SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Pritor Plus. For information on changes after approval please refer to module 8.

1. Introduction

The goal of management of hypertension is to reduce morbidity and mortality by the least intrusive means possible. This may be accomplished by achieving and maintaining the systolic blood pressure (SBP) below 140 mmHg and the diastolic blood pressure (DBP) below 90 mmHg and lower if tolerated. The other modifiable risks factors for cardiovascular disease should also be controlled. In addition, the management of hypertension is aimed at preventing, detecting and treating the complications of hypertension. Finally, the adherence to hypertensive therapy should be encouraged since this remains a major therapeutic challenge contributing to the lack of adequate control in more than two-thirds of the patients with hypertension. In addition to the lifestyle modifications (such as weight loss, limitation of alcohol and sodium intake) the decision to initiate a pharmacological treatment of hypertension requires consideration of several factors: the degree of blood pressure elevation, the presence of target organ damage and the presence of clinical cardiovascular disease or other risks factors. Evidence of beneficial effects on overall mortality and fatal and non-fatal cardiovascular events has been observed mainly for three classes of antihypertensives: diuretics, β-blockers and ACE inhibitors.

The current guidelines concerning the clinical assessment of the efficacy of a medicinal product in the treatment of hypertension include the assessment of efficacy in lowering blood pressure, effects on morbidity and mortality and target organ damage.

The application is a new combination of two active ingredients telmisartan and hydrochlorothiazide. Telmisartan is an antagonist of the subtype 1 of the angiotensin II receptor (known as the AT_1 receptor) already approved in the EU through the centralised procedure on 11 December 1998. The currently approved indication of telmisartan is the treatment of essential hypertension. Hydrochlorothiazide is a diuretic belonging to the family of thiazide diuretics. These two substances have been developed in fixed dose combinations containing 40 mg/12.5 mg and 80 mg/12.5 mg of telmisartan and hydrochlorothiazide. The proposed combination of telmisartan/hydrochlorothiazide reflects a combination treatment already in clinical use.

Four such combinations of angiotensin II antagonists and hydrochlorothiazide are already authorised in the European Union: losartan, valsartan, irbesartan or candesartan with 12.5 mg of hydrochlorothiazide.

The Applicant presented a dossier consisting of results of tests and trials with telmisartan as mono-component and in combination with hydrochlorothiazide, together with published literature on hydrochlorothiazide as mono-component. Therefore the application was submitted in accordance with Article 4.8a) ii) of Council Directive 65/65/EEC requiring the demonstration of a "well established use" of hydrochlorothiazide, as required by Commission Directive 1999/83/EC. The scientific assessment of the application confirmed that hydrochlorothiazide has been widely used with regular application in patients in the European Union. Hydrochlorothiazide has been made available in the European Union for more than 40 years for the treatment of hypertension (either alone or, more recently, in combination with other medicinal products such as ß-blockers, angiotensin-converting enzyme inhibitors and now with angiotensin II receptor antagonists). It still attracts a high degree of scientific interest as shown by publications, the availability of new combination treatments with hydrochlorothiazide and its inclusion in therapeutic guidelines on the treatment of high blood pressure.

The documentation submitted by the applicant for hydrochlorothiazide covered all aspects of the safety and efficacy assessment (as detailed in the sections below on Part III and Part IV).

The extent of the post marketing experience with hydrochlorothiazide in the European Union was reflected in the literature presented in the application.
It can therefore be concluded that the applicant demonstrated that hydrochlorothiazide has a "well-established use", with an acceptable level of safety and recognised efficacy in the proposed indication and suitable for use in combination therapy with telmisartan.

2. Chemical, pharmaceutical and biological aspects

Composition

This application concerns a new combination of two previously authorised active substances telmisartan and hydrochlorothiazide in the combinations 40 mg/12.5 mg and 80-mg/12.5 mg respectively, in the form of two-layer tablets. The tablets are packed in foil/laminate blisters.

Active substance

Boehringer-Ingelheim International has developed Telmisartan, and all relevant quality characteristics of this active substance have previously been evaluated for the product Micardis. Hydrochlorothiazide is a well-known substance, which is the subject of a European Pharmacopoeia (Ph. Eur.) monograph. Information on this active substance has been provided in the form of a European Drug Master File (EDMF).

Telmisartan

(Information on the synthesis, control and stability of this active substance has already been considered as being satisfactory when the product Micardis was authorised in the EU).

Hydrochlorothiazide
Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide. It is a white or almost odourless white, crystalline powder free from visible contaminations and there are no asymmetric centres and the molecule is freely soluble in aqueous solutions. A detailed quality document concerning the synthesis and control has been provided by the AIM in the form of an EDMF.

Specification

The specification is in accordance with the Ph. Eur. Monograph.

Stability

The stability results for three production batches packed in double polyethylene bags in HDPE drums for 6 months under accelerated conditions (40 °C / 75 % r.h.) and under 'ambient' conditions for 36 months (25 °C / 60 % r.h.) indicate the satisfactory stability of this established pharmacopoeial active substance.

No degradation products could be detected and no significant changes were observed in any of the test parameters (e.g. description, loss on drying, related substances, assay) when examined by validated methods. The results support the retest period.

Other ingredients

The other ingredients are listed in Section 6.1 of the SPC.

The most excipients used in the production of telmisartan/hydrochlorothiazide oblong-tablets were tested in accordance with the requirements of the Ph. Eur. (in current edition) or other recognized pharmacopoeias.

Meglumine (N-methyl-D-glucamine) is specified according to the monographs of BP, Ph. France (current edition).

Sorbitol as a diluent in the tablet compressing process has an additional specification for sieve analysis when used for the manufacture of telmisartan/hydrochlorothiazide tablets.

Magnesium stearate was tested in accordance with the Ph. Eur., contains the monograph on Products with risk of transmitting agents of animal spongiform encephalopathies (Ph. Eur. Suppl. 2001).

Adequate information has been provided concerning transmissible spongiform encephalopathies (TSE) safety for magnesium stearate and lactose monohydrate. No other ingredients of bovine origin are used in the production of telmisartan/hydrochlorothiazide tablets.

Product development and finished product

The pharmaceutical properties of the active substance telmisartan have already been reviewed in the centralised procedure. Telmisartan is characterised by a poor aqueous solubility and an important polymorphism. Developing a two-layer tablet solved compatibility problems between the two actives substances.

Bioequivalence of the bilayer tablet with both components to the separate single entity tablets as applied in phase III- clinical studies, has been demonstrated.

Manufacture

The manufacturing process is systematically described, supported by three flow-charts of the manufacturing process.

Product Specification

The limits proposed for the chemical and physical tests for both tablet strengths of telmisartan/hydrochlorothiazide tablets at the time of release and throughout shelf life have been well justified. All quantitative tests have been validated and shown to be suitable for the intended purpose. This is in agreement with the EU-guidelines.

Batch analytical data confirm that the process is under control, and indicate a uniform product in compliance with the agreed specifications.

Stability of the Product

Information supplied in this context includes data on the stability of the intermediate product, the SD granulate. During storage no significant decomposition or loss in content has been observed.

Concerning the finished product, a stability program for the both tablet strengths was developed and was concordant with the ICH guideline. The testing program was based on three registration batches, packed in aluminium blisters for climatic zones II and I.

At the time of submission, two years data were available for the long-term studies, and 6 months for the accelerated studies.

The results indicate that telmisartan/hydrochlorothiazide tablets of different strengths are comparable in their stability properties. There appears to be no significant ‘interference’ of one layer with the next. Humidity and light appear to be the most important stability-limiting parameters, and this necessitates a blister package for maximum protection. In general the results support the shelf life of the product as defined in the summary of product characteristics.

Discussion on chemical, pharmaceutical and biological aspects

Manufacture of telmisartan takes place under well- defined conditions, which have already been approved for the product Micardis. Description of the analytical procedures are adequate, validation is plausible and detailed. The quality of hydrochlorothiazide is defined in the EDMF.

The development of this combination product has presented a number of difficulties, particularly concerning incompatibility of the two active substances. This has been solved by the formulation of separate 'matrices' for each active substance, then compressing into a bilayer tablet of two separate layers.

In general, the applicant has demonstrated that a product of acceptable quality can be manufactured. However, at the time of the CPMP opinion there were a number of remaining minor quality issues concerning hydrochlorothiazide, which had no impact on the clinical efficacy and safety of the product as a whole. Therefore the CPMP required a letter of commitment from the applicant to resolve these issues as post-opinion follow-up measure.

3. Toxico-pharmacological aspects

Pharmacodynamics

Telmisartan

The pharmacodynamics of telmisartan has been investigated *in vitro* and *in vivo* in rodents, guinea pigs, rabbits and dogs.

Data from *in vitro* studies support that telmisartan is a potent specific antagonist of the angiotensin II subtype 1 (AT_1) receptor (K_i = 3.7 nM). Up to micromolar concentrations, telmisartan had no affinity to the angiotensin II subtype 2 receptor (AT_2) or to other receptors tested in particular. Telmisartan does not bind to or block other hormone receptors or ion channel known to be important in cardiovascular regulation. .

Repeated administration of 3 mg/kg/day of telmisartan for 5 days to conscious, chronically instrumented spontaneously hypertensive rats (SHR) reduced mean arterial blood pressure (MAP) significantly and persistently with a maximum decrease in MAP of about –36 mmHg.

Telmisartan induces an increase of both plasma renin activity and plasma angiotensin II concentrations. Elevated plasma angiotensin II concentrations could induce a stimulation of other subtypes of angiotensin II receptors (e.g. subtypes 2 [AT_2 receptors) leading possibly to additional effects since these receptors are not blocked by telmisartan.

E.g the following effects have been ascribed to stimulation of AT_2 receptors by angiotensin II: anti-angiogenic and antiproliferative effects, activation of the kinin/NO/cGMP-system, leading to vasodilatation and pressure natriuresis, stimulation of K^+ channels and inhibition of Ca^{2+} channels.

Some studies suggest that in patients with infarction or heart failure, the increase in AT_2 receptors may be salutary at first, opposing hypertrophy and fibrosis, but, conversely, chronic stimulation of AT_2 receptors in the myocardium might have cumulative deleterious effects, including stimulation of apoptosis. In addition, in human heart failure, AT_2 receptors are up regulated in the diseased myocardium. However, in clinical trials in patients with heart failure comparing the AT_1 receptor antagonist losartan versus the angiotensin converting enzyme ACE inhibitor captopril (ELITE I and II), both drugs led to comparable reverse remodelling with reduced left ventricular diastolic volume, and no exacerbation of mortality resulted from the AT_1 receptor antagonist, i.e. from the unopposed action of angiotensin II on the AT_2 receptor. However, while the ELITE I study showed an association between losartan and a survival benefit in elderly heart-failure patients compared with captopril, in the ELITE II study losartan was not superior to captopril in improving survival.

Thus, the exact role of AT_2 receptors is still not clearly defined. These uncertainties are reflected in the Summary of Product Characteristics.

Hydrochlorothiazide

Hydrochlorothiazide reduces blood pressure in volume-dependent and in salt-induced hypertension, as well as in renin-dependent hypertensive rat models.

Telmisartan/hydrochlorothiazide

On the SHR model of hypertension, 10 mg/Kg/day of telmisartan/hydrochlorothiazide induced a significantly greater antihypertensive effect compared to the single components with a maximum reduction of MAP of about – 53 mmHg. A slight, significant increase in heart rate (~ 20 bpm) was observed during the combination treatment, which recovered to control values in the washout period.

The effects of telmisartan and of hydrochlorothiazide on diuresis were confirmed in SHR rats. On day 5 of the administration of telmisartan, hydrochlorothiazide and combination, blood pressure was significantly reduced compared to untreated animals (average = 189 mmHg) by 34, 21 and 47 mmHg respectively.

The combination of telmisartan and hydrochlorothiazide showed no significant effect on urinary excretory function with the exception of ameliorating the alteration in potassium balance when compared with hydrochlorothiazide alone.

In addition, the effect of telmisartan with and without hydrochlorothiazide on action potential duration (APD) was investigated in dog Purkinje fibres under normal (1 Hz) and low (0.2 Hz) stimulation rates. Both telmisartan and the telmisartan/hydrochlorothiazide combination had no effects on APD up to concentrations of 3 μM. At higher concentrations ($\geq$ 10 μM), a dose-dependent increase of APD was observed, but no early after depolarisations occurred.

Pharmacokinetics

Telmisartan

Pharmacokinetic studies of telmisartan were performed in mice, rats, rabbits and dogs. Telmisartan was rapidly absorbed after oral administration in all species (t_{max} values were 2 hours in mice, rats and dogs and 7 hours in rabbits). Bioavailability was 56-75% in mice, 66% in rats and 14-22% in dogs.

Species comparison of pharmacokinetic parameters of telmisartan after oral administration of 1 mg/kg to mice, rats, rabbits and dogs are given in the table below (pharmacokinetic parameters in man after oral administration of 40 mg of telmisartan are given for comparison):

	Mouse	Rat	Rabbit	Dog	Man
C_{max} (ng/ml)	162	44	133	52	45
Cl/f (ml/min/kg)	12	27	5	50	19
$t_{1/2}$ (h)	7	11	13	8	14
AUC (ng*h/ml)	1365	732	3410	334	491

Binding of telmisartan to plasma proteins is high (99.0 - 99.6%). The extent of plasma protein binding was similar in rats and humans with about 0.4% of telmisartan remaining unbound. The volume of distribution of telmisartan was about 3-5 fold higher when compared to total body water (5.3 l/kg in rats, 1.7-3 l/kg in dogs), indicating a preferential distribution of the product into the tissue. Elimination half-life of telmisartan from plasma after oral administration ranged from 11 hours (in mice) to 14 hours (in dogs).

Tissue distribution was examined by whole body autoradiography in rats. Radioactivity was mainly located in the liver. Radioactivity in the central nervous system was only between $1/20^{th}$ and $1/30^{th}$ of those in blood. After 8 hours, most of the tissues were free of radioactivity except the liver and the intestine.

In pregnant rats, telmisartan and/or its metabolites crossed increasingly the placenta with increasing time of gestation, so that when applied at day 18 of pregnancy, the foetus had a higher concentration than the maternal blood. Radioactivity from the foetus decreased slowly. Therefore, in pregnant women, telmisartan can be expected to cross the placenta. Lactating rats readily excreted telmisartan and/or its metabolites into breast milk, and the concentration of the radioactivity was about 2 fold when compared to the concentration of radioactivity in plasma. The radioactivity levels became below the quantitable level 72 hours after administration.

The metabolism of telmisartan was similar in all species and consisted mainly of glucuronidation to a 1-O-acylglucuronide. Telmisartan is glucuronidated by a member of the UGT1-gene family of the UDP-glucuronosyltransferases. Telmisartan circulated preferentially (80-90%) as parent compound in the plasma of most species. In male rats treated orally with 25-mg/kg/day telmisartan for 3 days, no evidence for enzyme induction by telmisartan was observed.

The major route of elimination of orally or intravenously administered telmisartan was via the faeces (> 98% of the dose) via biliary elimination of the 1-O-acylglucuronide telmisartan. Only very small amounts (< 1%) of the dose underwent a renal elimination. The major portion of the compound is excreted within 24 hours after oral administration.

Telmisartan/hydrochlorothiazide

A possible interaction of telmisartan and hydrochlorothiazide was studied in rats and dogs after single oral dosing. The telmisartan/hydrochlorothiazide combination was administered in rats at a respective dose of 3/10 mg/kg and in dogs at a dose of 1/0.3 mg/kg. The pre-clinical pharmacokinetic data did not completely support the lack of interaction between telmisartan and hydrochlorothiazide in rats and dogs. In fact, hydrochlorothiazide impaired the clearance and prolonged the elimination $t_{1/2}$ (half-life) of 3 mg/kg telmisartan in the rat. The historical controls were given 1 mg/kg telmisartan. In this species the pharmacokinetics of telmisartan is not linear, clearance and volume of distribution changing with dose. In the dog the mean telmisartan clearance was lower and exposure was higher than in the historical group when hydrochlorothiazide was co-administered.

In the rat co-treatment with telmisartan/hydrochlorothiazide increases the AUC of telmisartan and reduces the clearance. In the dog AUC data following administration of telmisartan alone or in combination with hydrochlorothiazide do not clarify whether there is a significant effect of hydrochlorothiazide on the pharmacokinetics of telmisartan. However, it is noteworthy that human data following single administration of telmisartan and hydrochlorothiazide did not show any significant interaction between the two chemicals. In the human study, the point estimates for both AUC and C_{max} are close to 1.0, with 7 % higher AUC and C_{max} of the combination. Although the 90 % confidence interval limits were outside the bioequivalence acceptance range of 0.8 – 1.25, it was concluded that the small average increase of 7 % in AUC and C_{max} of telmisartan on co-administration with hydrochlorothiazide does not indicate a relevant effect of hydrochlorothiazide on the pharmacokinetics of telmisartan.

Toxicology

Telmisartan

The toxicity of single doses of telmisartan has been investigated in rats (after oral and IV administration) and in dogs (after oral administration). No clinical signs of toxicity and no deaths occurred at doses of up to 2000 mg/kg/die. After intravenous administration of telmisartan to rats the minimum lethal IV dose was 200 mg/kg, and deaths occurred due to circulatory collapse.

The main findings observed in the chronic toxicity studies were renal toxicity (increased plasma urea, plasma creatinine and serum potassium at doses > 4 mg/kg/day in rats and > 5 mg/kg/day in dogs) and gastrointestinal toxicity (duodenal mucosal erosions and ulcers in rats). Renal tubular damage was observed in dogs at doses > 5 mg/kg/day. Telmisartan induced also a renal juxtaglomerular hyperplasia with hypertrophy of the afferent glomerular arterioles of the kidneys in

rats and dogs. The renal effects were considered to be caused by a pharmacological action of high doses of telmisartan.

In addition, telmisartan induced decreases in heart weights (this effect has also been observed with ACE inhibitors and with other AT_1 antagonists) and a decrease in red blood cells parameters in rats, mice and dogs.

Hydrochlorothiazide

In the National Toxicology Program of the National Institute of Environmental Health Science (1989), toxicity and carcinogenicity studies of hydrochlorothiazide have been performed in rats and in mice with oral administration for 3 months to 2 years. Hydrochlorothiazide induced in mice changes of the urinary bladder (inflammation, epithelial hyperplasia, calculi). In rats, nephrosis and mineralisation at the corticomedullary junction of the kidneys already at the lowest tested dose of 25 mg/kg/day. After prolonged oral treatment of rats for periods up to 2 years, hydrochlorothiazide induced severe chronic renal disease (nephropathy with tubular degeneration, glomerulonephritis, interstitial fibrosis and inflammation, cysts in the renal cortex) with secondary parathyroid hyperplasia and fibrous osteodystrophia of the bone marrow. Furthermore, calcification was evident in the media of blood vessels and heart muscle, stomach and alveolar walls. In dogs after oral administration for periods of up to 9 months, hydrochlorothiazide induced enlarged, hyperactive parathyroid glands.

Telmisartan/hydrochlorothiazide

The toxicological profile of telmisartan and hydrochlorothiazide was examined in oral and intravenous single-dose toxicity studies in rats and mice, oral range-finding toxicity studies in rats and dogs, 26 weeks oral toxicity studies in rats and dogs, and a developmental toxicity study in rats. All these studies used dose levels, which fully explored the potential toxicity of the telmisartan/hydrochlorothiazide combination.

Acute oral toxicity of telmisartan in combination with hydrochlorothiazide was low in rats and mice. In both species, the maximum non-lethal dose, minimum lethal dose and approximate lethal dose (ALD) exceeded 2000 mg/kg. The association of telmisartan with hydrochlorothiazide was only moderately toxic after single intravenous doses to rats and mice. The addition of hydrochlorothiazide did not change the toxicity of telmisartan observed after oral and intravenous administration.

The chronic oral toxicity studies were performed in rats treated for 9 or 26 weeks with telmisartan/hydrochlorothiazide. The main target organs of the telmisartan/hydrochlorothiazide combination in repeated dose toxicity were the kidney and the gastrointestinal tract. Renal changes involved alterations of the juxtaglomerular apparatus (hypertrophy and hyperplasia of the juxtaglomerular cells, granularity, vacuolation). Proximal tubular atrophy was observed at 50 mg/kg/day telmisartan with and without hydrochlorothiazide. With low incidence, gastric lesions (erosion, ulceration, inflammation) were observed. Hydrochlorothiazide seemed to enhance slightly the gastric toxicity induced by telmisartan.

The animals experienced a decrease in blood pressure and there seemed to be a dose-dependent potentiating effect of hydrochlorothiazide on the hypotensive effect of telmisartan. Effects on heart rate were not observed. There was a reduction of red blood cell count, haematocrit and haemoglobin. Serum potassium concentrations were decreased in the presence of hydrochlorothiazide alone, but increased at doses of $\geq$ 4/1.25 mg/kg/day telmisartan/hydrochlorothiazide. Increases in blood urea nitrogen were observed after doses of $\geq$ 4/1.25 mg/kg/day of the combination and seemed to be more pronounced after addition of hydrochlorothiazide. Increases in serum creatinine were observed after 50 mg/kg/day telmisartan with or without hydrochlorothiazide. Both effects were reversible after cessation of treatment. Heart weights were decreased after doses of $\geq$ 4/1.25 mg/kg/day telmisartan/hydrochlorothiazide. Overall, clinical laboratory and pathomorphological changes were similar to those observed in previous toxicity studies in rats with telmisartan alone; no new toxicity was observed with hydrochlorothiazide.

In chronic toxicity studies with the combination of telmisartan with hydrochlorothiazide in dogs the principal toxicological target organ was the kidney. Degenerative changes in cortical and medullary tubular epithelium of the kidneys were observed. Hypertrophy and hyperplasia of the juxtaglomerular apparatus accompanied by cortical tubular hypertrophy, cortical tubular dilatation and cortical tubular basophilia was observed in all dose groups. In the chronic oral toxicity study, two dogs experienced a life-threatening secondary uremia (with gastrointestinal erosions and ulcerations and foci of tissue mineralisation). In addition, the animals experienced a decrease in blood pressure. Dogs given the telmisartan/hydrochlorothiazide combination at doses of > 1.6/0.25 mg/kg/day and dogs given telmisartan alone exhibited decreases in red blood cell counts, haemoglobin and haematocrit. Blood urea nitrogen was elevated in all telmisartan/hydrochlorothiazide combinations at doses of > 1.6/0.25 mg/kg/day. Elevations in serum creatinine and potassium were observed. Finally, plasma renin concentrations were increased in all groups given telmisartan.

It has been suggested that renal toxicity after administration of AT1 receptor antagonists to normotensive animals may be due to a reduction of renal perfusion secondary to systemic hypotension, leading to a decrease in glomerular filtration rate and tubular urinary flow rate and subsequently to reduced creatinine clearance and increased urea nitrogen reabsorption in renal tubules
In conclusion, in dogs the principal target organ was the kidney. Hydrochlorothiazide potentiated both the hypotensive effect and the renal toxicity of telmisartan.

Reproduction toxicity studies

AT_1 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, telmisartan-concentrations increased in the foetal compartment during late pregnancy from about 27% on day 12 of pregnancy to about 60% on day 18. Moreover telmisartan was excreted in milk (rats) at concentrations of 1.5 - 2 fold the maternal plasma concentration 4 - 8 hours post dosing and remained detectable for more than 48 hours.

A slight maternal toxicity was observed with the combination of telmisartan/hydrochlorothiazide embryo-/foetotoxic effects were seen. Therefore, the no toxic effect level of telmisartan/hydrochlorothiazide combination for embryo-/foetotoxicity resulted in an average systemic exposure to telmisartan/hydrochlorothiazide about 20/10 times the systemic exposure in humans receiving 80/12.5 mg/kg/day telmisartan/hydrochlorothiazide. However, reproduction toxicity studies were not performed in rabbits, which have a known higher sensitivity to compounds acting on the renin-angiotensin system.

In humans this class of drugs is expected to be foetotoxic and is therefore contraindicated during the second and third trimester of pregnancy.

Mutagenicity and carcinogenicity studies

Mutagenicity or carcinogenicity studies were not conducted with the combination of telmisartan and hydrochlorothiazide, since these studies were previously conducted for both products separately and there is no evidence for relevant mutagenic and carcinogenic effect for these two products.

Environmental risk assessment

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

Discussion on toxico-pharmacological aspects

Telmisartan increases plasma renin activity and angiotensin II concentrations. Angiotensin II is a mitogen, stimulating the growth, for example, of vascular smooth muscle cells and cardiomyocytes, the release of growth factors and the expression of certain proto-oncogenes. Elevated plasma angiotensin II concentrations could stimulate other angiotensin II subtypes receptors than to the subtype 1 (e.g. AT_2 or AT_4 receptors), possibly leading to undesirable effects. Therefore, there is a theoretical possibility that telmisartan could evoke undesirable - especially growth stimulating - effects by increasing plasma angiotensin II.

The pharmacokinetics data suggest that hydrochlorothiazide impairs the clearance and prolongs telmisartan elimination half-life in the rat. In the dog the mean clearance of telmisartan was clearly lower and exposure in terms of C_{max} and AUC higher when telmisartan was co-administered with hydrochlorothiazide than in the historical group.

Acute oral toxicity of telmisartan/hydrochlorothiazide was studied in rats and mice. In both species, the maximum non-lethal dose, minimum lethal dose and approximate lethal dose (ALD) exceeded 2000 mg/kg. The addition of hydrochlorothiazide did not change the toxicity profile of telmisartan observed after oral and intravenous administration.

Chronic oral toxicity study in rats. Clinical laboratory and histopathological changes were similar to those observed in previous toxicity studies in rats with telmisartan alone; no new toxicity was observed with hydrochlorothiazide, except for a slightly increased severity of gastric mucosal damage. The No Effect Level (NOEL) in the 26-week chronic toxicity study in rats was 0.1/0.03 mg/kg/day telmisartan/hydrochlorothiazide.

Chronic oral 26-week toxicity study in dogs. No new manifestations of toxicity were seen after the addition of hydrochlorothiazide in dogs, in which nephrotoxicity was and remained the major adverse effect. The antagonists of subtype 1 of the angiotensin II receptor (AT_1 antagonists) seem to reduce - via a reduced systemic blood pressure - both glomerular filtration rate (GFR) and tubular urine flow rates, thereby leading to a reduced creatinine clearance and an increased urea nitrogen reabsorption in the renal tubules, respectively. These effects occur in the absence of renal damage. Histopathological evidence of renal injury induced by AT_1 receptor antagonists is consistent with reduced renal perfusion as a consequence of hypotension, leading to decreased renal perfusion and tubular hypoxia with tubular cellular degeneration and necrosis. Furthermore, the telmisartan/hydrochlorothiazide combination induced juxtaglomerular cell hyperplasia. The NOTEL for the telmisartan/hydrochlorothiazide combination in dogs was 0.25/0.08 mg/kg/day, based on clinical pathology as well as macroscopic and microscopic evaluation.

Peri- and post-natal 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. Slight maternal toxicity was seen at telmisartan/hydrochlorothiazide doses of 15.0/4.7 and 50.0/15.6 mg/kg (weight gain, body weight and food consumption). The NOTEL for embryo-foetal toxicity is about 6/12 times the maximum human recommended dose of telmisartan/hydrochlorothiazide. This dose resulted in mean exposure to telmisartan/hydrochlorothiazide about 20/10 times the systemic exposure in humans receiving telmisartan/hydrochlorothiazide (80/12.5 mg/day). Since maternal toxicity is easily induced in rabbits by compounds acting on the renin-angiotensin system, the animals would tolerate only very low doses of the telmisartan/hydrochlorothiazide combination.

No carcinogenicity, mutagenicity, or fertility studies were conducted with the combination of telmisartan and hydrochlorothiazide, since these studies were previously separately conducted for telmisartan and hydrochlorothiazide and the two products are reported not to interact in humans.Part IV: Clinical aspects

Clinical pharmacology

Pharmacodynamics

Telmisartan

The pharmacodynamic profile of telmisartan in humans has been established through a program of 23 studies involving 384 healthy volunteers and patients. These studies showed that telmisartan dose-dependently inhibited the pressor response to angiotensin II infusion. In addition, telmisartan induced a significant increase of sodium and potassium urine excretion. Finally in several studies, plasma renin activity and plasma angiotensin II levels increased.

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic, widely used in therapeutics as an antihypertensive agent that increases sodium, chloride, water and potassium excretion, and produces a mild but progressive volume contraction and secondary activation of the renin angiotensin system. The blood pressure lowering effects require several weeks to reach a maximum.

Telmisartan/hydrochlorothiazide

The combination of telmisartan with hydrochlorothiazide (40 mg/12.5 mg and 80 mg/12.5 mg) is expected to benefit patients with hypertension who are not adequately responsive to telmisartan alone.

Pharmacokinetics

The pharmacokinetic properties of both telmisartan and hydrochlorothiazide are already characterised. Three additional pharmacokinetic studies in healthy men and women volunteers aged between 18 and 55 years have been performed. These studies show that the disposition of hydrochlorothiazide is not significantly affected by the co-administration of telmisartan. The disposition of telmisartan is variable and possibly non-linear and it was not significantly affected by co-administration of hydrochlorothiazide.

As previously stated for telmisartan, pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100%. In patients with mild to moderate hepatic impairment the posology should not exceed 40 mg/day of telmisartan. In addition, telmisartan should not be used in patients with severe hepatic impairment.

- Interaction studies

A study (U96-3069) designed according to a three-way crossover protocol studied a possible pharmacokinetic interaction between telmisartan and hydrochlorothiazide. The study U96-3069 compared the steady state pharmacokinetics of telmisartan (160 mg, as two 80 mg tablets) and hydrochlorothiazide (25 mg) once daily either singly or concurrently. Each treatment was administered for seven days with a 14 days washout period in between.

Absorption of telmisartan after the last dose on day 7 was rapid after either monotherapy (t_{max} 0.88 h) or in combination with hydrochlorothiazide (t_{max} 0.9 h). Thereafter, the plasma concentrations of telmisartan declined according to a biexponential elimination with a terminal elimination half-life $t_{1/2}$ of about 22 h regardless of the treatment. Due to wide inter-subject variability, equivalence for the mean trough concentrations between days 6-8 was not demonstrated at the -20% to +25% acceptance limits, but only at -30% to 43%. This is considered acceptable since telmisartan due to wide inter-subject variability and considering that telmisartan has a wide therapeutic window.

Mean trough hydrochlorothiazide plasma concentrations at days 6, 7 and 8 were similar for mono- and combined therapy. The steady state was reached by day 7 in both cases. On day 7, after the last

dose, mean plasma concentration of hydrochlorothiazide peaked at approximately 2 h, and thereafter declined biexponentially with a terminal elimination $t_{1/2}$ of about 10 h. The mean bioavailability parameters and urinary excretion of hydrochlorothiazide did not change when telmisartan was co-administered. Inter-subject variability was low when hydrochlorothiazide was administered alone (20% for AUC_{24h} and 25% for C_{max}) and slightly higher when it was administered with telmisartan. Telmisartan and hydrochlorothiazide AUC_{24h} and C_{max} tended to be higher in females than males with both treatments, suggesting no apparent drug interaction in either sex.

A further analysis of the data from study U96-3069 showed that the point estimates (mean treatment ratios) for both AUC and C_{max} were close to 1.0, with 7 % higher AUC and C_{max} of the test treatment (telmisartan with hydrochlorothiazide). Due to the high intra-individual variability of 58 % of C_{max} and the limited number of subjects (12 healthy volunteers completing all treatment periods) the 90 % confidence intervals limits were outside the bioequivalence acceptance range of 0.8 - 1.25. However, taking into account the wide therapeutic margin of telmisartan, the average increase of 7% in AUC and C_{max} of telmisartan observed during the co-administration with hydrochlorothiazide was not considered has having clinically relevant consequences and did not indicate an important effect of hydrochlorothiazide on the pharmacokinetics of telmisartan.

In conclusion, the study showed that at doses of 160 mg telmisartan and 25 mg hydrochlorothiazide over seven days there was no clinically relevant pharmacokinetic interaction between telmisartan and hydrochlorothiazide when co-administered. There was a gender effect in terms of non-significant higher values for area under the curve (AUC) and C_{max} in female subjects for both drugs, especially for telmisartan.

- Bioequivalence studies:

Two studies (U00-1275, and U99-1401) addressing the bioequivalence of the fixed dose combination of telmisartan 40 mg/hydrochlorothiazide 12.5 mg and telmisartan 80 mg/hydrochlorothiazide 12.5 mg and of the compounds given separately at the same doses (telmisartan 40-mg or 80 mg and hydrochlorothiazide 12.5 mg) have been performed.

The study U00-1275 investigated the relative bioavailability of telmisartan 40 mg/hydrochlorothiazide 12.5 mg as a fixed dose combination in comparison with the two components. This single dose open-label randomised four ways crossover study involved 32 subjects (16 males and 16 females). C_{max}, AUC and the amount of hydrochlorothiazide excreted unchanged in urine over 48 hours (Ae_{48h}) were the primary variables for evaluating the bioequivalence of the fixed dose combination tablets (test formulation) and the separate tablets (reference formulation). The primary criterion for the assessment of hydrochlorothiazide bioequivalence was conventional average bioequivalence. The primary criterion for the assessment of telmisartan bioequivalence was averaged scaled bioequivalence. Secondary criteria were conventional average bioequivalence and individual bioequivalence.

For hydrochlorothiazide the assessment of standard average bioequivalence showed that the confidence intervals of standard average bioequivalence fell in the bioequivalence range of 80% to 125%. For telmisartan the confidence intervals for AUC also fell in this range (standard average bioequivalence assessment) while the confidence interval for C_{max} extended slightly over the upper bounds of the bioequivalence range. Individual equivalence with respect to the primary pharmacokinetic parameters (secondary analysis) could also not be shown for telmisartan. However, average scaled bioequivalence was shown with respect to both primary variables, and the secondary variable AUC_{24h}.
A similar study (U99-1401) investigated the relative bioavailability of 80 mg telmisartan and 12.5 mg hydrochlorothiazide as a fixed dose combination in comparison to the individual 80 mg telmisartan and 12.5 mg hydrochlorothiazide tablets, in 20 healthy subjects. As in the previous study the primary pharmacokinetic variables were AUC and C_{max} (for both telmisartan and hydrochlorothiazide) and Ae_{48h} (for hydrochlorothiazide only). Again, conventional average bioequivalence was evaluated with respect to hydrochlorothiazide pharmacokinetic variables. With respect to telmisartan pharmacokinetic parameters, conventional average bioequivalence, average

scaled bioequivalence, and individual bioequivalence (as secondary analysis) were evaluated, using a moment-based scaled approach. The test (fixed dose combination) and reference formulations (individual tablets) were considered has being bioequivalent with respect to all pharmacokinetic variables. For telmisartan, bioequivalence was shown for AUC and C_{max}, using the average scaled bioequivalence approach. Bioequivalence could also be shown for AUC and C_{max} using the individual equivalence approach and for AUC (and the secondary variable AUC_{48h} but not C_{max}) using the criterion of conventional average bioequivalence. Hydrochlorothiazide disposition was similar to the pharmacokinetic profile in previous studies.

In summary, all three studies taken together, confirm the pharmacokinetic findings already noted with telmisartan, namely variable telmisartan plasma concentrations, non-linear pharmacokinetic properties and a long mean terminal elimination half-life. No relevant pharmacokinetic interaction between telmisartan and hydrochlorothiazide was detected and two studies consistently demonstrated bioequivalence of both fixed combinations with the single tablets of the respective individual components. Thus, the interaction potential for the combination of both drugs in healthy subjects is thought not to differ from the interaction potential of the individual drugs. There remains a gender effect for telmisartan with AUC and C_{max} higher in females than in males. Since this effect appears to be consistent between the fixed combination and the monotherapy tablets this finding does not seem to be related to the new formulation.

Clinical efficacy

The rationale for the doses submitted in this application are related to the second-line strategy proposed for the combination. The dose of telmisartan 40 mg/hydrochlorothiazide 12.5 mg is proposed in patients not adequately controlled by 40 mg telmisartan alone. Similarly, the dose of telmisartan 80 mg/hydrochlorothiazide 12.5 mg is proposed as an additional step for the subjects not adequately controlled by 80 mg telmisartan monotherapy.

The efficacy of the fixed dose combinations telmisartan 40 mg/hydrochlorothiazide 12.5 mg and telmisartan 80 mg/hydrochlorothiazide 12.5 mg was investigated in 4 clinical trials: one dose-finding study using a 4x5 factorial design, one titration study and two active-controlled studies in patients not adequately controlled with telmisartan monotherapy (non-responders studies). The dose response study and the two non-responder studies are considered to be pivotal for efficacy in respect to telmisartan and hydrochlorothiazide (40 mg/12.5 mg and 80 mg/12.5 mg). The design of these studies fulfils the requirements mentioned in the CPMP Guideline on hypertension for second line fixed combinations. Altogether 2272 patients with mild to moderate hypertension were enrolled in these controlled trials. A total of 818 patients was included in non-responder clinical trial of whom 406 patients received telmisartan and hydrochlorothiazide (246 patients the association of telmisartan 80 mg/hydrochlorothiazide 12.5 mg and 159 patients telmisartan 40 mg/hydrochlorothiazide 12.5 mg).

All efficacy studies were conducted in patients with mild to moderate essential hypertension. In the main efficacy studies, 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.

The long-term safety (and efficacy) of the fixed combinations were investigated in two open label studies.

Dose response study

In order to be certain of finding the appropriate combinations of dose a dose-response study (U97-3070) using a multi factorial design has been conducted on a double blind, randomised and placebo-controlled basis. The multi factorial design is a 4 x 5 factorial design (20 different treatment groups), which aimed at identifying the dose combinations of telmisartan (0, 20, 40, 80, 160 mg) and hydrochlorothiazide (0, 6.25, 12.5, 25 mg), which were more effective than either of the individual components, and were safe in patients with mild-moderate essential hypertension. The study was

planned to assign 75 patients to the doses considered most important, i.e. placebo, telmisartan 40 and 80 mg, hydrochlorothiazide 12.5 mg, telmisartan/hydrochlorothiazide 40/12.5 mg, and telmisartan/hydrochlorothiazide 80/12.5, and only 20 or 30 patients per arm were assigned to the remaining 14 regimens.

The fixed dose combination of telmisartan/hydrochlorothiazide 40 mg/12.5 mg and 80 mg/12.5 mg are more effective than either individual component with respect to supine SBP and DBP (see table).

Comparison of mean changes from baseline in trough supine blood pressure (mmHg) of intent-to-treat patients in the six key treatment groups

Treatment Comparison	Diastolic BP Difference (mmHg)	p-value[1]	Systolic BP Difference (mmHg)	p-value[1]
T40 vs. Placebo	- 6.9	< 0.01	- 9.3	< 0.01
T80 vs. Placebo	- 7.7	< 0.01	- 12.5	< 0.01
H12.5 vs. Placebo	- 3.5	< 0.01	- 4.0	0.04
T40/H12.5 vs. T40	- 1.9	0.08	- 6.6	< 0.01
T40/H12.5 vs. H12.5	- 5.3	< 0.01	- 11.9	< 0.01
T80/H12.5 vs. T80	- 3.4	< 0.01	- 8.5	< 0.01
T80/H12.5 vs. H12.5	- 7.6	< 0.01	- 17.0	< 0.01

[1] One-sided tests.

When comparing the reductions in supine trough DBP of the active monotherapies with that of the placebo treatment group, each was superior ($p < 0.01$) with incremental reductions of 6.9, 7.7 and 3.5 mmHg for telmisartan 40 mg or 80 mg and hydrochlorothiazide 12.5 mg, respectively. Telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg was also superior ($p < 0.01$) to both of the component monotherapies for reduction in DBP. The mean increases in the reduction in DPB were 3.4 and 7.6 mmHg over telmisartan 80 mg and hydrochlorothiazide 12.5 mg, respectively. For the combination therapy of telmisartan 40 mg in combination with hydrochlorothiazide 12.5 mg, there was a significant increase in the mean reduction in supine DBP over hydrochlorothiazide 12.5 mg but not over telmisartan 40 mg alone. The number of patients enrolled in the study might not be sufficient to have a sufficient power to demonstrate a significant difference compared to 40 mg telmisartan. The combinations telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg and telmisartan 40 mg with hydrochlorothiazide 12.5 mg were superior to both of its monotherapies for supine SBP.

The same effect of the fixed dose combination is reported on standing DBP and SBP. However, these effects are observed also in a small number of patients exposed to the fixed dose combination telmisartan 20 mg/hydrochlorothiazide 12.5 mg (see table below). Moreover, hydrochlorothiazide 25 mg reduced trough supine SBP and DBP with the same effect as telmisartan.

Adjusted mean changes from baseline in trough supine BP (mmHg) in each treatment group.

		Telmisartan (mg)				
		0	20	40	80	160
HCTZ (mg)	Systolic					
	0	-2.7 (1.7)	-9.9 (2.9)	-12.1 (1.6)	-15.4 (1.6)	-17.2 (2.5)
	6.25	-3.7 (3.0)	-12.9 (3.0)	-23.3 (3.1)	-16.9 (3.3)	-16.0 (2.6)
	12.5	-8.1 (1.7)	-21.5 (3.1)	-18.8 (1.7)	-24.0 (1.7)	-21.0 (2.5)
	25	-17.9 (2.9)	-20.5 (2.9)	-19.6 (3.0)	-23.4 (2.4)	-25.8 (2.6)
	Diastolic					
	0	-3.2 (1.0)	-9.9 (1.7)	-10.7 (0.9)	-11.3 (1.0)	-12.2 (1.5)
	6.25	-4.5 (1.8)	-10.8 (1.8)	-13.4 (1.8)	-11.0 (1.0)	-11.7 (1.5)
	12.5	-7.2 (1.0)	-12.1 (1.8)	-12.6 (1.0)	-15.1 (1.0)	-12.8 (1.5)
	25	-11.1 (1.7)	-14.5 (1.7)	-13.4 (1.7)	-14.1 (1.4)	-17.5 (1.5)

Percentage of intent-to-treat patients in the six key treatment groups with control of diastolic BP[1], adequate systolic BP response[2], and full diastolic blood pressure response[3]

	Adequate SBP Response[1] Telmisartan (mg)			DBP Control[2] Telmisartan (mg)			Full DBP Response[3] Telmisartan (mg)		
	0	40	80	0	40	80	0	40	80
HCTZ(mg) 0	29%	60%	66%	21%	49%	55%	29%	67%	69%
HCTZ(mg) 12.5	36%	81%**	85%**	38%	56%NS	64%NS	47%	63%NS	79%NS

[1]Control defined as a trough supine DBP<90 mmHg
[2]Adequate response defined as ≥ 10 mmHg reduction from baseline in trough supine SBP
[3]Full response defined as ≥ 10 mmHg reduction in trough supine DBP from baseline and/or trough supine DBP ≤ 90 mmHg
**p ≤ 0.01 for combination vs. both monotherapies (Mantel-Haenszel Test)
NS not significantly different from one or both monotherapies

The results in the table above show that blood pressure normalisation rate was slightly higher with the association of telmisartan 40 mg/hydrochlorothiazide 12.5 mg (47%) compared to telmisartan 40 mg (43%). In addition, there is no more probability of responding for patients in the telmisartan 80 mg or telmisartan 40 mg/hydrochlorothiazide 12.5 mg groups than in the telmisartan 40 mg group. The analysis of the blood pressure normalisation shows an addictive effect of the single components of the proposed fixed dose combination and confirms a flat dose-response curve. The blood pressure normalisation rate with the combination telmisartan 20 mg/hydrochlorothiazide 12.5 mg (10/21, 48%) does not differ from that reported with telmisartan 40 mg/hydrochlorothiazide 12.5 mg (33/70, 47%) and telmisartan 80 mg/hydrochlorothiazide 12.5 mg (41/73, 56%). (It should be noted that this study was performed in *de novo* hypertensive patients or in patients already receiving monotherapy)

Therapeutic confirmatory trials

Pivotal studies

Documentation of efficacy is based on two pivotal trials of the fixed dose combination telmisartan in combination with hydrochlorothiazide, 40/12.5 [study 502.323 (U00-3262)] and 80/12.5 mg [study 502.261 (U00-3112)] compared with the relative telmisartan monotherapies. An additional study (502.215, U97-0052) submitted in the original marketing authorisation applicaton is presented as a supportive study.

The two main studies adopted the same design and outcome measures. They enrolled patients into an open-label period of telmisartan monotherapy so as to identify non-responders (defined as having a DBP > 90 mmHg while receiving the treatment with telmisartan). These patients were subsequently randomised to continue telmisartan monotherapy or shift to fixed dose combination. Primary and secondary outcome measures were respectively seated trough DBP and seated trough SBP assessed after eight weeks. Demographic characteristics were similar in the two studies and were well balanced within studies. In study 502.323, 327 patients were randomised, and 321 constituted the intent to treat population. In study 502.261, 491 patients were randomised, and 475 completed the eight-week observation.

In study 502.323 treatment with fixed dose combination 40/12.5 was significantly more effective than telmisartan 40 mg in reducing the mean seated DBP (-3.5 mmHg, 95%CI = [-4.8, -2.1]) and SBP (-7.4 mmHg, 95%CI = [-9.8, -5.1]) in non-responders to telmisartan 40 mg alone. The percentage of patients achieving a BP response was consistently greater with fixed dose combination 40/12.5 than telmisartan 40 mg alone: patients with normalised blood pressure (SBP ≤140 mmHg, and DBP ≤90

mmHg) were 51.6% and 23.5% in the respective treatment groups. The fixed dose combination 40/12.5 or telmisartan 40 mg had no effect on the change from reference values for seated heart rate.

In study 502.261 the fixed dose combination 80/12.5 was significantly more effective than telmisartan 80 mg in reducing mean seated DBP (-3.1 mmHg, 95%CI [-4.2, -2.0]) and SBP (-5.7 mmHg, 95%CI = [-7.7, -3.6]) in non-responders to telmisartan 40 mg alone. The percentage of patients achieving a BP response was consistently greater with fixed dose combination 80/12.5 than telmisartan 80 mg alone: patients with normalised BP were 41.5% and 26.1% in the respective treatment groups. The fixed dose combination 40/12.5 or telmisartan 40 mg had no effect on the change from reference values for seated heart rate.

The results of this trial confirm that the fixed dose combination 40 mg/12.5 mg and 80 mg/12.5 mg are significantly more effective in reducing seated blood pressure than the relative telmisartan monotherapy in patients who do not respond to telmisartan alone, regardless of age and sex. It remains to be established whether the fixed dose combination 40/12.5 or telmisartan 80 mg is the treatment of choice in non-responders to telmisartan 40 mg, and the fixed dose combination 80/12.5 or alternative antihypertensive strategies is the treatment of choice in non-responders to telmisartan 80 mg.

In these trials, it is noteworthy that the response rate was low in both monotherapy and fixed dose combination groups, although normal blood pressure was achieved in one fourth of patients with telmisartan monotherapies and half with the relative fixed dose combination with hydrochlorothiazide.

Study 502.215, which was submitted in the original application for telmisartan, is considered supportive in respect of this application. This was a parallel group, 26 weeks trial, in which after a placebo run-in phase 363 patients were randomised to one of the following four treatments:

1. Telmisartan 40 mg once daily (response based titration to telmisartan 40 mg and hydrochlorothiazide 12.5 mg per day - 114 patients enrolled in this arm of the study).
2. Telmisartan 80 mg once daily (response based titration to telmisartan 80 mg and hydrochlorothiazide 12.5 mg per day 121 patients enrolled).
3. Hydrochlorothiazide 12.5 mg once daily (response based titration to hydrochlorothiazide 25 mg - 62 patients enrolled).
4. Hydrochlorothiazide 12.5 mg once daily (response based titration to hydrochlorothiazide 12.5 mg and telmisartan 80 mg - 66 patients enrolled).

The primary outcome measure was the proportion of patients whose last available trough supine DBP was < 90 mmHg. The primary end-point analysis looked at the patients who failed to meet the goal on monotherapy and then sought the proportion of those patients achieving DBP control.

The goal response (DBP <90 mmHg) was achieved in 30% of patients receiving initially telmisartan 40 mg, 39% of those receiving telmisartan 80 mg, 17% and 23% respectively of those receiving initially hydrochlorothiazide 12.5 mg. After titration, goal response was achieved by 57% (telmisartan/hydrochlorothiazide 40/12.5), 58% (telmisartan/hydrochlorothiazide 80/12.5), 48% hydrochlorothiazide 25 mg and 57% (hydrochlorothiazide/telmisartan 12.5/80) of non-responders to monotherapy.

This study adds important information to the two pivotal studies. It provides the only data to support the possibility of shifting from hydrochlorothiazide monotherapy to the fixed dose combination. This was tested only for telmisartan 80 mg, while telmisartan 40 mg, and even telmisartan 20 mg, may well achieve similar effects. This is suggested (at least for telmisartan 40 mg) by the fact that there is little difference between the BP lowering effect of the sequence hydrochlorothiazide + telmisartan 80 mg (14.6±0.7 [mean±SE] mmHg) and that of the sequence telmisartan 80 mg + hydrochlorothiazide (13.2±1.0 mmHg). It also shows that there is no difference between telmisartan 40 mg + hydrochlorothiazide (15.1±0.7 mmHg) and telmisartan 80 mg + hydrochlorothiazide. Therefore, it could be assumed that the sequence hydrochlorothiazide + telmisartan 40 mg is as effective as hydrochlorothiazide + telmisartan 80 mg. However, this was not tested, and the finding regarding the shift from hydrochlorothiazide to hydrochlorothiazide+ telmisartan 80 mg is not adequately backed by

dose-response testing to be adopted *per se*. The sample size in each group is too small to draw any conclusions. Therefore, the shift to the fixed dose combination telmisartan 80 mg/hydrochlorothiazide in non-responders to hydrochlorothiazide cannot be recommended. It is noteworthy that in this study as well, responders in terms of DBP (not of BP normalisation) to telmisartan monotherapies were about one third of the population. This figure increased to half to two thirds after adding hydrochlorothiazide.

Finally no study investigated the efficacy of the fixed dose combination telmisartan 80 mg/hydrochlorothiazide 12.5 mg in patients who failed to respond adequately to the fixed dose combination telmisartan 40 mg/hydrochlorothiazide 12.5 mg.

Supportive studies: trials conducted in the treatment of severe hypertension

The efficacy of telmisartan in the treatment of severe hypertension has not been established. It has been assessed in the study U97-3210. This was an open-label randomised (2:1) comparison of telmisartan 80 mg (with up-titration to telmisartan 160 mg) and enalapril 20 mg (with up-titration to enalapril 40 mg) in 86 patients. The outcome measure was the response to treatment defined as DBP <90 mmHg.

Of 57 patients entering the telmisartan arm, 25 were controlled, 13 were prematurely discontinued, and 19 were uncontrolled at the end of the study. The probability of control on telmisartan monotherapy was 7.5%. The probability of control on monotherapy or telmisartan plus hydrochlorothiazide was 33.9%. The addition of amlodipine increased the probability of control to 55.2%.
Both the telmisartan and hydrochlorothiazide doses tested are higher than those used in pivotal trials of fixed dose combination. In addition, the maximum authorised posology of telmisartan (as stated in the Summary of Products Characterisitcs for the medicinal products containing telmisartan) is 80 mg once daily. In contrast, the comparator was used at the maximal recommended dose of 40 mg. This might explain why 25 of the 57 patients (43.8%) started with telmisartan had DBP controlled, compared with only 8 of the 28 patients (28.6%) started on enalapril. Treatment discontinuations should be considered as failures: therefore uncontrolled patients are 32/57 (56.1%) in the telmisartan group and 20/28 (71.4%) in the enalapril group. The BP normalisation rate is not reported but this would have been a more suitable outcome measure.

Clinical safety

The telmisartan + hydrochlorothiazide clinical trials safety database includes data from 16 initial/follow-up clinical trials involving 4697 patients allocated initially to comparator (872), hydrochlorothiazide (249), placebo (157), telmisartan monotherapy (2584) and the combination of telmisartan with hydrochlorothiazide (835). The inclusion of open-label treatment (follow-up or *de novo*) studies means the telmisartan safety database includes data from 27 trials involving 7968 patients divided by randomisation to comparator (2060), placebo (599), or telmisartan monotherapy (5309) and telmisartan in combination with hydrochlorothiazide (2180).

The incidence of adverse reactions occurring in at least 1% of the population enrolled in randomised hypertension trials by general treatment groups (see details in Part IV of this report) shows no interaction between telmisartan and hydrochlorothiazide, the figures often being lower for the fixed dose combination than for the single components.

Serious adverse reactions/deaths

The serious adverse reactions considered related to telmisartan or telmisartan + hydrochlorothiazide is reported in the table below.

Serious adverse reactions considered to be possibly related to the telmisartan or to the association of telmisartan with HCTZ

Trial No.	Patient No.	Follow-up Study	Dose	Reported Term	AE day of Onset
502.204	6096	502.219	T80	Increased hypertension	27
502.204	6060	502.219	T80 + HCTZ12.5	Syncope	273
502.207	1345	502.220	T40	Dizzy	100
502.207	1003	502.220	T80 + HCTZ12.5	Atrial fibrillation	101
502.207	1030	502.220	T80 + HCTZ25	Haematemesis	332
502.207	1034	502.220	T80 + HCTZ25	Chest pain (cardiac) Occasional palpitation	174 174
502.207	1121	502.220	T80 + HCTZ12.5	Atrial flutter	137
502.207	1123	502.220	T80 + HCTZ12.5	Angina	92
502.210	4072	-	T40	Abducens palsy	38
502.210	4239	-	T20	Glaucoma	136
502.214	2018	-	T40	Cardiac arrest	13
502.215	3578	-	T80	Chest pain (non-cardiac)	27
502.215	3189	-	T80 + HCTZ12.5	Epistaxis	37
502.216	3112	502.220	T40	Orthostatic circulatory dysfunction	1004
502.209	2029	-	Enalapril (E) 20	Oedema lips	15
502.210	4069	-	E20	Stroke	98
502.210	4178	-	E5	Chest pain Dizziness/ vertigo	3 3
502.210	4298	-	E10	Constipation	27
502.214	1813	-	LI20	Chest pain	169
502.214	1869	-	LI10	Cellulitis right leg Right groin adenitis	69 69
502.216	3327	-	AT100	Apoplectic insult	181
502.238	8086	-	E40 + HCTZ25	Angioedema facial	32

A total of 7 patients treated with 80 mg Telmisartan plus hydrochlorothiazide experienced serious adverse reactions. No drug-related serious adverse reactions occurred with the 40 mg telmisartan/hydrochlorothiazide combination therapy, 7 serious adverse reactions were reported under telmisartan monotherapy.

Of 17 deaths reported, one case of cardiac arrest was considered related to the intake of telmisartan 40 mg on day 13. All but three deaths occurred beyond 100 days of treatment. Of the 17 deaths, 13 occurred in patients on telmisartan monotherapy, four while the patients were being treated with the combination of telmisartan with hydrochlorothiazide.

Safety in special populations

Patients with diabetes mellitus

Hydrochlorothiazide is known to alter blood sugar concentrations and possibly affect diabetic control. According to the Expert a total of 123 diabetic patients were treated with telmisartan + hydrochlorothiazide in the fixed dose combination programme. Diabetes mellitus and aggravated diabetes mellitus were reported in 2 and 8 patients respectively and hyperglycaemia in 2 patients. The adverse reactions reported from the individual trial reports do not appear to have been severe, and one patient previously controlled on diet was started on an oral hypoglycaemic agent. The point appears adequately covered in the proposed labelling.

Patients with history of renal disease/impairment

Due to the hydrochlorothiazide component the fixed dose combination should not be used in patients with severe renal dysfunction (creatinine clearance < 30 ml/mn).

In 30 patients with mild to moderate hypertension, renal hemodynamics were studied in an 8-week randomised double-blind trial (U97-3064): 15 received telmisartan 80 mg and 15 telmisartan 80 mg+ hydrochlorothiazide 12.5 mg. Four patients had a history of calculus and one of renal impairment but all patients had normal renal function at baseline. No significant change from baseline was observed in all renal functions. Three patients and hyperuricaemia reported gout in four. There were two reports of abnormal renal function.

Of the total trial population treated with telmisartan/telmisartan + hydrochlorothiazide, 307 patients were reported to have a previous renal diagnosis, suggesting possible renal impairment in 51. Edema was reported in eight patients on telmisartan mono and in only one on telmisartan/hydrochlorothiazide, attacks of gout in one patient on telmisartan monotherapy and three on fixed dose combination and hyperuricaemia in none and four patients respectively. There were no reports of raised BUN/creatinine in the population. "Abnormal renal function" was reported in two patients receiving telmisartan + hydrochlorothiazide.

BUN and creatinine measurements in the 'renal' population were available for 124 patients (33 females, 91 males) treated with telmisartan alone, and 105 (18 females, 87 males) receiving telmisartan + hydrochlorothiazide. There was a marked increase in BUN in one patient receiving telmisartan and in seven patients receiving telmisartan + hydrochlorothiazide. Two marked increases in creatinine were observed with telmisartan + hydrochlorothiazide, none with telmisartan alone.

In the post-marketing study (U00-1835) serum creatinine was available in 316 of 414 patients with a history of renal impairment and in 245 it was >1.2 mg/dL at baseline. Almost half the patients had a final measurement at the end of treatment, while 84 and 154 had first and second follow-up measurements. Of the 316 patients with baseline creatinine measurements 140 were receiving telmisartan alone and 176 telmisartan plus a diuretic.

Incidence of adverse effects in trials of hypertension and hypertensive non-responders was numerically lower in telmisartan/hydrochlorothiazide than in telmisartan groups for patients with chronic liver disease (37/64, 57.8% and 84/115, 73.0% respectively, in the two treatment groups), with gastro-intestinal dysfunction (139/215, 64.1% and 241/343, 70.3%), or with cardiovascular disease (319/496, 64.3% and 533/781, 68.2%).

Laboratory changes

Hypokalaemia as an adverse reaction occurred with the 12.5 and 25 mg/day doses of hydrochlorothiazide, as expected. These are relatively low doses of hydrochlorothiazide, but still result in clinically relevant changes in serum potassium in some patients. Laboratory evaluation of serum potassium also confirmed a dose response in this parameter, as well as elevations in uric acid, cholesterol, BUN and possibly glucose.

Post-marketing experience

The fixed dose combination at both strengths has recently been approved and launched in the USA, but to date it is too early to have any information on post marketing experience on this fixed dose combination. Telmisartan (in monotherapy) is already marketed in many countries for the indication of essential hypertension and may be used in combination with other agents particularly hydrochlorothiazide. There is, therefore, a significant volume of combination data with hydrochlorothiazide already available with the free combination.

In conclusion, the incidence of adverse events on active treatment was generally higher than that for placebo treatment No new safety signal possibly associated with the combinations other than those for telmisartan and hydrochlorothiazide alone has been identified. The overall numbers of serious adverse events distributed by age show an increasing incidence with increasing age. Assessment of the individual case report shows no particular pattern relative to age.

No new safety signal (inconsistent with the safety profile of telmisartan) has been identified from the long term uncontrolled safety data and no data indicates that the addition of hydrochlorothiazide to telmisartan increases noticeably the incidences of adverse reactions.

Based on the submitted individual studies, it can be concluded that the fixed combinations of telmisartan 40 mg/hydrochlorothiazide 12.5 mg and telmisartan 80 mg/hydrochlorothiazide 12.5 mg do not raise any particular concern in relation to the safety profile.

Overall conclusions, benefit/risk assessment and recommendation

Quality

The applicant has demonstrated that a product of acceptable quality can be manufactured. From the view of pharmaceutical and technological quality authorisation of the combination product can be recommended. There are no unresolved quality issues that have an impact on the benefit/risk balance of the product.

Preclinical pharmacology and toxicology

No new toxicity, carcinogenicity, mutagenicity, or fertility concern has been identified with the combination of telmisartan and hydrochlorothiazide. The two products are already widely used in humans. The only issue lies in the fact that elevated plasma angiotensin II concentrations could stimulate other angiotensin II subtypes receptors than to the subtype 1 (e.g. AT_2 receptors) possibly leading to undesirable effects.

Efficacy

The efficacy of the fixed dose combinations telmisartan 40 mg/hydrochlorothiazide 12.5 mg and telmisartan 80 mg/hydrochlorothiazide 12.5 mg was investigated in 4 clinical trials. The dose-response study showed a significant benefit for the telmisartan 80 mg/hydrochlorothiazide 12.5 mg combination compared to each component treatments in mean change in trough supine DBP after eight weeks treatment. This group also had significant benefits over the component treatments for mean change in trough SBP. However, a significant difference in supine diastolic blood pressure could not be demonstrated for the dose combination telmisartan 40 mg/hydrochlorothiazide 12.5 mg compared with telmisartan 40 mg monotherapy. The difference became apparent after *post-hoc* adjustment of trial results by race and plasma renin activity.

The two pivotal non-responder studies showed that treatment with the fixed dose combinations (telmisartan 40 mg/hydrochlorothiazide 12.5 mg and telmisartan 80 mg/hydrochlorothiazide 12.5 mg) was found to be significantly more effective in reducing seated and standing DBP and SBP. The percentage of patients achieving BP response was consistently greater for patients receiving fixed dose combination telmisartan 80 mg/hydrochlorothiazide 12.5 mg or telmisartan 40 mg/hydrochlorothiazide 12.5 mg than for patients continuing on telmisartan 80 mg or telmisartan 40 mg alone, respectively.

The response rates with the two fixed dose combinations confirmed the flat dose-response relationship observed with telmisartan alone. This suggests that it is unlikely that non-responders to telmisartan 40 mg/hydrochlorothiazide 12.5 mg respond to the higher dose of the fixed dose combination. In any case no study investigated the efficacy of the higher fixed dose combination (telmisartan 80 mg/hydrochlorothiazide 12.5 mg) in patients who failed to respond adequately to fixed dose combination telmisartan 40 mg/hydrochlorothiazide 12.5 mg. Moreover the results in patients who failed to respond on hydrochlorothiazide can be considered only supportive because of limited number of patients who received additional telmisartan to hydrochlorothiazide. Therefore, the indication is restricted to patients not adequately controlled on telmisartan.

The fixed dose combination telmisartan 20 mg/hydrochlorothiazide 12.5 mg may be as effective as fixed dose combinations including higher doses of telmisartan in reducing both supine, standing SBP and DBP. However, the efficacy of this combination has not been adequately tested. The efficacy of telmisartan in the treatment of severe hypertension has not been proven.

Safety

No new safety concern has been identified in the studies included in the application. Three deaths occurred after final treatment discontinuation. Their possible relation with the washout period, which hypertensive patients undergo before starting randomised treatment, was ruled out. However, the Applicant has reported four serious adverse reactions during the washout phase of clinical trials.

Benefit/risk assessment

On the basis of the data submitted the fixed dose combination of telmisartan (40 mg and 80 mg) with hydrochlorothiazide (12.5 mg) has a positive benefit/risk balance in patients not adequately controlled on telmisartan alone.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of PritorPlus in the treatment of essential hypertension was favourable. PritorPlus fixed dose combination (40mg telmisartan/12.5mg hydrochlorothiazide and 80mg telmisartan/12.5mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on telmisartan alone. Therefore the CPMP recommended the granting of the marketing authorisation.