SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 June 2002. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Inhibition of the renin-angiotensin system is a well-proven approach to the treatment of arterial hypertension. It can be achieved by inhibiting the angiotensin-converting enzyme (ACE) that converts angiotensin I into its active form angiotensin II (AGII), or by blockade of angiotensin II (type AT_1) receptors.

Telmisartan is a new active substance. It is a benzimidazole derivative antagonist of subtype 1 angiotensin II receptors (AT_1) intended for the treatment of essential arterial hypertension. Other specific angiotensin II receptor antagonists like losartan, valsartan, irbesartan, eprosartan, and candesartan have already been approved in the European Union.

2. Chemical, pharmaceutical, and biological aspects

Composition

The medicinal product is available in the form of white to off-white tablets containing 20, 40 or 80 mg of telmisartan. The qualitative and quantitative composition is adequately described. The ratio of excipients to active substance remains constant throughout the dosages.

Development pharmaceutics

A full development pharmaceutics package has been provided including the active ingredient characterisation and the compatibility studies with the excipients. There have been no substantial changes in the tablet formulation during development.

The formulation proposed for commercial use is identical to that used in phase III controlled clinical studies, except for a change in the grade of sorbitol due to issues involving content uniformity that occurred during scale-up. The effects of changes in production site, production scale and change in the sorbitol grade were addressed in a series of *in vitro* dissolution tests, which demonstrated equivalence of 40 and 80 mg clinical batches. These results of the *in vitro* tests are considered to be predictive with regard to the *in vivo* bioequivalence.

After the initial Marketing authorisation, the company has developed a 20mg tablet in order to improve the administration of the 20 mg dose. The 20 mg strength is homologous with the strengths already approved and all the strengths are prepared from the same final mixture.

The main physicochemical properties of telmisartan are high lipophilicity and polymorphism. Structure identification of telmisartan has been provided.

The finished product is hygroscopic and the selected packaging material (moisture resistant aluminium blisters) is considered adequate.

Manufacture

The manufacturing process is clearly described. Telmisartan tablets are manufactured in two steps. The active substance is processed into a spray dried granulate, which is then mixed with sorbitol and magnesium stearate to give a ready-to-compress final mixture. The mixture is compressed to give tablets of the stated strengths.

The manufacturing process of the tablets was subject to prospective validation in accordance with the approved validation plan. The defined critical process parameters of the final mixture were checked and evaluated at full scale.

Control of starting materials

Active substance

Synthesis is performed in a 5-step procedure. The description of the synthesis, in process controls details of conditions; controls of raw materials and yield achieved are considered acceptable. The specification includes: description, identification, solubility, colour of solution, tests on related substances, residual solvents, heavy metals, water, loss on drying, sulphated ash and assay.

Impurities

Four substances have been identified as potential impurities of telmisartan. The proposed limits are acceptable, according to the levels observed in batches used during preclinical and clinical studies and in accordance with the ICH guideline. No significant degradation products in the solid state have been observed.

A fifth impurity (impurity V), which gave the most intense impurity peak by HPLC, was the primary focus for evaluation, but its structure could not be conclusively assigned. At least seven other unknown impurities have been separated by the HPLC procedure for related substances. All the unknown impurities are found at levels < 0.1%. Other impurities include heavy metals (< 10 ppm) and residual solvents (< 0.1 % each).

Determination and assay of the potential impurities was accomplished by a reverse HPLC method with UV detector. This method has been adequately validated for selectivity, sensitivity, linearity, accuracy, precision and robustness. The detection and quantitation limits for possible impurity I, II, III and IV were provided.

Since possible impurity V could not be isolated, validation of its determination by HPLC is not possible. The cause of the problem is that it degrades into three separate compounds during isolation. The specification of telmisartan limits the levels of impurity V to not more than 0.2 %. This compound was present in development batches and has therefore been qualified by toxicological studies. In accordance with ICH guideline a qualification of impurities > 0.1% is necessary when the highest single dose is > 2 g/day.

Residual solvents have been determined and assayed by direct injection GLC. Validation of the chromatographic method has been accomplished according to the ICH guidelines. Tetrahydrofuran and formic acid have been determined and assayed by two head space GLC validated procedures.

Other ingredients and packaging material

All ingredients have been adequately tested. All packaging material has been tested according to specifications, which ensure their suitability.

Control tests on intermediate products

The spray dried granulate has been tested for appearance, identification, active substance decomposition and assay of the drug substance. The test methods are adequately validated.

The specifications include the test parameters, particle size and dissolution rate with the corresponding analytical methods. These investigations were undertaken to decide which parameters should be included in the stability program. Therefore the influence of particle size on the dissolution rate was investigated. Commercial SD granulate with its typical and reproducible particle size distribution leads to tablets with dissolution rate consistent with the dissolution rate specifications for the tablets irrespective of slight variations in the particle size distribution.

Control tests on the finished product

The limits proposed for the chemical and physical tests at the time of release and throughout shelf-life are justified. All quantitative tests have been validated and shown to be suitable for the intended purpose. The specifications for all strengths include the following tests: identification, uniformity of weight, active substance decomposition, assay of the drug substance, dissolution and microbial contamination. The test methods are adequately validated.

The granulate batch numbers used for the manufacturing of the tablets are reported in the stability reports of the finished product.

Stability

Active substance

Three batches of the proposed 40 mg and 80 mg tablet strengths were stored in polyethylene bags in fibre drum for 24 months at 25 °C/60% RH and for 6 months at 40 °C/75% RH. Parameters tested were appearance, odour, colour and clarity of solution, melting behaviour, decomposition and assay of the drug substance. No change in organoleptic, physico-chemical and chemical criteria was observed. A slight decoloration was noticed after xenon light irradiation, and therefore telmisartan should be protected from direct sunlight.

The active substance stability under extreme conditions was found to be stable in alkaline media but to decompose under acidic conditions. Treatment with hydrogen peroxide resulted in formation of additional products. These decomposition products did not show up during the accelerated and long term testing investigation.

No chemical instabilities are to be expected during storage in any climatic zone. The stability testing will be continued in ongoing stability trials.

Intermediate product

One batch was stored for 8 months at 25 °C/60% RH and 40 °C/75% RH and was investigated for appearance and chemical stability. Two batches were stored at 25°C/60% RH and 40 °C/75% RH for 6 months, and analysed for appearance, loss on drying and chemical stability.

An increase in loss on drying was observed at 25 °C/60% RH. The granulate has therefore to be kept in tight containers during storage and transport.

Finished product

Three batches of 40 mg and 80 mg strengths were stored in the proposed marketing package aluminium blister at 25 °C/60% RH and 40 °C/75% RH for 12 months. Two batches of telmisartan 20 mg tablets were stored in the proposed aluminium blister at marketing package 25°C / 60% rel. hum. for up to 24 months and for six months at 40°C / 75% rel. hum. Parameters tested were appearance, average mass, disintegration time, dissolution rate, hardness, decomposition and assay of telmisartan, assessment of the packaging material (aluminium blisters).

The parameters tested did not change upon storage, with the exception of the hardness which increased at 40°C / 75% RH after 6 months and the dissolution rate which decreased slightly at 25°C/ 60% RH. Further stability data on the 40 and 80 mg strengths were provided covering 18 months real time date at the submission of the responses to the consolidated list of questions and 36 months real time data with the application for a shelf-life extension. Further stability data should be provided on the 20 mg strength. The shelf life for telmisartan tablets packed in tight packaging material protected from direct sunlight is 36 months for 40 mg and 80 mg tablets and 24 months for 20 mg tablets.

3. Toxico-pharmacological aspects

Pharmacodynamics

Data from *in vitro* studies support that telmisartan is a specific antagonist of the AT_1 subtype receptor with a Ki value of 3.7 nM. Up to the micromolar concentration, telmisartan had no affinity to the AT_2 receptor or to other receptors tested. Its affinity is higher than that of losartan and approaches that of AGII. The binding of telmisartan to AT1 receptors is slowly reversible as shown by *In vitro* receptor binding experiments and *in vivo* experiments in pithed rats. The latter experiments indicate that telmisartan is displaced very slowly from the AT_1 receptor by exogenously administered AGII under normal physiological conditions. The apparent non-competitive aspects of its pharmacodynamics and the persistence of its pharmacological activity (reduction of pressor response to AGII as well as of normal and high blood pressure, duration of inhibition, timecourse of the effect) will be subject of further preclinical investigations performed by the company.

In *in vivo* studies, telmisartan antagonised AGII induced pressor responses in all species studied. Telmisartan effectively reduced blood pressure in different animal models of hypertension

(renovascular hypertensive rats, low-renin hypertensive transgenic rats, and although apparently less in spontaneously hypertensive rats and stroke prone spontaneously hypertensive rats).

The AGII antagonistic effect appears within one hour (in rats and rabbits) and two hours (in dogs) after oral dosing and lasts for several hours (at least 24 h in the dog). The onset of hypotensive effect is dose-dependent and apparently slower than that of AGII antagonism in normal animals. However, significant reduction of arterial pressure may be achieved in a few hours after a single oral administration of 0.3-1 mg/kg. The hypotensive effect is long lasting (>24 h after high doses 3-6 days after repeated doses).

Telmisartan interference with feedback regulation makes plasma renin activity and AGII levels rise. Theoretically this might cause problems during chronic treatment, inducing rebound hypertensive states in the case of poor compliance, or requiring higher drug dosages to overcome competition by increasing endogenous AGII levels. This issue was addressed in (mREN2) 27-transgenic rats, a model of low-renin hypertension, in which recovery of the pre-treatment mean BP after escalating doses (0.5, 1.0 and 2.0 mg/kg daily) of telmisartan for three weeks was slow. In this model, however, only higher doses or longer treatment with telmisartan were shown to increase plasma renin activity and AGII levels.

The long-term antihypertensive effect of telmisartan was investigated in several additional preclinical studies submitted with the responses to the CPMP consolidated list of questions. These data further confirmed the sustained efficacy of temisartan with medium (6 weeks) to long-term (8 month) administration. No rebound hypertension was observed in another study during a ten-day washout period. In addition, repeated challenge with telmisartan in the same animals at three week intervals also suggest there is no adaptive change of the AT_1 receptor after pharmacological blockade with the AT_1 receptor antagonist in the rat.

With regard to the high levels of angiotensin II during AT_1 receptor blockade, it is considered that rebound hypertension after discontinuating the AGII antagonist is unlikely since the half-life of telmisartan is much longer than that of renin (10 and 15 minutes). Therefore there is enough time for renin release to continuously adjust to the decreasing levels of the active compound.

No major effects on heart rate were observed. In rats and guinea pigs, telmisartan at high doses had effects on the ECG (elevations of the ST-segment, shortening of the QT-interval, ventricular tachycardia and AV-block with bradycardia). *In vitro* electrophysiology studies were not performed because cardiac effects occurred in guinea pigs *in vivo* at toxicological doses far beyond those, which are anticipated to be in the therapeutic range. These effects were considered to be non-specific and unrelated to the mechanism of action. These data were confirmed by additional *in vitro* experiments in cardiac preparations from rats and guinea pigs. Only very high doses had a non-specific positive inotropic effect due to the high concentration used. Additionally in chronic toxicity studies, telmisartan had no effects on the ECG in dogs.

The pharmacology safety programme adressed among others, effects on central and autonomous nervous system, cardiovascular and renal systems and did not reveal any adverse effects at relevant dose levels and/or concentrations.

Pharmacokinetics

Pharmacokinetic studies were performed in mice, rats, rabbits and dogs. Telmisartan was rapidly absorbed in mice and rats (T_{max} values of 2 hours), more slowly in rabbits and dogs (T_{max} values of 7 hours). Bioavailability was 56-75 % in mice, 66 % in rats and 14-22 % in dogs. No clear gender differences in telmisartan plasma concentrations were observed in rats and dogs, whereas telmisartan plasma concentrations were higher in female mice compared to males. Values of AUC and C_{max} were proportional to doses of up to 500-mg/kg day in dogs, but increased proportionally with doses of $\geq$ 30 mg/kg/day in rats.

In vitro binding to plasma proteins was high in all species studied (about 99.6% in mice, rats and 98.7% in dogs). Apart from interaction studies with hydrochlothiazide, indomethacin and meloxicam, the potential for interaction with other medicinal products likely to be used in patients with cardiovascular disease (other antihypertensive drugs, antiplatelet agents, anticoagulants, antidiabetics, cholesterol-lowering drugs) is still not known.

Volume of distribution of telmisartan was 3-5 fold higher than that of total body water indicating a wide distribution. Half-life of elimination of telmisartan from plasma after oral administration was between 4 and 20 hours in all species. Tissue distribution studies showed that telmisartan-related radioactivity was mainly located in the liver, and only small amounts were detected in the central nervous system. In pregnant rats, telmisartan crossed the placenta and was excreted in the breast milk of lactating rats.

The metabolism of telmisartan was similar in all species (mice, rats, dogs and humans) and consisted mainly in glucuronidation to a 1-O-acylglucuronide. This metabolite did not demonstrate antagonistic activity at AT_1 receptors. The parent compound represented the majority of the radioactivity in plasma. Metabolism predominantly occurs during the passage through the intestinal wall, but also liver and other tissues (such as the kidney) contribute to its metabolism.

A supraproportional increase of exposure was observed in a number of toxicokinetic studies. Additional data from tissue distribution studies of ^{14}C-telmisrtan after single and multiple dosing in rats demonstrated that there is no accumulation and/or retention of radioactivity in any tissue after multiple doses compared to the acute schedule.

Excretion is primarily faecal (86-100%) and concerns the inactive 1-O-acylglucuronide glucuronide metabolite eliminated through the bile, within six hours of administration (29% in mice to 83% in rats).

Toxicology

Acute oral toxicity in rats and dogs was low. The toxicological target organs were the kidney and the gastrointestinal tract.

Kidney effects

After oral administration, telmisartan induced toxicity to the kidneys (increased in plasma urea, plasma creatinine and serum potassium at doses ≥ 4 mg/kg/day in rats, and in dogs at ≥ 5 mg/kg/day), gastric and/or duodenal mucosal erosions, and ulcers (in rats at doses ≥ 4 mg/kg/day and in dogs at ≥ 40 mg/kg/day). When the extent of plasma protein binding was taken into account, exposure of animals (rats and dogs measured) at toxic doses overlapped or exceeded AUC measured in humans. However, small or absent safety margins have similarly been reported for both ACE inhibitors and AGII antagonists.

The induced kidney tubular damage observed at doses ≥ 5 mg/kg/day in dogs is consistent with the reduced renal perfusion as a consequence of hypotension, leading to tubular hypoxia with tubular cellular degeneration and necrosis. However, in humans telmisartan is not expected to induce a hypotensive state with a concomitant reduction of renal blood pressure and ensuing renal lesions.

In rats and dogs, telmisartan induced renal juxtaglomerular hyperplasia with hypertrophy of the afferent glomerular arterioles of the kidneys. These effects are considered to be caused by the pharmacological action of high doses of telmisartan (blockade of the AGII induced inhibition of the renin release and thereby stimulation of renin producing cells) and have also been observed with ACE inhibitors and other AT_1 antagonists. Hypertrophy of the juxtaglomerular cells induced by AT_1 antagonists and ACE inhibitors is seen at doses in excess of therapeutically applied doses and it is considered not to be relevant to the therapeutic use in humans.

Gastrointestinal effects

The rat and rabbit seemed to be the most sensitive species towards telmisartan-induced gastrointestinal toxicity, whereas the dog seemed to be less susceptible. No gastrointestinal adverse effects were observed in mice. Gastrointestinal damage (ulcers and erosions) was not due to local irritation because they were observed after both oral and intravenous administraton of telmisartan. In an initial study performed in Chbb:THOM rats with oral administration for 7 days, the ulcerogenic potential of telmisartan was high, although similar to losartan and less than lisinopril. In further studies with two other strains of rat, Sprague Dawley and SHR Charles River, telmisartan demonstrated less gastrointestinal toxicity than previously shown in the Chbb:THOM strain. The mechanism of the gastrointestinal toxicity is not known.

Cardiac effects

Telmisartan induced reversible decreases in the heart weight of rats at ≥ 1.0 mg/kg/dayafter oral and at

≥ 20 mg/kg/day after intravenous administration. In dogs at ≥ 5 mg/kg/day after oral administration, the reduction was less pronounced and only after a longer exposure period. Significant decrease was observed only in the 5-week study at doses up to 500 mg/kg/day. Furthermore in 2 years carcinogenicity studies in mice and rats, telmisartan induced decreases in heart weights and reduced the incidence of age-related myocardial inflammation and fibrosis.

The pharmacological effect is a reduction of the hypertrophied cardiomyocytes to normal size rather than a pathological reduction of the myocyte diameter. These effects have also been observed with ACE inhibitors and with other AT_1 antagonists. The reduction of heart weight is attributed to the absence of the trophic effects of AGII on growing heart muscle cells. The heart weight reduction seems to result from the prevention of cardiac hypertrophy but it apparently does not imply a cardiac dysfunction due to loss of contractile activity of smooth muscle cells. In fact the diameter of smooth muscle cells has been shown to be reduced, but their number and cellular composition are reportedly unchanged.

Other

Additionally, telmisartan induced reductions in red cell parameters. These effects are well known effects of ACE inhibitors and AT_1 antagonists in chronic toxicity studies, since the renin angiotensin system seems to be involved in the regulation of erythropoietin in the kidneys.

Reproduction toxicity studies

Telmisartan does not affect fertility and has no teratogenic or embryogenic toxicity in rats. Angiotensin receptor antagonists are known to decrease placental perfusion and to cause renal damage to the rat foetus during late gestation and early lactation. In the rat, the concentrations of telmisartan increased in the foetal compartment during late pregnancy from about 27 % to about 60 % from day 12 to day 18 of pregnancy. Moreover in rats, telmisartan was excreted in milk at concentrations of 1.5-2 fold the maternal plasma concentration 4-8 hours post dosing and remained detectable for more than 48 hours. In rats, it reduced birth weight and slowed body weight gain during lactation.

There are no adequate data on the use of telmisartan in pregnant women. Animal studies do not indicate teratogenic effect, but have shown foetotoxicity. Therefore, as precautionary measure, telmisartan should preferably not be used during the first trimester of pregnancy. Telmisartan is contraindicated during the 2nd and 3rd trimester of pregnancy and breastfeeding because of the known foetotoxic effects drugs acting on the RAS system.

Carcinogenicity and mutagenicity studies

In two year carcinogenicity studies, no telmisartan-related carcinogenic effects were observed at oral doses of up to 1000 mg/kg /day in mice, and up to 100 mg/kg/day in rats. No evidence of mutagenicity or relevant clastogenic activity was observed in a standard battery of *in vitro* and *in vivo* genotoxicity tests.

Safety margins

Chronic treatment with telmisartan shows a small safety margin also with regard to effects on renal function in the dog (increase in serum urea nitrogen and creatinine) and gastrointestinal lesions in the rat (no safety margin) and dog (low safety margin). Giving oral saline prevents both these toxic effects, which are shared by ACE inhibitors and other AGII antagonists too. Despite this, gastrointestinal toxicity is considered unrelated to reduced gastric mucosal blood flow, which is reportedly increased during treatment. Although this toxic effect seems to be species-specific (the dog is less susceptible than the rat, the mouse is not sensitive at all) and rare in man for both ACE inhibitors and AGII antagonists, a better understanding of its nature could help predict and prevent its impact in patients.

Environmental risk assessment

Tests on the biodegradability and on the ecological effects of telmisartan suggest that there is no significant impact of its proposed introduction.

4. Clinical aspects

Human pharmacology

Pharmacodynamics

The clinical pharmacology program consists of 23 studies involving 384 healthy volunteers and patients.

Study 502.103

The suppression of blood pressure response to AGII challenge after 20, 40 and 80 mg telmisartan once daily per os in healthy young male volunteers (n=48) was investigated in this double blind, randomised, parallel group, placebo-controlled trial to determine pharmacodynamics, pharmacokinetics and safety of telmisartan.

Telmisartan dose-dependently inhibited the pressor response to AGII infusion with a maximum inhibition for diastolic blood pressure which was statistically significant ($p<0.05$) for all dose groups compared to placebo, and ≥ 80 % occurring at doses ≥ 40 mg statistically significant ($p< 0.05$) compared to 20 mg. The 20 mg dose of telmisartan showed an increase in median maximum inhibitory effect of up to 62 %, which was significantly different from that seen with placebo, but significantly less than that seen following doses of 40 and 80 mg (80% and 96 %, respectively). At 24 hours after dosing, the inhibiting effect was statistically significant for telmisartan doses ≥ 80 mg compared to placebo. Doses ≥ 40 mg showed a fast onset of action (0.3 hour) and a long duration of action (≥ 35.4 hours).

Significant increase of sodium and potassium excretion together with urine volume were observed within the first 3 hours post dose compared to the same phase at the pre-test day after telmisartan, whereas creatinine excretion remains stable.

In several studies, plasma renin activity and plasma angiotensin II levels increased as expected while aldosterone were reduced sometimes below the limit of detection. A specific, clinically relevant substrate for these changes is still unknown but similar effects have been described with other AGII antagonists or to some degree after angiotensin converting enzyme inhibition.

No specific trials in humans were performed to investigate the effects of telmisartan on cardiac function or impulse formation and conductivity. No relevant changes were found in the 365 healthy volunteers, 6 volunteers with renal insufficiency or 13 volunteers with hepatic failure. Telmisartan was not shown to alter heart rate in healthy volunteers.

In one interaction study with glibenclamide no changes induced by telmisartan comedication were found with respect to the pharmacodynamic parameters (glucose, C-peptide and insulin plasma levels).

Pharmacokinetics

The pharmacokinetics of telmisartan have been evaluated in the 23 phase I studies in normotensive subjects (N=384) and in 4 clinical studies in hypertensive patients (N=48 [502.201]; N=l14 [502.202]; N=274 [502.203]; N=9 [502.211]).

The pharmacokinetics of orally administered telmisartan was investigated in human volunteers after single (up to 160 mg once daily) or repeated doses (up to 320 mg once daily).

Telmisartan was rapidly absorbed after oral administration as solution, capsule or tablet. The time to peak plasma concentrations, T_{max}, was in the range of 0.5 - 3.0 hours and tended to decrease with higher doses.

Administration of telmisartan resulted in a disproportionate increase of C_{max}, a moderate non-proportional increase of AUC on increasing the doses above 40 mg after single and repeated administration, and showed high inter- and intra-individual variability. No appreciable drug accumulation was observed.

Pharmacokinetics was further characterised by rapid clearance (1000 - 2500 ml/min) and a high volume of distribution. The mean terminal half-life was greater than 20 hours.

The pharmacokinetics of telmisartan at steady state was assessed in patients with mild to moderate hypertension using capsules (40, 80 and 120 mg) and tablets (20, 40, 80, 120 and 160 mg) administered once daily for 28 days. These studies showed that steady state was achieved within 7

days of dosing. Results from these studies confirmed the previous results in that telmisartan plasma concentrations were highly variable, no drug accumulation was observed, plasma concentration increased disproportionately, and the mean terminal elimination half-life was in the range of 22 to 38 hours.

After oral administration of radioactive labelled telmisartan, 50% of the total radioactivity was detected in the plasma. One hour after administration, the parent compound represented approximately 85% and the inactive glucuronide approximately 11 % of total radioactivity in plasma. The absolute bioavailability of orally administered telmisartan was on average 43%. Similarly, after infusion 84% of total activity was recovered in the plasma as unchanged compound and up to 13% of activity as glucuronidate of telmisartan. No other metabolites could be quantified either after oral or after intravenous administration.

The main and only metabolite excreted in urine was glucuronidated telmisartan, only 6% of total urine activity could be identified as unchanged telmisartan, which corresponds to 0.06% of, totally administered radioactivity.

Telmisartan undergoes saturable first pass elimination in the gastrointestinal tract. The fraction of the parent compound, which is not conjugated to glucuronic acid during first pass, is taken up and systemically and eliminated predominantly by the liver. The liver capacity for uptake of telmisartan is high but saturable. Saturation of both pathways (intestinal first-pass conjugation and liver uptake) occurring after doses greater than 40 mg results in high and non proportional systemic concentrations of telmisartan.

Most of the administered dose (>98%) was excreted faecally within 144 h as the parent compound independent of route of administration. In human faeces, only the parent compound is found. Additionally since no data in patients with cholestasis are available, telmisartan is contraindicated in patients with biliary obstructive disorders.

Telmisartan was highly bound to plasma proteins (99.7 %, 99.9% of which bound to serum albumin).

Renal impairment

One controlled multicenter trial (502.211) investigated the efficacy and safety of telmisartan (40 to 80 mg) compared to enalapril (10 to 20 mg) given once daily in 71 hypertensive patients with moderate renal impairment (defined by a Cl_{crea} value between 30 and 80 ml/min inclusive) over a 12-week period. No relevant change in the telmisartan plasma concentration was seen in the subgroup of patients (n = 9) for whom these levels were determined.

Hypertensive patients with moderate renal impairment responded to telmisartan treatment in a comparable manner to enalapril. There were no relevant changes in creatinine clearance in both groups during treatment period. The plasma concentrations of telmisartan in patients with moderate renal failure were comparable with those of healthy volunteers.

The pharmacokinetic profile of telmisartan was also evaluated in 6 dialysis dependent subjects receiving single oral doses of 120 mg telmisartan (502.118). Both C_{max} and the AUC_{0-24h} were approximately 4-fold lower compared with values obtained in healthy controls. The terminal elimination half-life remained nearly unchanged.

The decrease in AUC in severe renal impairment seems to reflect the changes in serum proteins known for these patients. This leads to a higher percentage of unbound fraction of telmisartan so that distribution and elimination processes virtually reduce plasma levels. Total clearane is already very high and most probably not further increased by an increase in telmisartan free raction. The reason for the lower plasma levels is most probably a decrease in absorption. However, due to the small number of patients and the high variability of the measured pharmacokinetic parameters, telmisartan is contraindicated in patients with severe renal impairment.

Hepatic impairment (Study 502.123)

The pharmacokinetics of orally administered telmisartan was investigated in liver impaired patients (CP class A (n = 8) and class B (n = 4)). Patients with severe hepatic impairment were not investigated. The mean C_{max} was increased by a factor of 3 and AUC_{0-8} was 2.7-fold higher with oral doses of 20 mg and 120 mg telmisartan, than in the control group (healthy subjects). The mean

terminal elimination half-life remained unchanged. The bioavailability of telmisartan increased in the liver impaired volunteers to approximately 100% compared to 42-57% in healthy subjects indicating a significant decrease of the first-pass effect (hepatic shunt mechanisms, resulting in liver bypass).

A statement in the Summary of Product Characteristics has been added mentioning that the recommended dose in patients with mild to moderate hepatic impairment should not exceed 40 mg. Telmisartan treatment is contraindicated in patients with severe hepatic impairment.

Elderly (Study 502.124)

One study was conducted in 12 normotensive elderly healthy subjects (age range: 65 to 78 years; mean: 70 years) who received doses of 20 mg and 120 mg telmisartan for 7 days. This study confirmed the non-linear pharmacokinetics of telmisartan. No relevant differences in pharmacokinetic parameters were seen between elderly and younger volunteers. Thus, no dose adjustment is required for elderly patients.

Gender effects

In female subjects C_{max} and AUC_{ss} were approximately 3- and 2-fold higher, respectively, when compared to male subjects. These gender differences are not pronounced for other AGII antagonists or ACE inhibitors. Due to this unusual finding, the gender effect was investigated in nearly all-clinical efficacy studies. The company was asked to further address this issue during oral explanation in July 1998. Although the AUC is higher in females than males, no gender differences were observed with regard to human pharmacodynamics, clinical efficacy or safety.

No relevant differences were seen between females and males with respect to blood pressure reduction and adverse events. Thus, a dosage adjustment in females does not seem to be necessary.

Bioavailability and bioequivalence

The absolute bioavailability of telmisartan tablets was investigated in 2 studies comparing 2 oral formulations with intravenous infusion in 12 subjects each, one at 40 mg, and the other at 160 mg. For the 40 mg tablet, absolute bioavailability was 42%, and relative to an oral reference solution bioavailability was 90%.

A comparison of the plasma concentration time curve observed with the oral solution, capsule and tablet at the 80 mg dose levels showed that the elimination characteristics of all three formulations were similar. When comparing the AUC, capsules and tablets are bioequivalent.

A production batch of telmisartan 80 mg tablets was demonstrated to be bioequivalent to a clinical batch of 80 mg tablets in a trial including 32 healthy subjects (16 female and 16 male). No bioavailability studies have been submitted comparing the 40 mg tablet intended for marketing with the respective clinical batches used in the pivotal clinical studies. However, this issue is considered as satisfactorily addressed taking into consideration the absence of substantive changes during the pharmaceutical development, the *in vitro* dissolution tests, and the non-linear pharmacokinetics of the 80 mg strength.

Since in the lower dose range (10-40 mg) telmisartan pharmacokinetic behaviour is linear and all tablet strengths are prepared from the same blend and thus contain proportional amounts of all ingredients, the bioavailability of the 20 mg and 40 mg strengths can be assumed to be comparable.

Interaction studies

Effects of telmisartan on the pharmacokinetic and/or pharmacodynamics of other drugs as well as on food and on cytochrome P450 enzymes were investigated in 9 studies.

Interaction studies were performed with digoxin, warfarin, HCTZ, amlodipine, glibenclamide, ibuprofen, paracetamol and digoxin. No relevant change was seen with the exception of digoxin. Individual increases of digoxin trough levels of up to 39 % have been observed. However the 90% confidence interval was within the acceptance limits of no interaction. Considering the narrow therapeutic range of digoxin the elevation of trough levels may be of clinical relevance for individual cases. In view of these limited available data, a warning to recommend monitoring of plasma levels in patients taking both telmisartan and digoxin has been included in the summary of product characteristics.

No relevant inhibition or activation of the cytochrome P450 family was observed. Therefore, clinically relevant drug-drug interactions caused by therapeutic doses of telmisartan are unlikely to occur with drugs as substrates of cytochrome P450 enzymes.

Effect of food

Administration of telmisartan with food reduced $C_{max,ss}$ and increased the time to maximum plasma concentrations ($T_{max,ss}$). The pharmacokinetic/pharmacodynamic analyses showed a positive correlation between blood pressure reduction and pharmacokinetic parameters, suggesting that telmisartan 40 mg fasted, telmisartan 80 mg fed and telmisartan 80 mg fasted may all be on the plateau of the dose response with telmisartan 40 mg fed somewhat lower. Therefore dosing telmisartan with food does not appear to result in diminished therapeutic efficacy.

A statement was included in section 5.2 pharmacokinetic properties of the summary of product characteristics.

Clinical experience

The efficacy of telmisartan in patients with hypertension was investigated in 18 clinical trials conducted in North America and in Europe.

The primary endpoint was the effect on supine diastolic blood pressure at trough, measured as the mean change from baseline at study endpoint. The results were analysed using the intent-to-treat population. Beneficial effects of telmisartan on mortality and morbidity are currently unknown.

Placebo controlled dose response studies

Study 502.202 was a placebo-controlled study in which 207 hypertensive patients (DBP 100-114 mmHg) were randomised to receive 40 mg (n=40), 80 mg (n=41), 120 mg (n=41), telmisartan, 20 mg enalapril (n=42), or placebo (n=43), once daily for four weeks.

All telmisartan doses significantly lowered diastolic and systolic blood pressure compared to placebo after 28 days of treatment. For all dose groups a trough to peak ratio > 80% was found for both systolic and diastolic blood pressure lowering effect.

Study 502.203 was a placebo-controlled study in which 274 hypertensive patients (DBP 100 to 114 mmHg) were randomised to receive 20 mg (n=47), 40 mg (n=47), 80 mg (n=44), 120 mg (n=45), and 160 mg (n=45), or placebo (n=46) once daily for four weeks.

All doses of telmisartan significantly lowered the diastolic and systolic blood pressure compared to placebo after four weeks of treatment. However no dose-response relationship was established among telmisartan doses for supine diastolic blood pressure. There was statistically significant evidence for a linear dose-response relationship among telmisartan doses for supine systolic blood pressure with doses ≥ 40mg being significantly more effective than 20 mg. Trough to peak ratios of the diastolic blood pressure lowering effect were found to be > 80% for all dose groups, while for systolic blood pressure with a ratio ≥ 66% only doses ≥ 40mg exceeded the 50% threshold. The mean trough plasma concentration of telmisartan was dose-dependent.

This study confirms that a considerable proportion (about 1/5) of hypertensive patients may benefit from the 20 mg dose. The systolic BP lowering effect of the 20 mg dose is shorter-lasting than with higher doses. From 11 h post-dose onwards no significant reduction of systolic BP was found, although the reduction of diastolic BP was still significantly greater than with placebo at 12 and 24 h. Though questionable on the basis of the available data, the alleged shorter-lasting effect indicated by the lower trough-to-peak ratio might be a problem. The 20 mg dose might require better compliance in order to maintain satisfactory control of BP.

The trough-to-peak ratio for the 20 mg dose is 49%, just below the accepted criteria for once-daily regimen (at least 50% of the peak effect remaining at the end of the 24 hours). When trough-to-peak ratios are calculated individually for patients rather than by treatment group, the medians range from 31% to 53% for supine systolic BP. This means that for most patients, also from dose groups other than the 20 mg one, the trough-to-peak ratio might actually be too low.

Study 502.206 was a placebo-controlled study in which 440 hypertensive patients (supDBP 95-114 mmHg) were randomised to receive 40, 80, 120 and 160 mg telmisartan, 20 mg enalapril or

placebo once daily for 12 weeks.

All doses of telmisartan significantly lowered the diastolic and systolic blood pressure compared to placebo.

Results of studies 502.202, 502.203 and 502.206 demonstrate that telmisartan given at doses of 20, 40, 80, 120 and 160 mg once daily for 4 to 12 weeks is more effective than placebo in lowering diastolic and systolic blood pressure. However, there was no relevant dose-related decrease in diastolic blood pressure response or increase in response rates among the telmisartan groups. Neither a minimum effective dose nor a plateau in the dose-response curve was identified.

Due to the limited number of patients involved in these studies, the time to recovery of baseline BP after discontinuation of treatment with telmisartan, and its dose relationship was difficult to assess. There was an apparent trend to dose relationship for the time to recovery of baseline SBP whereas data concerning DBP were inconsistent.

Placebo-controlled studies

Two placebo-controlled studies were performed using a dose titration scheme with either one (502.207) or two titration steps (502.208). The design included the additional active comparison against atenolol (502.207) and amlodipine (502.208).

With respect to blood pressure measurements both trials were identical to the previously described fixed dose trials, while study 502.208 also included 24h ambulatory blood pressure monitoring.

Study 502.207 was a placebo-controlled, randomised parallel-group dose-titration multicenter study with mild to moderate essential hypertension (mean supDBP $\geq$95 and $\leq$114 mmHg). 236 patients were randomised to receive either 40 mg telmisartan (uptitration to 80 mg), 80 mg of telmisartan (uptitration to 120 mg), or 50 mg atenolol, (uptitration to 100 mg), or placebo once daily for 8 weeks.

Both telmisartan regimens showed statistically significant reductions in supDBP and supSBP compared to placebo. There were no statistically significant differences between the telmisartan regimens or between the telmisartan regimens and atenolol.

Study 502.208 was a placebo-and active controlled, randomised parallel-group dose titration multicenter study in patients with mild to moderate hypertension (mean supDBP = 95 = 114 mmHg). 232 patients were randomised to receive either 40 mg telmisartan (uptitration to 80 mg and 120 mg), or 5 mg amlodipine (uptitration to 10 mg), or placebo once daily for 12 weeks.

The telmisartan regimens showed statistically significant reductions in supDBP and supSBP compared to placebo. There were no statistically significant differences between the telmisartan and amlodipine regimens.

Results of studies 502.207 and 502.208 demonstrate the antihypertensive efficacy and safety of telmisartan monotherapy in the treatment of mild to moderate hypertension in a once daily dosing regimen with telmisartan 40-120 mg compared to placebo for the period of 2 to 3 months. The antihypertensive effect was comparable to atenolol and amlodipine. However, the 120 mg dose resulted in no greater antihypertensive effect than 80 mg. It also appeared from the data that a certain group of patients who did not respond to 40 mg or 80 mg dose was unlikely to achieve the target BP response at higher doses (120 mg). These data also confirmed the results of the dose-finding studies demonstrating no relevant dose-related decrease in diastolic blood pressure response or increase in responder rates among the different telmisartan dose regimens. In study 502.208, 48% of telmisartan-treated patients responded to the 40 mg dose whereas in study 502.207 this proportion of patients was 45%.

Long-term active controlled studies

The long-term efficacy and safety of telmisartan was evaluated in 4 double blind active controlled studies. Two studies (502.214 and 502.216) are described and evaluated in this section. The other two long-term studies are assessed under studies in elderly (502.210) and under controlled studies in combination with other antihypertensive agents (502.215).

Study 502.214 was a randomised, double blind, active controlled, parallel group in patients with mild to moderate essential hypertension (supDBP = 95 and = 114 mmHg). 578 patients were randomised to

telmisartan (40 mg with uptitration to 80 and 160 mg once daily) compared to lisinopril (10 mg with uptitration to 20 and 40 mg once daily), with addition of open-label HCTZ (12.5 or 25 mg). The total duration of treatment was 52-60 weeks (up to 12 weeks titration and 48 weeks maintenance period).

Study 502.216 was a double blind, active controlled parallel-group study in patients with mild to moderate essential hypertension (mean supDBP = 95 = 114 mmHg). 533 patients were randomised to telmisartan (40 mg to 80 mg to 120 mg once daily) or atenolol (50 mg to 100 mg, once daily). The duration of double blind active treatment was 26 weeks. In case of insufficient response HCTZ was added at week 8.

Results from studies 502.214 and 502.216 confirmed the usefulness of telmisartan regimen starting with 40 mg, but offered less information beyond the 80 mg dose. Furthermore, the results showed that the addition of HCTZ to telmisartan had a greater additional antihypertensive effect than uptitration to the highest telmisartan dose. Efficacy and safety were comparable to the treatments with lisinopril and atenolol. Both the clinically irrelevant increasing hypotensive effect on increasing the dose above 80 mg daily and the positive interaction with HCTZ are mentioned in the Summary of Product Characteristics.

Long-term uncontrolled studies

Long-term efficacy of telmisartan in patients with mild to moderate essential hypertension was evaluated in 4 open-labelled, uncontrolled studies (502.219, 502.220, 502.221, 502.228). Two studies (502.219, 502.220) were long-term open-label extensions of controlled clinical trials.

These studies demonstrated that telmisartan is effective and safe in long-term use. The proportion of patients with normalised blood pressure by telmisartan monotherapy (40 or 80 mg) was approximately 63% (ranging from 41-73% in the studies). The addition of HCTZ in patients who were not controlled with monotherapy resulted in an increase of approximately 17% of the proportion of controlled patients. Overall, approximately 80% of the patients were controlled (i.e. had a DBP < 90 mmHg) at last available trough.

Active controlled studies in severe hypertension

Two trials were conducted in patients with severe hypertension [502.209, 502.238]. Study 502.209 had to be discontinued prematurely due to recruitment difficulties and is, therefore, not suitable to demonstrate efficacy.

Study 502.238 is an interim report of an open-label comparison of the antihypertensive efficacy and safety of telmisartan (80 and 160 mg once daily) versus enalapril (20 and 40 mg once daily), with the optional addition of 25 mg HCTZ and 5 mg amlodipine, in 48 patients (telmisartan: n=34, enalapril: n=14) with severe essential hypertension (supDBP $\geq$ 115 and $\leq$ 1.30 mmHg) over a treatment period of 8 weeks.

Efficacy and safety of telmisartan monotherapy in patients with severe essential hypertension was not demonstrated in proper controlled clinical trials. However, it appeared that the addition of HCTZ to telmisartan is effective in patients with severe hypertension. Therefore, it is proposed that the indication should include all degrees of essential hypertension with the option to add HCTZ to telmisartan monotherapy in case of non-response.

Studies in elderly patients

The efficacy of telmisartan in elderly (= 65 years old) was investigated in one active controlled study as well as in subgroup analyses in the controlled clinical trials.

Study 502.210 was a randomised, double blind, active controlled parallel group trial in patients with mild to moderate essential hypertension. 278 patients were randomised either to telmisartan (20-40-80 mg once daily), or enalapril (5-10-20 mg once daily) alone and in combination with HCTZ (12.5 mg to 25 mg once daily). The duration of the study was 26 weeks. 26% of patients were over 75 years of age.

Blinded titration steps were planned for both drugs (telmisartan starting dose 20 mg) every four weeks for the first 12 weeks on the basis of diastolic BP. Telmisartan 20 mg controlled diastolic BP adequately in the first four-week titration period in 33.1% of patients. Only one out of four patients (24.1%) who failed to respond to telmisartan 20 mg at week 4 became responders at week 8 after

taking 40 mg for four further. At week 12 telmisartan had normalised diastolic BP in 63.2% of patients; 16.9% were still on monotherapy with telmisartan 20 mg.

Results showed that oral doses of 20 to 80 mg telmisartan once daily (with or without addition of HCTZ) lowered blood pressure as well as oral doses of 5-20 mg enalapril once daily (with or without addition of HCTZ). No significant differences were observed between both treatments groups. The response rates were high in both treatment groups.

Subgroup analyses in the controlled clinical studies showed no relevant difference in mean blood pressure changes between elderly and younger patients.

Controlled studies in combination with other antihypertensive agents

Two controlled trials investigated the combination of telmisartan with HCTZ (502.204, 502.215).

Study 502.204 is a factorial design placebo-controlled study that evaluated telmisartan alone (20, 40, 80, 160 mg), HCTZ alone (6.25,12.5, 25) and all possible combinations of the two products during an 8 week treatment period. A total of 818 patients were randomly assigned to one to the 20 different treatment groups.

Telmisartan alone, 20 to 160 mg, significantly decreased trough DBP and SBP compared to placebo. HCTZ decreased DBP and SBP in a dose-related manner over the range of 6.25 to 25 mg. The response at trough to 6.25 mg was not significantly greater than placebo.

The benefit of the combination was confirmed by the response surface analysis of adjusted means of all treatment groups, which indicated that most of the combination treatments resulted in better response than the respective individual components. Telmisartan 80 mg/HCTZ 12.5 combination was significantly better than its individual components in decreasing both systolic and diastolic blood pressure after 8 weeks. The combination telmisartan 40 mg/HCTZ 12.5 showed smaller benefits compared to the components.

These results suggest that the 20 mg dose is not to be disregarded. In some patients the reduction of both systolic BP and diastolic BP may be achieved better by adding hydrochlorothiazide to 20 mg telmisartan than by increasing the dosage of the latter.

Subgroup analysis showed that the magnitude of the DBP and SBP reduction with telmisartan monotherapy was less in black than in white patients. Numerous studies have already demonstrated that black hypertensive patients are less responsive than whites to blood pressure-lowering effects of ACE inhibitors. Although not supported by specific data on the relation between the PRA and telmisartan effect in blacks, the lower hypotensive effect of telmisartan in this population is mentioned in the summary of product characteristics.

Study 502.215 was a controlled long-term comparison of monotherapy with telmisartan 40 mg and 80 mg compared with combination therapy of telmisartan 40 or 80 mg with HCTZ 12.5 mg The study involved 363 hypertensive patients and aimed to evaluate the percentage of patients achieving a response defined by a reduction of DBP to < 90 mmHg. The treatment duration was 26 weeks.

Overall, 57.4% of patients (81/141) who failed to meet the goal response with either 40 mg or 80 mg telmisartan as monotherapy met the goal response with combination therapy (telmisartan and HCTZ).

Studies 502.210, 502.214, 502.216 were 3 other controlled long-term studies in which HCTZ was added in an open way if blinded titration of study drugs failed to control diastolic blood pressure. The addition of HCTZ resulted in normalisation rates of diastolic blood pressure in between 40 and 70 % of non-responders, which is in good agreement with those seen in studies 502.204 and 502.215.

On the basis of these results it is recommended that a thiazide diuretic like HCTZ can be added to telmisartan if patients do not respond to telmisartan monotherapy. Other antihypertensive agents were not investigated in controlled studies in combination with telmisartan.

Safety

Overall extent of exposure and premature discontinuation

384 subjects received telmisartan in 23 clinical pharmacology trials. A total of 4,441 adult patients were enrolled in clinical trials of hypertension, 2,969 of which started treatment with telmisartan, 396

patients received placebo and 1,076 patients were treated with comparative antihypertensive agents including enalapril, atenolol, lisinopril, amlodipine and HCTZ.

Overall, including patients switched to telmisartan from other treatment groups in open extension studies, 3,445 patients were treated with telmisartan either alone or in combination with HCTZ.

A total of 1,400 patients in the safety database received telmisartan for 6 months or more, and a total of 415 patients received telmisartan for more than one year. Telmisartan was used as monotherapy in 3,156 patients, 841 of which received monotherapy for six months or more. Of these, 253 patients received monotherapy for one year or more. The combination telmisartan/HCTZ was used by a total of 1,331 patients, of which 614 were treated for = 3 months.

The majority of the patients received 40 mg and 80 mg doses of telmisartan. 169 patients were treated with the 80 mg telmisartan regimen for more than one year.

The incidence of premature discontinuation in the telmisartan group due to adverse events was low (4.8%), similar to the discontinuation rate of placebo (5.8%), and lower than the discontinuation rate of the comparator (7.9%).

Analyses of adverse experiences

Altogether, 2,144 of 3,445 patients treated with telmisartan (62.2%) experienced at least one treatment emergent adverse event during the course of clinical hypertension trials, which ranged from one week to more than 52 weeks.

The most frequently reported adverse events include headache (11.8 %), upper respiratory tract infection (10.7%), pain (7.6%), dizziness (6.6%), back pain (6.0%), fatigue (4.6%), diarrhoea (4.4%) sinusitis and bronchitis (both 4.1 %), coughing (3.2%), influenza-like symptoms (3.0%), dyspepsia (2.7%), chest pain (2.5%), myalgia (2.4%), nausea (2.2%), pharyngitis and urinary tract infections (both 2. 1 %).

The adverse event profile of telmisartan treatment in placebo-controlled trials appeared comparable to that of placebo. Events occurring with more than a 1% difference with telmisartan than placebo included backpain, pharyngitis, diarrhoea and urinary respiratory infection. No treatment-emergent adverse events occur with increasing frequency with escalating telmisartan doses; no adverse events appear to have a dose-related frequency of severity.

Because of the greater extent of exposure, the adverse event incidence rates in the long-term controlled trials were higher than in placebo-controlled studies, but the reported events were similar in the telmisartan or comparator groups with the exception of diarrhoea and upper respiratory infection which were about 1 % higher in the telmisartan group.

The adverse event profile in the long-term uncontrolled studies did not differ from that of long-term controlled studies. Only a few events, which were below the 1% threshold in randomised, controlled long-term studies appeared at this threshold (= 1 %) in uncontrolled long-term studies. These included gastritis, unspecified gastrointestinal symptoms, angina pectoris and eczema; but all occurred in less than 1.5 %.

Serious adverse events

100 (2. 9%) of 3,445 patients treated with telmisartan in 19 clinical hypertension trials experienced serious adverse events.

Three patients had serious adverse events that resulted in death while receiving telmisartan treatment. No deaths occurred during treatment with placebo or other antihypertensive agents.

A presumed myocardial infarction resulting in death in study 502.202 was considered by the investigator to be related to study medication. For the second case (cardiac arrest), both the investigator and clinical monitor felt that there was a reasonable possibility that the event was caused by the study drug in the second case. For the third case (cerebrovascular disorder) both the investigator and clinical monitor considered the event to be unrelated to study drug.

Among events concerning the cardiovascular system, the most frequent serious adverse events reported with telmisartan were myocardial infarction (9 patients, 0.3%), angina pectoris (7 patients, 0.2%), chest pain (6 patients, 0.2%) hypertension, atrial fibrillation (4 patients, 0.1%) and coronary disorder

(2 patients, 0.1 %). The events were judged to be possibly related to telmisartan by the investigator or sponsor in three of the angina pectoris cases, in three cases of hypertension, and in one case each of atrial fibrillation, chest pain, cardiac arrest and palpitations.

Serious adverse events pertaining to the gastrointestinal system were reported in six patients (0.2%) treated with telmisartan. None of these events was considered related to telmisartan.

There was one report of a serious renal adverse event with telmisartan. This occurred in a patient with pre-existing renal impairment who was hospitalised for a severe urinary tract infection. Telmisartan was discontinued and the urinary tract infection was treated with antibiotics. Two days later the patient developed a worsening of renal insufficiency that was considered by the investigator to be possibly related to telmisartan.

The incidence as well as the type of serious adverse event with telmisartan is comparable with other already licensed angiotensin antagonists. No additional risks were seen on the basis of the submitted data.

Analyses of laboratory parameters

The incidence of marked changes in the majority of laboratory parameters was less than 1 % and similar for both telmisartan and placebo in the six placebo-controlled trials. Triglycerides were the parameter with the highest incidence (16.3% vs. 14.4%). The increase in uric acid (0.5% vs. 0%), and the decrease in haemoglobin (0.8% vs. 0.3%), and platelet count (0.8% vs. 0 %) were more frequent in the telmisartan group than in the placebo group.

In the total telmisartan population (n=3,445) the incidence of marked changes was similar to the placebo-controlled trials. Marked changes in triglyceride levels (19.3%) and platelet counts (3%) occurred with a higher frequency than other parameters for all telmisartan-treated patients. In addition, marked increases in BUN were noted in 3.4% of all telmisartan patients, which were more frequent during treatment with telmisartan/HCTZ combination therapy (4.2% versus 1.0%). Among patients with normal baseline of renal functioning, the incidence of marked increases in BUN was 0.5% on telmisartan monotherapy.

Fourteen patients (0.4%) experienced hepatic adverse events of increased γ-GT, SGOT, SGPT or abnormal hepatic function. The intensities of these events were mild for nine patients and moderate for five patients.

Altogether, laboratory adverse events led to permanent discontinuation of telmisartan treatment for 4 patients (0.1%). Laboratory test parameters leading to discontinuation were hyperuricemia, increased BUN and increased serum creatinine in one patient, granulocytopenia in one patient, and abnormal hepatic function in 2 patients.

Subgroup analysis of adverse events by age in clinical trials of hypertension

1,606 out of 2,591 patients (62.0%) experienced at least one adverse event in the = 64 years group, compared to 436/686 (63.6%) in the 65-75 years group and 101/168 (60.1%) in the = 75 years group.
There were no individual events, or patterns of events, for which elderly telmisartan patients experienced a markedly higher incidence including orthostatic events, dizziness, fatigue and cough.
In general, in the therapeutic study population the overall incidence of adverse events was not higher in the = 65 years group than in the < 65 years group.
The safety data in the enalapril-controlled long-term study 502.210 in elderly show no difference in the incidence rates of adverse events between telmisartan and enalapril in elderly (each 70.5%).

Events of special interest

Orthostatic changes

Fifty-six (1.6%) telmisartan patients experienced adverse events, which involved postural changes. Almost half of the telmisartan patients were using HCTZ at the initial onset of the orthostatic event. Most of the events were mild and did not result in discontinuation.

Rebound hypertension

Rebound hypertension following discontinuation of telmisartan treatment was reported in one of 74 patients treated with telmisartan 40-120 mg who participated in the ten-day no-treatment washout period in placebo-controlled trial 502.202. This period of aggravated hypertension in a patient non-responding to telmisartan during active drug treatment was not considered drug related by the investigator.

Cough

The incidence of cough occurring with telmisartan was similar to that reported for placebo-treated patients (1.6%) in six placebo-controlled trials and was significantly less frequent than with enalapril and lisinopril.

Gastrointestinal adverse events

Telmisartan plasma concentrations in man for some doses studied in phase III were similar to or exceeded those seen at the minimal toxic level at which gastric erosions/ulcers were seen in preclinical studies in rats and dogs. Therefore, clinical trial protocols included prospective monitoring of gastrointestinal adverse events.

Overall, gastrointestinal adverse events were reported by 15.1 % of patients treated with telmisartan in clinical hypertension trials. Diarrhoea was the most common gastrointestinal adverse event (4.4%), followed by dyspepsia (2.7%), nausea (2.2%) and abdominal pain (1.7%).

The discontinuation rate for gastrointestinal adverse events during telmisartan therapy was 27/3445 patients (0.8%). Telmisartan was discontinued in ten patients (0.3%) due to diarrhoea, in five (0.1%) due to dyspepsia, and in three patients each (0.1%) due to nausea and abdominal pain.

Data showed that despite the absence of dose dependent gastrointestinal toxicity, there was a relatively high incidence of gastrointestinal adverse events (from 6.0 to 8.5%, in patients without gastrointestinal history; from 8.0 to 23.1% in patients with gastrointestinal history; from 6.2 to 9.0% overall). Data from the long-term active control trials suggested that duration of exposure to telmisartan may increase the risk of gastrointestinal toxicity.

Comparable data were found for patients treated with active comparator drugs (140/975, 14.4% in patients without gastrointestinal history, 24/101, 23.8% in patients with gastrointestinal history, 164/1076, 15.2% overall).

The risk of gastrointestinal adverse events in telmisartan treated patients was clearly higher in the presence of gastrointestinal history than in patients without gastrointestinal history (16.2 % vs. 8.9 %). The risk in the telmisartan group compared to placebo was much higher in patients with gastrointestinal history (16.2% vs. 7.4%) than in patients without it (8.9% vs. 7.4%). These findings were reported in the Summary of Product Characteristics.

Melena occurred in seven patients (0.2%), duodenal ulcer in three (0.1%), rectal haemorrhage in two

(0.1%), and gastric ulcer, haemorrhagic gastric ulcer and peptic ulcer in one patient each (<0.05%). One of these events was a serious adverse event. One melena and one rectal bleeding were judged by the investigator to be related to study drug. All other gastrointestinal bleedings were considered not to be drug related. Gastrointestinal bleeding or ulcer was reported in one placebo-treated patient.

Considering the low incidence of gastrointestinal bleeding, the relative risk of telmisartan compared to controls could not be reliably estimated.

Angioedema

There was one report of angioedema among 3,445 telmisartan-treated patients (0.02%). considered to be drug-related.

5. Overall conclusions and benefit/risk assessment

Benefit

Efficacy and safety were assessed in 14 randomised controlled trials (13 double blind, 1 open label) in patients predominantly with mild to moderate hypertension. The controlled studies include 6 placebo-controlled trials with treatment duration up to 12 weeks. Five of these trials also had control groups in which patients were treated with active antihypertensive drugs. In the 4 other trials, the efficacy of telmisartan was compared against active treatment over a long-term period (3-12 months). One of these long-term studies includes only elderly people. A further 4 studies investigated special populations (severe hypertensives) or special (renal) effects Four additional uncontrolled trials cover study periods of at least one year.

As many as 2647 patients were exposed to telmisartan doses of 20 mg to 160 mg in controlled trials; 1568 patients were enrolled in the 4 long-term uncontrolled studies, 1340 of whom had previously participated in controlled studies.

The antihypertensive effect of telmisartan was compared with other BP-lowering drugs, including atenolol, lisinopril, enalapril, but not with other AGII receptor antagonists, such as losartan. Telmisartan lowered mean arterial pressure to much the same extent as all the other drugs.

Telmisartan was given at doses of 20, 40, 80, 120 and 160 mg once daily. There was no relevant dose-related difference in decrease in diastolic blood pressure response or increase in related response rates among the telmisartan groups. Neither a minimal effective dose nor a plateau in the dose-response curve was identified.

Telmisartan was effective in both male and female patients, younger and elderly, in all ethnic subgroups, and in the long-term treatment of hypertension without evidence of tolerance.

The usually effective dose is 40 mg daily since 40% to 50% of the included hypertensive patients responded to this dose. Despite the lack of apparent advantage in terms of safety and tolerability, some patients may already benefit at a daily dose of 20 mg. Doses greater than 80 mg do not contribute to any further antihypertensive effect.

Risk

Telmisartan has been administered to 3,445 patients and has been found to be safe and well tolerated. A total of 1,400 patients received telmisartan for 6 months or more, and a total of 415 patients received telmisartan one year or more.

Major adverse events did not occur and side effects were comparable to those reported with ACE inhibitors, but the incidence of coughing was halved in the telmisartan patients.

In placebo-controlled clinical trials, the overall incidence of adverse events with telmisartan was similar to placebo. Only the incidence of back pain, pharyngitis, diarrhoea and upper respiratory infection reportedly was at least 1% higher in telmisartan-treated patients compared to placebo group. Compared to enalapril, incidence of dry cough was halved in telmisartan treated patients.There was no relationship between dose and incidence or severity of adverse events. There were no individual events, or patterns of events, for which elderly patients treated with telmisartan experienced a

markedly higher incidence. The incidence as well the type of serious adverse events with telmisartan was comparable with other already licensed AGII antagonists. No additional risks are seen on the basis of the submitted data.

Gastro-intestinal bleeding and ulcers occurred rarely, but more frequently than in the placebo group.. The incidence of gastro-intestinal adverse events in the subgroup of patients with either a history or an active baseline condition of gastric or duodenal ulcer or stomach dysfunction was higher than in the population of all telmisartan-treated patients (21.9% vs. 15.1%). Similar results were found for patients treated with active comparator drugs (23.8% vs. 15.2%)

In view of the gastro-intestinal toxicity seen in preclinical studies, and the clinical data regarding gastrointestinal adverse events, the company presented, during the oral explanation in July 1998, the post-marketing program plan to further investigate the potential gastrointestinal risk and the feasibility of comparative trials with other antihypertensive agents of the same class. The CPMP agreed on the company's proposal to perform an observational study with a target population of 10,000 denovo patients on telmisartan to provide further evidence regarding general safety and in particular gastrointestinal adverse events. This study will be handled as a follow-up measure to the marketing authorisation.

During the oral explanation the company also presented data, which showed that although the distribution of baseline risks and exposure time were not in favour of telmisartan, combination with ASA or other NSAID's does not carry an incremental risk in gastrointestinal adverse events as compared to active comparators. Furthermore, efficacy of telmisartan was shown to be maintained during concomitant use with ASA or other NSAID's.

Conclusion

Pritor is a benzimidazole derivative antagonist of sub-type 1 angiotensin II receptors and has been shown in animals and man to exert a hypotensive effect.

The quality of Pritor tablets, as demonstrated in the chemical, pharmaceutical documentation, is considered acceptable.

Pritor has demonstrated efficacy in patients with essential hypertension. The concerns rose with regard to the possible gender effect, concomitant use with ASA or NSAID's and gastrointestinal side effects, have been adequately addressed. Therefore, the CPMP considered the benefit to risk assessment positive and recommended the granting of a Marketing Authorisation for all strengths and presentations of this medicinal product.

6. Post-Authorisation

Interactions
Reversible increases in serum lithium concentrations and toxicity have been very rarely reported during concomitant administration of lithium with telmisartan. Co-administration of lithium and telmisartan should be done with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

Based on the experience with the use of other medicinal products that blunt the renin-angiotensin system, concomitant use of telmisartan with products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporin or other medicinal products such as heparin sodium) may lead to increases in serum potassium. Monitoring of potassium plasma levels is advised when such medicinal products are co-prescribed.

Adverse drug reactions

Since the introduction of telmisartan in the market, cases of erythema, pruritus, faintness, insomnia, depression, stomach upset, vomiting, hypotension, bradycardia, tachycardia, dyspnoea, eosinophilia, thrombocytopenia, weakness and lack of efficacy have been reported rarely.

As with other angiotensin II antagonists, isolated cases of angioedema, pruritus, rash and urticaria have been reported.