combination of PRITOR® and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of hyperkalaemia, renal failure, hypotension and syncope compared with groups receiving telmisartan alone or ramipril alone (see also CLINICAL TRIALS). Concomitant use of PRITOR® and ramipril is therefore not recommended in patients with already controlled blood pressure.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE-inhibitor or angiotensin receptor antagonist, an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

Aortic and mitral valve stenosis, and obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Hyperkalaemia

During treatment with medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium levels in patients at risk is recommended.

Based on experience with the use of medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase the potassium level (e.g., heparin, etc.) may lead to an increase in serum potassium and should, therefore, be co-administered cautiously with PRITOR®.

Hepatic impairment

The majority of telmisartan is eliminated in the bile. Patients with biliary obstructive disorders or severe hepatic insufficiency can be expected to have reduced clearance. PRITOR® is, therefore, contraindicated for use in these patients.

PRITOR® should only be used with caution in patients with mild to moderate hepatic impairment (see DOSAGE AND ADMINISTRATION).

Sorbitol

PRITOR® contains approximately 338 mg of sorbitol per maximum recommended daily dose. Patients with rare hereditary condition of fructose intolerance should not take this product.

Sodium- and/or volume-depleted patients

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions, especially volume and/or sodium depletion, should be corrected before the administration of PRITOR®.

Use in cardiac failure

Telmisartan may be used in patients with congestive heart failure. However patients should be carefully observed for hypotension when initiating therapy.

Other

As observed for angiotensin converting enzyme inhibitors, angiotensin receptor antagonists including PRITOR® are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

<u>Effects on Fertility</u>

Fertility of male and female rats was unaffected at oral telmisartan doses up to 100 mg/kg/day.

Use in Pregnancy (Category D)

Angiotensin II receptor antagonists should not be initiated during pregnancy. The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy.

Although there is no clinical experience with telmisartan in pregnant women, *in utero* exposure to drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and even death. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. Therefore, when pregnancy is detected, PRITOR® should be discontinued as soon as possible.

Preclinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

Angiotensin II receptor antagonists 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, hyperkalaemia). Oligohydramnios reported in this setting, presumably resulting from decreased fetal renal function, has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to occur when drug exposure has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Women of child-bearing age should be warned of the potential hazards to their fetus should they become pregnant.

Unless continued angiotensin II receptor antagonist 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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension, oliguria and hyperkalaemia.

Telmisartan has been shown to cross the placenta in rats. There were no teratogenic effects when telmisartan was administered orally to rats and rabbits during the period of organogenesis at doses up to 50 and 45 mg/kg/day, respectively. However, fetal resorptions were observed at the highest dose level in rabbits. Administration of 50 mg/kg/day telmisartan to rats during pregnancy and lactation caused a decrease in birth weight and suppression of postnatal growth and development of the offspring.

The no-effect dose level in rabbits was 15 mg/kg/day, and corresponded to a plasma AUC value that was about 9 times higher than that anticipated in women at the highest recommended dose. Plasma drug levels were not measured at the high dose level in

rats, but data from other studies suggest that they would have been similar to those in women at the maximum recommended dose.

Use in Lactation

PRITOR® is contraindicated during lactation since it is not known whether it is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk. No clinical trials have been carried out in lactating women. Therefore, lactating women should either not be prescribed PRITOR® or should discontinue breastfeeding, if PRITOR® is administered.

Telmisartan is excreted in the milk of lactating rats. When administered orally to lactating rats at 50 mg/kg/day, telmisartan suppressed postnatal growth and development of the offspring.

Use in Children

PRITOR® is not recommended for use in children below 18 years due to limited data on safety and efficacy.

Effects on ability to drive and use machines

There are no data to suggest that PRITOR® affects the ability to drive and use machines. However, when driving or operating machinery it should be taken into account that with antihypertensive therapy, occasionally dizziness or drowsiness may occur.

Carcinogenicity

Two-year studies in mice and rats did not show any increases in tumour incidences when telmisartan was administered in the diet at doses up to 1000 and 100 mg/kg/day, respectively. Plasma AUC values at the highest dose levels were approximately 60 and 15 times greater, respectively, than those anticipated in humans at the maximum recommended dose.

Genotoxicity

Telmisartan was not genotoxic in a battery of tests for gene mutations and clastogenicity.

Interactions with Other Medicines

PRITOR® may increase the hypotensive effect of other antihypertensive agents.

Other interactions of clinical significance have not been identified. Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine.

When telmisartan was co-administered with digoxin, an increase in digoxin AUC (22%), C_{max} (50%), and C_{min} (13%) values was observed. It is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under- digitalisation.

In one study, the co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1 fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16% respectively. The clinical relevance of this observation is not fully known. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamics effects of the combined drugs and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Combining telmisartan with ramipril in the ONTARGET trial resulted in a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope compared to telmisartan alone or ramipril alone (see also CLINICAL TRIALS). Concomitant use of PRITOR® and ramipril is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function (see also PRECAUTIONS).

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Cases have also been reported with angiotensin II receptor antagonists including PRITOR®. Careful monitoring of serum lithium levels is recommended during concomitant use.

Treatment with NSAIDs (ie. aspirin at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the renin-angiotensin system like telmisartan may have synergistic effects. Patients receiving NSAIDs and PRITOR® should be adequately hydrated and be monitored for renal function at the beginning of combined treatment. A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

Telmisartan is not metabolised by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit, or are metabolised by, cytochrome P450 enzymes.

ADVERSE EFFECTS

Adverse reactions have usually been mild and transient in nature and have only infrequently required discontinuation of therapy. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients.

Treatment of Hypertension:

The overall incidence of adverse reactions reported with PRITOR® was comparable to placebo in placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20-160 mg) for up to 12 weeks. Therefore, the following information refers to adverse events irrespective of their causal relationship.

Adverse events with an incidence of 1% or more in telmisartan-treated patients and greater than placebo are shown in Table 1. The frequency of these adverse events was not significantly different between the telmisartan-treated and placebo patients.

Table 1 Frequency of adverse events (%) in placebo-controlled trials.

	Telmisartan monotherapy (n = 1041)	Placebo (n = 380)
General		
Pain	3.5	4.7
Fatigue	3.0	3.7
Influenza like illness	2.1	1.8
Chest pain	1.3	1.3
Nervous System		
Headache	9.7	17.4
Dizziness	4.2	6.3
Gastrointestinal		
Diarrhoea	2.8	1.6
Dyspepsia	1.9	1.6
Nausea	1.1	1.6
Abdominal pain	1.0	0.8
Respiratory		
Coughing	1.4	1.6
Musculoskeletal / Connective tissue / Bone	3.2	1.1
Back pain	1.4	1.1
Myalgia		
Infections / Infestations		
Upper respiratory tract infections	6.9	6.1
Sinusitis	2.2	2.4
Pharyngitis	1.1	0.0
Urinary tract infections (including cystitis)	1.2	1.1

In addition, the following adverse events occurred in more than 1% of the 3455 patients treated in all trials with telmisartan although causal association of these events with telmisartan could not be established: bronchitis, insomnia, arthralgia, anxiety, depression, palpitation, muscle spasms (cramps in legs) and rash.

In addition to those listed above, adverse events that occurred in less than 1% but more than 0.3% of 3500 patients treated with PRITOR® monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to PRITOR® tablets:

Infections and infestations: upper respiratory tract infections (including rhinitis), bronchitis, urinary tract infections (including cystitis), infection, fungal infection, abscess, otitis media

Immune system disorders: allergy

Metabolism and nutrition disorders: gout, hypercholesterolaemia, diabetes mellitus

Psychiatric disorders: anxiety, insomnia, depression, nervousness

Nervous system disorders: somnolence, migraine, paraesthesia, hypoaesthesia

Eye disorders: visual disturbance, conjunctivitis

Ear and labyrinth disorders: vertigo, tinnitus, earache

Cardiac disorders: tachycardia, palpitation, angina pectoris

Vascular disorders: flushing, cerebrovascular disorder

Respiratory disorders: dyspnoea, asthma, epistaxis

Gastrointestinal disorders: dry mouth, flatulence, stomach discomfort, vomiting, constipation, gastritis, haemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache

Skin and subcutaneous tissue disorders: eczema, pruritus, hyperhidrosis, rash, dermatitis

Musculoskeletal, connective tissue and bone disorders: arthralgia, involuntary muscle contractions or muscle spasms (cramps in legs) or pain in extremity (leg pain), arthritis

Renal and urinary tract disorders: micturition frequency

Reproductive system and breast disorders: impotence

General disorders and administration site conditions: malaise, fever, leg oedema, dependent oedema

Investigations: abnormal ECG

Laboratory findings

No significant differences in changes in laboratory test parameters were observed in clinical studies with telmisartan.

Haemoglobin decreased: A greater than 2 g/dL decrease in haemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anaemia.

Blood creatinine increased: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Hepatic enzymes increased: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Prevention of cardiovascular morbidity and mortality:

Because common adverse reactions were well characterised in studies of PRITOR® in hypertension, only adverse events leading to discontinuation and serious adverse events were recorded in subsequent studies of PRITOR® in the prevention of cardiovascular morbidity and mortality.

The safety profile of PRITOR® in patients treated for the prevention of cardiovascular morbidity and mortality was consistent with that obtained in hypertensive patients.

In ONTARGET (N=25620, 4.5 years mean duration of follow up), discontinuations due to adverse events were 8.7% on telmisartan, 11.0% on ramipril and 12.4% on combination of telmisartan and ramipril.

In TRANSCEND (N=5926, 4 years and 8 months of follow up), discontinuations due to adverse events were 8.4% on telmisartan and 7.6% on placebo.

In PRoFESS (N=20332, 2.5 years follow up), discontinuations due to adverse events were 14.5% on telmisartan and 11.2% on placebo. Because of the factorial design of the

PRoFESS trial, the discontinuation rates observed in the telmisartan and placebo groups could also be due in part to the concomitant administration of either antiplatelet study medication (clopidogrel or aspirin + dipyridamole).

Adverse events in TRANSCEND occurring at least 1% more common in telmisartan-treated patients than in placebo-treated patients are shown in Table 2. Additionally for these events the incidences from ONTARGET are also presented. The data is derived from all serious adverse events reported during the study.

Table 2 TRANSCEND adverse events (%) occurring at least 1% or more common in patients treated with telmisartan than in patients treated with placebo, including ONTARGET incidences

	TRANSCEND*		ONTARGET*		
	Telmisartan (*n*=2954)	Placebo (*n*=2972)	Telmisartan (*n*=8542)	Ramipril (*n*=8576)	Telmisartan /Ramipril (*n*=8502)
Intermittent claudication	7	6	8	8	8
Skin ulcer	3	2	4	4	3

*Based on serious adverse events collected during the trial.

Combining telmisartan with ramipril in the ONTARGET study resulted in a higher incidence of hyperkalemia, renal failure, hypotension and syncope compared to telmisartan or ramipril alone.

In clinical studies with patients at high risk of developing major cardiovascular events, cases of sepsis, including some with fatal outcomes, have been reported. In the PRoFESS trial, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70 % versus 0.49 %; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33 %) versus patients taking placebo (0.16 %). The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known.

Post-Marketing Experience

In addition, the following have also been reported since the introduction of telmisartan in the market:

Blood and lymphatic system disorders: anaemia, eosinophilia, thrombocytopenia

Immune system disorders: anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders: hyperkalaemia

*Nervous system disorders: s*yncope (faint)

Cardiac disorders: bradycardia

Vascular disorders: hypotension, orthostatic hypotension

Hepatobiliary disorders: hepatic function abnormal / liver disorder

Skin and subcutaneous tissue disorders: angioedema, erythema, urticaria, drug eruption, toxic skin eruption

Musculoskeletal, connective tissue and bone disorders: tendon pain (tendinitis like symptoms)

Renal and urinary tract disorders: renal impairment including acute renal failure (see PRECAUTIONS)

General disorders and administration site conditions: asthenia (weakness)

Investigations: blood uric acid increased, blood creatine phosphokinase (CPK) increased

DOSAGE AND ADMINISTRATION

Treatment of hypertension:

Adults: The recommended dose is 40 mg once daily. In cases where the target blood pressure is not achieved, telmisartan dose can be increased to 80 mg once daily. Telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide which has been shown to have an additive blood pressure lowering effect with telmisartan. When considering raising the dose, it must be borne in mind that, while reduction in blood pressure is achieved after the first dose, the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment.

Prevention of cardiovascular morbidity and mortality:

The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of telmisartan are effective in preventing cardiovascular morbidity and mortality.

When initiating telmisartan therapy for the prevention of cardiovascular morbidity and mortality, monitoring of blood pressure is recommended, and if appropriate, adjustment of medications that lower blood pressure may be necessary.

PRITOR® may be administered with or without food.

Elderly: No dosing adjustment is necessary.

Renal impairment: No dose adjustment is required for patients with renal impairment, including those on haemodialysis. Telmisartan is not removed from blood by haemofiltration.

Hepatic impairment: In patients with mild to moderate hepatic impairment, the dosage should not exceed 40 mg once daily (see PRECAUTIONS).

OVERDOSAGE

In case of overdose, advice can be obtained from the Poisons Information Centre (telephone 13 11 26).

Limited information is available with regard to overdose in humans. The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia also occurred. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by haemodialysis.

PRESENTATION AND STORAGE CONDITIONS

PRITOR® tablets are white to off-white, oblong tablets. Tablets containing 40 mg and 80 mg of telmisartan are available. PRITOR® 40 mg tablets are engraved with “GXEG1”

on one side and blank on the other. PRITOR® 80 mg tablets are engraved with “GXEF7” on one side and blank on the other.

PRITOR® tablets are available in blister packs containing 7, 28, 56 and 98 tablets.

Store PRITOR® tablets below 30°C. Protect from light and moisture.

PRITOR® tablets should not be removed from their foil pack until required for administration.

NAME AND ADDRESS OF THE SPONSOR

BOEHRINGER INGELHEIM PTY LIMITED
ABN 52 000 452 308
78 WATERLOO ROAD
NORTH RYDE NSW 2113

POISON SCHEDULE

Schedule 4

Text approved by the Therapeutic Goods Administration on 18 February 2010