SCIENTIFIC DISCUSSION

Invented Name: PritorPlus

International Nonproprietary Name: telmisartan + hydrochlorothiazide

Extension for a new strength of PritorPlus (80mg telmisartan/25mg hydrochlorothiazide) with the indication:

PritorPlus fixed dose combination (80mg telmisartan/25mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on MicardisPlus (80mg telmisartan/12.5mg hydrochlorothiazide) or patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

1 Introduction

PritorPlus is a fixed dose combination of telmisartan and hydrocholorothiazide (HCTZ) approved via the centralised Procedure on 19 April 2002. Telmisartan is an orally effective, specific angiotensin II receptor antagonist whereas HCTZ is a diuretic belonging to the family of thiazide diuretics; both are indicated in the treatment of essential hypertension. HCTZ is the subject of a Ph. Eur. and U.S.P. monograph.

In Europe the fixed dose combinations of 40mg telmisartan/12.5mg HCTZ and 80mg telmisartan/12.5mg HCTZ are approved for the treatment of essential hypertension indicated in patients whose blood pressure is not adequately controlled on telmisartan alone.

The MAH applied for an extension to the marketing authorisation in order to introduce a new strength of 80mg telmisartan/25 mg HCTZ of layered tablet. The strength 80mg telmisartan/25 mg HCTZ (2x 40mg/12.5mg tablets) has been developed to optimise treatment compliance. It is indicated in patients whose blood pressure is not adequately controlled on PritorPlus 80mg/12.5mg or patients who have been previously stabilized on telmisartan and HCTZ given separately. It was authorised in the US on 19 April 2004.

The Applicant has provided quality and clinical information to support the commercialisation of the new strength, whilst a reference to the first MAA is made for the pre-clinical documentation.

Two Scientific Advices concerning this strength were received from EMEA in September 2004 and the follow-up in July 2006 respectively. Data submitted are in line with the Scientific Advices received; in particular as the pivotal efficacy trial was conducted with the production scale commercial products the applicant did not add new bioequivalence (BE) data for this line extension. Furthermore, the applicant can now prove the interchangeability of 2x 40mg telmisartan/12.5mg HCTZ tablets vs. 1 80mg telmisartan/25 mg HCTZ tablet with clinical data.
Two randomised double-blind placebo-controlled clinical trials have been performed vs. 160mg valsartan/25mg HCTZ fixed dose combination and vs. placebo in hypertensive patients with stage 1 and 2 hypertension in the US. These trials had identical design, entry criteria, and endpoints, as well as comparable study population. Trial 502.421 was performed with two tablets 40mg telmisartan/12.5mg HCTZ as trial medication and trial 502.476 with one tablet 80mg telmisartan/25 mg HCTZ (in both trials once daily administration in the morning).

For the establishment of the clinical efficacy and safety of the fixed dose combination 80mg telmisartan/25 mg HCTZ, data of 12 clinical trials performed in patients with mild to moderate hypertension were used (see table 1 below). The core clinical development programme consisted of the pivotal trial 502.480 and its follow-up study 502.491, which were designed and conducted following the Scientific Advice obtained from the EMEA in 2004. Supportive evidence comes from 10 trials investigating the efficacy and safety of the free and fixed-dose combination 80mg telmisartan/25 mg HCTZ. In accordance with the proposed indication for the new strength, the submission focused on the comparison of the approved fixed dose combination 80mg telmisartan/12.5 mg HCTZ with the new fixed dose combination 80mg telmisartan/25 mg HCTZ.

There is no paediatric development program.

Table 1 Overview of trials in the dossier and information on efficacy groupings

Trial number Reference number	Main trial characteristics	Duration	Number of patients[1]	
			Total	T80/H25
Double-blind pivotal FDC efficacy trial (EFF-1)				
502.480 [U07-1110]	T80/H25 vs. T80/H12.5 in non-responders to T80/H12.5; Europe, Asia, South Africa	8 weeks[2]	971[3]	352
Open-label FDC follow-up trial (EFF-2)				
502.491 [U07-1143-01]	T80/H25, FU trial of 502.480; Europe, Asia, South Africa	26 weeks	432[4]	432
Double-blind, placebo-controlled, forced-titration trials (EFF-3)				
502.421 [U04-3553]	T80/H25 vs. V160/H25 vs. placebo; USA	8 weeks[5]	1073	467
502.476 [U07-3028]	T80/H25 vs. V160/H25 vs. placebo; USA	8 weeks[5]	1128	504
Double-blind, titration-to-response, active-controlled trials (EFF-4)				
502.210 [U97-0059]	Titration T/H-based vs. E/H-based; patients ≥65 years; Europe	26 weeks[2]	50	25
502.214 [U97-3085]	Titration T/H-based vs. L/H-based; USA	52 to 60 weeks[2]	34	14
502.216 [U96-2613]	Titration T/H-based vs. A/H-based; Europe	26 weeks[2]	44	9
Open-label, titration-to-response, long-term trials (EFF-5)				
502.219 [U99-3073][6]	T/H-based titration; FU trial; USA	≥52 weeks	285	186
502.220 [U00-1806]	T/H-based titration; FU trial; Europe	≥52 weeks	299	188
502.221 [U97-3037]	T/H-based titration; USA	≥52 weeks	47	26
502.228 [U00-1707]	T/H-based titration; Germany	≥52 weeks	77	56
502.260 [U00-1706]	T/H-based titration; FU trial; Europe, South Africa	52 weeks	206	115

T = telmisartan, H = hydrochlorothiazide, E = enalapril, EFF = efficacy grouping, FU = follow-up, L = lisinopril, A = atenolol, V = valsartan, FDC=fixed dose combination

[1] The number of patients given is based on the patients included in the pooled analyses of safety, i.e. in the total column only patients exposed to the treatments of interest are displayed: T80/H25, T80/H12.5, V160/H25, or placebo.

[2] Duration of the double-blind phase

[3] Number of patients treated with T80/H12.5 during run-in. Of these, 713 were randomised to either T80/H25 or T80/H12.5.

[4] Number of patients in interim analysis

[5] Duration of the complete double-blind phase: 2 weeks of monotherapy followed by 6 weeks of combination therapy.

[6] For this trial, there is an interim report [U97-3043] in addition to the final report.

2 Quality aspects

Introduction

PritorPlus is presented as a two-layered tablet for oral use. The two strengths approved of PritorPlus (telmisartan/hydrochlorothiazide) are 40/12.5 mg and 80/12.5 mg. This is an application for a new strength of PritorPlus 80/25 mg which has been developed to optimize treatment.

The new strength is based on the formulation of the 80/12.5 mg strength with only minor differences between the compositions of the hydrochlorothiazide layer of the newly developed 80/25 mg strength and the 80/12.5 mg strength.

Drug Substance 1 (Telmisartan)

The data provided in section 3.2.S for the active substance telmisartan is based on the data registered for the related strengths of telmisartan/hydrochlorothiazide 40/12.5 mg and 80/12.5 mg.

- Manufacture

Telmisartan is synthesised in 4 steps from 3 starting materials.

- Specification

The active substance specification and analytical methods are the same as those currently approved for the authorised strengths of telmisartan/ hydrochlorothiazide.

Batch analyses data on three batches of telmisartan manufactured at each of the proposed manufacturing sites were provided. The results show that all batches conform to the specification.

- Stability

Based on the updated stability data provided by the MAH the proposed re-test period can be accepted, without any storage conditions.

Drug Substance 2 (Hydrochlorothiazide)

Hydrochlorothiazide is a pharmacopoeial active substance. The information provided in section 3.2.S is based on the European Pharmacopoeial monograph for hydrochlorothiazide, as well as the Certificates of Suitability provided by the two alternative manufacturers of the active substance.

- Manufacture

The information on the manufacture of hydrochlorothiazide is provided in the CEP.

- Specification

The active substance specification and analytical methods have been assessed during the certification procedure.

As a request of the CHMP, the MAH provided validation data for the laser diffraction method used for the control of the particle size of hydrochlorothiazide since this is not considered to be guaranteed by the CEP.

- Stability

The stability of hydrochlorothiazide is also been assessed during the certification procedure and a re-test period has been granted.

Medicinal Product

- Pharmaceutical Development

The strategy behind the development of the telmisartan/hydrochlorothiazide 80/25 mg tablet was the same as that used in the manufacture of the currently marketed 80/12.5 mg and 40/12.5 mg strengths.

The formulation has been developed as an oblong-shaped bilayer tablet, composed of a white telmisartan layer and a yellow hydrochlorothiazide layer. The qualitative composition of the telmisartan layer is identical to the corresponding telmisartan layer of the currently marketed strengths and is compressed to the double weight of the 40 mg telmisartan layer. Only minor differences exist between the composition of the hydrochlorothiazide layer of the newly-developed 80/25 mg strength and the currently registered 80/12.5 mg. The main differences are as follows:

  - Increase in hydrochlorothiazide and consequent reduction of lactose monohydrate

- The colouring pigment has been changed from red to yellow iron oxide to allow for a better differentiation between strengths.

In conclusion, the formulation of the newly developed 80/25 mg layered tablet is similar to the existing 80/12.5 mg dosage strength.

- Adventitious agents

None of the excipients used in telmisartan/hydrochlorothiazide tablets are of human or animal origin, except for lactose monohydrate. Information is available from the suppliers of lactose monohydrate that the lactose is derived from milk from healthy animals in the same conditions as milk collected for human consumption, in accordance with the CPMP "Note for Guidance on Minimizing the risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary medicinal Products".

- Manufacture of the Product

The manufacturing process of Telmisartan/hydrochlorothiazide 80/25 mg tablets is divided into four stages, as described below:

(1) Manufacture of the intermediate product Telmisartan SD granulate
(2) Manufacture of the final blend for the Telmisartan layer
(3) Manufacture of the final blend for the Hydrochlorothiazide layer
(4) Manufacture of the Telmisartan/Hydrochlorothiazide layered tablets

The manufacturing process is similar to the already approved telmisartan/hydrochlorothiazide strengths, exception being stage 3 where a new granulation method for the hydrochlorothiazide has been adopted.
The validation of the manufacturing process was performed on three full scale batches. Batch analysis results indicate that, as for the already authorised strengths of telmisartan/hydrochlorothiazide, the finished product can be reproducibly manufactured according to the finished product specifications.

- Product Specification

The product specifications are based on the registered specifications for the two strengths marketed as well as derived from the release and stability data obtained from development and stability batches of the new strength of the telmisartan/hydrochlorothiazide tablets (80/25 mg). The specifications include tests for appearance, identification of telmisartan (HPLC) and hydrochlorothiazide (HPLC), assay (HPLC), water content (Karl Fisher), hardness, degradation products (HPLC), dissolution, content uniformity, identification of the dyes (yellow iron oxide) and microbial quality. All analytical procedures have been adequately described and validated.

- Stability of the Product

The stability studies were performed according to the ICH guidelines. Accelerated and long-term stability data was provided for three production-scale batches of telmisartan/hydrochlorothiazide 80/25 mg tablets, packaged in aluminium blister packs, stored for 24 months under long-term conditions (25°C/60% RH) and for up to 6 months under accelerated test conditions (40°C/75% RH). The results showed that the new strength satisfy all shelf-life acceptance criteria.

Discussion on chemical, pharmaceutical and biological aspects

Telmisartan/hydrochlorothiazide (80/25 mg) has been developed based on the already authorised 80/12.5 mg and 40/12.5 mg strengths. The composition of the new strength is similar to the 80/12.5 mg strength. There are only minor differences between the compositions of the hydrochlorothiazide layers.

The results of tests carried out indicate satisfactory consistency and uniformity of product quality characteristics, as already demonstrated for the approved strengths, and these in turn lead to the conclusion that the new strength should have a satisfactory and uniform performance in the clinic.

3 Non-clinical aspects

Introduction

Since the approval of PritorPlus in 2002 (40mg/12.5mg and 80mg/12.5mg) no new non-clinical toxicological, toxicokinetic and pharmacological studies have been performed with either telmisartan or the fixed combination telmisartan/HCTZ.
Reference is made to the non-clinical pharmacology, pharmacokinetic, and toxicology data for the current approved strengths, generated previously, and filed under the approved marketing authorisation for the current PritorPlus strengths.
In the following particular emphasis is placed on specific non-clinical aspects of the new strength 80mg telmisartan/25 mg HCTZ.

Pharmacology

The pharmacological properties of telmisartan alone and in combination with HCTZ are well characterised. The data were assessed in support of the approved marketing authorisation for the current strengths of PritorPlus.

Pharmacodynamics

The pharmacodynamics of both telmisartan and HCTZ are both well characterised. The studies for telmisartan included *in vitro* and *in vivo* studies in rodents, guinea pigs, rabbits and dogs. Data from *in vitro* studies supported that telmisartan is a potent specific antagonist of the angiotensin II subtype 1 (AT1) receptor (Ki = 3.7 nM). 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 induced an increase of both plasma renin activity and plasma angiotensin II concentrations.
HCTZ reduced blood pressure in volume-dependent and in salt-induced hypertension, as well as in renin-dependent hypertensive rat models.

Pharmacokinetics

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.

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. 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.
HCTZ is not metabolised but is eliminated rapidly by kidney. At least 61% of the oral dose is eliminated as unchanged drug within 48 hours.

Toxicology

The toxicity and safety profiles of the individual compounds telmisartan and HCTZ in animals and man are well known. All observed adverse effects in kidney of rats and dogs (increase of blood urea nitrogen, plasma creatinine, serum potassium and renal juxtaglomerular hyperplasia) and GI tract lesions in rats (erosions and ulcers) following high level exposure of telmisartan are species-specific,

reversible and attributable to the exaggerated pharmacodynamic activity in normotensive animals. Gastric mucosal changes can be prevented by oral saline supplementation. All these adverse effects are also known from Angiotensin-Converting-Enzyme-inhibitors (ACE-inhibitors) and other Angiotensin II Antagonists indicating a class effect. In clinical and observational studies the safety, tolerability and efficacy of telmisartan was confirmed in a diverse patient population with arterial hypertension under conditions of normal clinical practice. There was no evidence for an increase of gastric or duodenal ulcer or other gastrointestinal pathologies attributable to telmisartan.

Chronic overdosing of rats and dogs with HCTZ resulted in a loss of electrolytes, e.g. hypokalaemia and urinary calculi associated with renal changes (tubular degeneration and interstitial fibrosis) due to persistent diuresis.

In addition to the full toxicity package with the individual compounds, acute and specific oral repeat-dose toxicity studies (26 week rat and dog, teratogenicity rat) were performed with the combination telmisartan/HCTZ to specifically address questions of any toxicological interaction and/or potentiation. However, no mutagenicity, carcinogenicity, fertility, pre- and postnatal or safety pharmacology studies were conducted with the drug combination.

Co-administration of telmisartan and HCTZ resulted in a slightly increased AUC in rats but not in dogs. However, human data did not show any significant pharmacokinetic interaction following single doses of telmisartan and HCTZ.

Due to the different mode of action of the individual drugs telmisartan or HCTZ, different metabolic pathways and different toxicological target organs in animals, no new manifestations of toxicity including any off-target organ toxicity were seen for the combination. The observed main adverse effects (GI and renal changes) are predominantly induced by telmisartan. All effects are associated with the exaggerated pharmacodynamic activity of T in normotensive animal models and also reported for ACE-inhibitors and other angiotensin II antagonists (class effect) without any clinical relevance at therapeutic use. This is supported by short- and long-term clinical studies.

In rats the maximum dose used in the fixed combination was 50 telmisartan/15.6 HCTZ mg/kg in 26wks study, corresponding to a C_{max} (ng/ml) of 16.6 telmisartan/2.7 HCTZ and to AUC (ng.h/ml) of 62.2telmisartan/8.4HCTZ. In dogs the higher doses used were 4 telmisartan/1.25 HCTZ mg/kg in 26wks study, corresponding to a C_{max} (ng/ml) of 577 telmisartan/563 HCTZ and to AUC (ng.h/ml) of 2253 telmisartan/1734 HCTZ.

TABLE A:20 Drug ranges tested, NOTEL[#] and MTD[#] of oral repeated dose toxicity studies with Telmisartan/HCTZ in the rat and the dog

Species	Drug Range Tested [mg/kg/day]	Duration [weeks]	NOTEL [mg/kg/day]	MTD [mg/kg/day]	Report
Rat	T: 3.2 / H: 1 - T: 96 / H: 15	9	not determined	not determined	U97-2645
	T: 0.1 / H: 0.03 - T: 50 / H: 15.6	26	0.1/0.03	4/1.25	U99-1556
Dog	T: 1.6 / H: 0.25 - T: 48 / H: 7.5	8	not determined	not determined	U98-3009
	T: 0.25 / H: 0.08 - T: 4 / H: 1.25	26	0.25/0.08	1/0.31	U99-3058

[#] NOTEL: no observed toxic effect level, MTD: minimum toxic dose

Based on the available toxicity studies (26 weeks) in rats and dogs and the clinical studies in volunteers (drug-drug interaction) and patients, the exposure at the high doses was estimated for co-administration of T/H based on body weight, C_{max} and AUC and is shown in TABLE C:

TABLE C High Dose Comparison of Exposure between Rat, Dog and Human

Group	Dose T/H (mg/kg)	Fold of human dose T80/H25 (based on mg/kg)	C_{max} (ng/ml) T/H	Fold of human dose T80/H25 C_{max}	AUC (ng.h/ml) T/H	Fold of human dose T80/H25 AUC
Rat: High Dose	50/15.6	31/31	16650/2722	24.4/17.0	62240/8396	16.7/7.7
Dog: High Dose	4/1.25	2.5/2.5	610/603	0.9/3.8	3602/1672	1.0/1.5
Man: T160/H25	3.2/0.5		2053/160		4464/1095	
Man: T80 [1]	1.6/--		681/--[1]		3728/--[1]	

[1] Data taken from clinical trial report U96-3062 for telmisartan

Following repeat oral dosing with telmisartan/hydrochlorothiazide at the highest dose in dogs and rats for 26 weeks, the exposure (Cmax) was 24/17-fold (rat) and 0.9/3.8- fold (dog) higher compared with the systemic exposure in human at the 80 mg/25 mg dose. The corresponding AUC-values exceeded human exposure by 17/8- (rat) and 1/1.5- fold (dog).

Ecotoxicity/environmental risk assessment

The Applicant submitted an environmental risk assessment showing no significant concerns for the aquatic compartment due to the use of telmisartan/hydrochlorothiazide 80mg/25mg tablets.

Discussion on the non-clinical aspects

No additional non-clinical studies have been performed for the new strength 80mg/25mg. In rats the maximum dose used in the fixed combination was 50 temisartan/15.6 HCTZ mg/kg in 26wks study, corresponding to a Cmax (ng/ml) of 16.6 telmisartan/2.7 HCTZ and to AUC (ng.h/ml) of 62.2 telmisartan/8.4 HCTZ. In dogs the higher doses used were 4 telmisartan/1.25 HCTZ mg/kg in 26 wks study, corresponding to a Cmax (ng/ml) of 577 telmisartan/563 HCTZ and to AUC (ng.h/ml) of 2253 telmisartan/1734HCZT. Following repeat oral dosing with telmisartan/hydrochlorothiazide at the highest dose in dogs and rats for 26 weeks, the exposure (Cmax) was 24/17-fold (rat) and 0.9/3.8- fold (dog) higher compared with the systemic exposure in human at the 80mg/25mg dose. The corresponding AUC-values exceeded human exposure by 17/8- (rat) and 1/1.5- fold (dog).

The statement in SPC section 5.3. has been revised accordingly for the new strength of the fixed dose combination (80mg/25mg): “No additional preclinical studies have been performed with the Fixed Dose Combination product 80mg/25mg. Previous preclinical safety studies performed with co-administration of telmisartan and hydrochlorothiazide in normotensive rats and dogs in doses producing exposure comparable to that in the clinical therapeutic range, caused no additional findings not already observed with administration of either substance alone. The toxicological findings observed appear to have no relevance to human therapeutic use.”

On the basis of the existing non-clinical experimental data it cannot be excluded that with the increase from 12.5 to 25mg HCTZ a negative impact on the safety of the fixed-dose combination 80mg/25mg in hypertensive patients might be observed. Nevertheless clinical data appear sufficient to accept the proposed new dose strength of 80mg telmisartan/25mg HCTZ.

4 Clinical aspects

Introduction

The core clinical development programme consisted of the pivotal trial 502.480 and its follow-up study 502.491, which were designed and conducted following the Scientific Advice obtained from the EMEA in 2004. Supportive evidence comes from 10 trials investigating the efficacy and safety of the free and fixed-dose combination 80mg/25mg.

The clinical trial data were collected in accordance with the relevant EMEA guidelines, particularly CPMP/EWP/238/95 Rev. 1 and 2 and CPMP/ICH/541/00. The database contains data from 645 patients exposed to the free- or fixed-dose combination (FDC) of 80mg/25mg for at least 6 months and 251 patients exposed to 80mg/25mg for at least 1 year; 280 patients were exposed to the FDC 80mg/25mg for at least 6 months. Additional active-controlled studies with long-term exposure to the FDC 80mg/25mg were not expected to reveal new information since this application is a line extension of an already approved product. In addition, the to-be-marketed formulation is already registered and has been used in clinical practice in the USA since 2004 without relevant safety concerns, as documented in periodic safety update reports.

For the establishment of clinical efficacy and safety of the FDC 80mg/25mg, results from all trials that specified the concomitant use of 80mg telmisartan and 25mg hydrochlorothiazide have been evaluated (see table 2).

Study	Comparison	Primary and Key Secondary Endpoints	Results
502.480	T80/HCTZ 12.5 FDC + placebo vs T80/H25 FDC	Adjusted mean change from baseline in DBP (SE) [mmHg] T80/H12.5: -5.5 (0.4) T80/H25: -7.1 (0.5) Difference: -1.6 (p=0.001) mean change from baseline in trough seated SBP	**DBP (SE) [mmHg]** **T80/H12.5: -5.5 (0.4)** **T80/H25: -7.1 (0.5)** **(SE) [mmHg]** **T80/H12.5: -7.1 (0.7)** **T80/H25: -9.8 (0.7)** **Difference: -2.7 (p=0.0003)**
502.491	T80/H25 FDC	The proportion of patients achieving DBP control (trough seated DBP <90 mmHg) after 6 months of treatment with T80/H25 Change in trough seated DBP and SBP (SD) [mmHg]	**No: 28.4%** **(DBP ≥90 mmHg)** **Yes: 71.6%** **(DBP <90 mmHg):** **Trough DBP: -3.7 (7.3)** **Trough SBP: -5.2 (10.7)**
502.421	T at 80 mg vs placebo V at 160 mg vs placebo Combination: T80/H25 vs placebo V160/H25 FDC vs placebo	Change in mean seated trough cuff DBP and SBP	**Seated trough DBP** **T80/H25: -17.6 (0.42)** **Difference to placebo: -10.8 (p<0.0001)** **Difference to V160/H25: -1.5 (p=0.0096)** **Seated trough SBP** **T80/H25: -24.0 (0.65)** **Difference to placebo: -19.6 (p<0.0001)** **Difference to V160/H25: -2.8 (p=0.0026)**

502.476	T at 80 mg vs placebo V at 160 mg vs placebo Combination: T80/H25 vs placebo V160/H25 FDC vs placebo	Change for mean seated trough cuff DBP and SBP	**Seated trough DBP** **T80/H25: -18.2 (0.39)** **Difference to placebo: -12.1 (p<0.0001)** **Difference to V160/H25: -1.2 (p=0.0254)** **Seated trough cuff SBP** **T80/H25: -24.6 (0.63)** **Difference to placebo: -20.6 (p<0.0001)** **Difference to V160/H25: -2.1 (p=0.0174)**
502.210	T at 20, 40, 80 mg E at 5, 10, 20 matching placebo if insufficient response, combination terapy: T80/H12.5, T80/H25 E20/H12.5, E20/H25	Changes in mean supine trough DBP and SBP	**DBP** **T: -12.8 (0.69)** **E: -11.4 (0.69)** **Difference:-1.44 (p=0.074)** **SBP** **T: -22.1 (1.76)** **E: -20.1 (1.79)** **Difference: -1.96 (p=0.350)**
502.214	T at 40, 80, 160 mg LIS at 10, 20, 40 mg matching placebo Combination therapy with HCT if insufficient response: T160/H12.5, T160/H25 LIS40/H12.5, LIS40/H25	Proportion of patients with final trough supine DBP Controlled on monotherapy: Patients controlled on combination with H Secondary endpoint Mean change trough supine SBP/DBP	**T: 28.2%** **LIS: 28.7%** **(p=0.86)** **T/H: 34.0%** **LIS/H: 35.1%** **T: −17.0/-13.3** **LIS: −15.3/-12.0** **(p=0.082 for DBP; p=0.306 for SBP))**
502.216	T at 40, 80, 120 mg A at 50, 100 mg Versus placebo And in case of insufficient response combination therapy with a titrated dose of H(12.5, 25)	Proportion of Patients with full DBP response (mean supine ≤90 mmHg or reduction from baseline ≥10 mmHg) Mean change trough supine SBP/DBP [mmHg]	**T: 84%** **A: 78%** **(odds ratio=1.55, p=0.0651,** **T: −20.9/-13.3** **A: −16.7/-11.7** **(p=0.086 for changes in DBP;** **p=0.0049 for changes in SBP)**
502.519	T at 40, 80 mg Combination: T80/H12.5 T80/H25 T80/H25/other antihypertensive drug	Percentage of patients who achieved the goal DBP response mean change trough supine SBP/DBP [mmHg]	**T40 (n=231): 86.6%** **T80 (n=124): 79.8%** **T80/H12.5 (n=95): 82.1%** **T80/H25 (n=94): 84.0%** **T80/H25+other (n=22): 68.2%** **T mono: -17.7/-14.5** **T80/H: -23.4/-16.5** **T80/H25/other: -27.8/-16.6**

502.220	T at 40, 80 mg Combination: T40/H12.5 (only one patient) T80/H12.5 T80/H25 T80/H25/other antihypertensive drug	Primary endpoint Percentage of patients who achieved the goal DBP response Mean change in trough supine DBP at maximum achieved dose (SD) [mmHg]	**T40 (n=369): 91.6%** **T80 (n=142): 83.0%** **T80/H12.5 (n=85): 80.2%** **T80/H25 (n=85): 77.2%** **T80/H25/other (n=72): 69.9%** **T80/H12.5: -16.5 (7.1)** **T80/H25: -16.9 (7.6)**
502.221	T at 40, 80 mg Combination: T80/H12.5 T80/H25 T80/H25/other antihypertensive dug	Percentage of patients who achieved the goal DBP response By maximum achieved dose level	**T40 (n=30): 86.7%** **T80 (n=22): 81.8%** **T80/H12.5 (n=19): 79.0%** **T80/H25 (n=18): 83.3%** **T80/H25/other (n=10): 40.0%**
502.228	T at 40, 80 mg Combination: T80/H12.5 T80/H25 T80/H25/other antihypertensive drug	Mean change from trough supine SBP/DBP [mmHg] Percentage of patients who achieved the goal DBP response By maximum achieved dose level: Mean change trough supine SBP/DBP [mmHg]	**T mono: -16.2/-13.4** **T/H: -20.8/-15.5** **T80/H25/other: -15.9/-12.9** **T mono (n=45): 88.9%** **T/H (n=42): 95.2%** **T80/H25/other (n=34): 79.4%** **T mono: ─21.5/-15.8** **T/H: ─30.0/-17.9** **T80/H25/other: ─26.9/-14.5**
502.260	T at 80 mg Combination therapy: T80/H12.5 T80/H25, T80/H25/other antihypertensive drug	Percentage of patients who achieved the goal DBP response by maximum achieved dose level: Mean change trough supine SBP/DBP [mmHg]	**T80 (n=277): 70.0%** **T80/H12.5 (n=86): 55.8%** **T80/H25 (n= 86): 54.7%** **T80/H25/other (n=34):64.7%** **T80: -23.5/-15.0** **T80/H12.5: -21.5/-14.0** **T80/H25: -25.3/-15.4** **T80/H25/other: -24.6/-16.4**
502.204	T at 20, 40, 80, 160 mg H at 6.25, 12.5, 25 mg matching placebo Combinations of T/H: 20/6.25, 20/12.5, 20/25; 40/6.25, 40/12.5, 40/25, 80/6.25, 8/12.5, 80/25, 160/6.25, 160/12.5, 160/25 m	Mean change in supine SBP/DBP[mmHg] DBP control (<90 mmHg):	**Placebo: -2.9/-3.8** **T40: -12.2/-10.7** **T80: -15.4/-11.5** **H12.5 -6.9/-7.3** **T40/H12.5: -18.8/-12.6** **T80/H12.5: -23.9/-14.9** **T80/H25: -23.7/-14.4** **Placebo: 21.0%** **T40: 49.0%** **T80: 55.0%** **H12.5 38.0%** **T40/H12.5: 56.0%** **T80/H12.5: 64.0%** **T80/H25: 59.0%**

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics and Pharmacodynamics

As the pivotal clinical trials (non-responder study 502.480 and 6-month follow up study 502.491) for this extension application were conducted with the production scale commercial products the applicant did not add new biopharmaceutical data, in particular bioequivalence (BE) data for this submission. This is in accordance with Scientific Advice received in 2004. In line with the Scientific Advice no additional pharmacokinetic/pharmacodynamic or food effect studies were conducted. The clinical pharmacology data assessed in support of the approved marketing authorisation for the current strengths of PritorPlus were considered to be sufficient.

Clinical efficacy

- Main studies

STUDY 502.480
A prospective randomised study to compare a fixed dose combination of telmisartan 80mg plus hydrochlorothiazide 25mg with a fixed dose combination of telmisartan 80mg plus hydrochlorothiazide 12.5mg in patients with uncontrolled hypertension who fail to respond adequately to treatment with a fixed dose combination of telmisartan 80mg plus hydrochlorothiazide 12.5mg.

METHODS

It was a non-responder, filter-design trial directly comparing the FDCs T80/H25 and T80/H12.5. Patients had to have an inadequately controlled blood pressure (BP) on existing antihypertensive treatment before enrolment into the study. Inadequate control was defined as seated DBP ≥95 mmHg on 1 current antihypertensive medication or DBP ≥90 mmHg on 2 or more current antihypertensive medications. After 6 weeks of open-label treatment with 80mg/12.5mg, patients who did not respond adequately, i.e. had a DBP ≥90 mmHg, were randomised to either continue with T80/H12.5 or to receive T80/H25 for 8 weeks. Additional antihypertensives were not allowed during the run-in and the randomised treatment periods.

Study Participants
Male or female patients (≥ 18Years of age) who had been diagnosed with essential hypertension and currently taking between 1 and 3 antihypertensive medications at a stable dose for at least 4 weeks before visit 1 were considered for randomisation. Further inclusion criteria were a not adequately controlled BP on existing antihypertensive treatment before study entry or failure to respond adequately to 6 weeks treatment with T80/H12.5 FDC therapy.
Pregnant or breast-feeding women as well as women of child-bearing potential not practising birth control were not eligible for study entry. Also patients with a known or suspected secondary hypertension, a mean SBP ≥ 200mmHg at the end of the run-in treatment period, clinically significant hepatic impaired or severely renal impaired were excluded form the study. Additional main exclusion criteria comprised patients post-renal transplant or with only one functioning kidney, clinically relevant hypokalaemia or hyperkalaemia, uncorrected volume or sodium depletion, primary aldosteronism, hereditary fructose intolerance, history of drug or alcohol dependency within the previous 6 months and chronic administration of any medication known to affect BP (other than the trial medication. The conditions of concomitant therapy with lithium, cholestyramine or colestipol resins, known allergic hypersensitivity to any component of the formulations under investigation and hypertrophic obstructive cardiomyopathy had to be considered for exclusion.

Treatments
During the run-in phase, all patients received the FDC T80/H12.5, one tablet per day. During the randomised phase, 2 treatments were administered to the patients, either T80/H12.5 FDC or T80/H25 FDC. Active study drugs were administered in a double-dummy fashion as tablets. Thus, during the randomised phase, each patient took one tablet of active drug and one placebo tablet matching the alternative active treatment every day. All tablets were taken orally, once daily in the morning.

Objectives
The primary objective of this trial was to demonstrate that a fixed-dose combination of telmisartan 80 mg plus HCTZ 25 mg (T80/H25) was superior in reducing BP after 8 weeks compared with a fixed dose combination of telmisartan 80 mg plus HCTZ 12.5 mg (T80/H12.5) in patients who failed to respond adequately treatment with T80/H12.5.

Outcomes/endpoints
The primary endpoint was the change from baseline in trough seated (i.e. at 24 hours after last dose) DBP after 8 weeks of randomised treatment or at last trough observation during the double-blind treatment period (i.e. last trough observation carried forward), as analysed by ANCOVA.

Secondary endpoints included change from baseline in trough seated SBP, trough standing SBP and DBP, proportions of patients achieving DBP control, DBP response and SBP response and proportions of patients with optimal, normal, high-normal and high BP. The efficacy endpoints were assessed after 8 weeks of double-blind treatment or at last trough observation during the double-blind treatment period (i.e. last trough observation carried forward).

The safety and tolerability of T80/H25 were compared with that of T80/H12.5. Safety and tolerability were measured by assessment of physical examination findings, heart rate, laboratory parameters, 12-lead ECG data and reported adverse events.

RESULTS
Of the 971 patients treated with run-in medication, 713 patients were randomised and treated with double-blind medication. Of the 687 patients evaluable for efficacy, 340 patients had been randomised to T80/H25 and 347 to T80/H12.5. The frequency of discontinuations was low in both treatment arms with 1.2% for T80/H25 and 2.3% for T80/H12.5.

The treatment groups were well balanced with respect to demographics and baseline characteristics. The overall mean age was 57.2 years. The majority of the patients were male (56.8%) and non-black (96.9%). Almost all patients (98.7%) had previously received treatment with antihypertensive medications. The mean BPs at the time of randomisation were 147.9/95.2 mmHg in the T80/H25 group and 147.4/95.0 mmHg in the T80/H12.5 group.

The adjusted mean changes from baseline to end of treatment for DBP and SBP are presented in Figure 1.

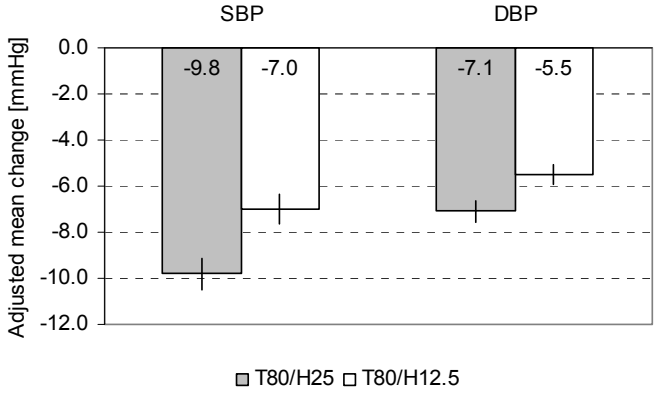


Figure 1. Adjusted (for baseline and country) mean change from baseline (with SE) of trough seated BP in the pivotal trial 502.480 (EFF-1)

Treatment with T80/H25 was superior to T80/H12.5 in reducing both DBP and SBP. The adjusted mean treatment difference in the DBP changes from baseline was −1.6 mmHg in favour of T80/H25

with a 95% confidence interval (CI) extending from −2.5 to −0.6 mmHg (p=0.0013). For trough seated SBP, the adjusted mean treatment difference was −2.8 mmHg in favour of T80/H25 with a CI of −4.2 to −1.3 mmHg (p=0.0002).

The BP-lowering effect analysed according to pre-defined response criteria (DBP control, DBP and SBP response), showed the superiority of T80/H25 over T80/H12.5 in this non-responder population (Figure 2). For all responder criteria with the exception of DBP control, the p-value for the comparison between treatment groups was <0.05.

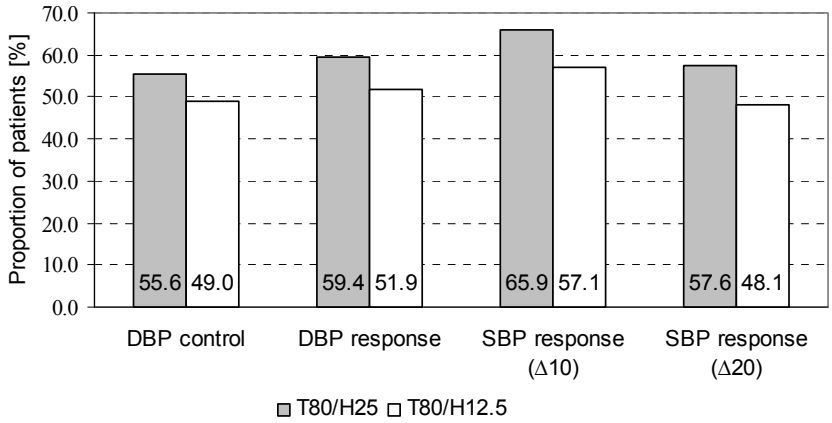


Figure 2. Proportions of patients with DBP control or BP response in the pivotal trial 502.480 (EFF-1)
DBP control was defined as seated DBP <90 mmHg. DBP response was defined as seated DBP <90 mmHg or reduction from baseline ≥10 mmHg. SBP response was defined as seated SPB <140 mmHg or reduction from baseline ≥10/20 mmHg.

STUDY 502.491
An open-label follow-up trial of the efficacy and safety of chronic administration of the FDC of telmisartan 80mg plus hydrochlorothiazide 25mg alone or in combination with other hypertensive medications in patients with hypertension

METHODS

Study Participants
A total of 432 patients were included into the interim analysis and received at least one dose of the open-label treatment (FDC T80/H25).
Male or female patients (≥ 18Years of age) who had been randomised to the preceeding trial 502.480 and had completed that trial within 14 days prior to visit 1 of study 502.491 were considered for inclusion in the study. Also the inclusion criteria as for trial 502.480 were applicable.
Patients who discontinued study 502.480 because of an adverse event or any other reason, or where during the preceeding trial of any medical condition was developed which could be worsened by the study treatment were excluded. In addition, most of the exclusion criteria of trial 502.480 were also applicable.

Treatments
All patients received T80/H25 in an open-label fashion for a period of 6 months, one tablet per day. The tablets were taken orally, once daily in the morning.

Objectives
The primary objective of the trial was to assess the efficacy and safety of the FDC T80/H25 alone or in combination with other antihypertensive medications during open-label, follow-up treatment (6 months) in patients who completed the preceding trial (502.480).

Outcomes/endpoints
The primary endpoint was the proportion of patients achieving DBP control (defined as seated DBP <90 mmHg under trough conditions, i.e. 24 hours after last dose) after 6 months of treatment with

T80/H25 or at last trough observation during the treatment period (i.e. last trough observation carried forward).
Secondary endpoints included change from baseline in trough seated DBP and SBP, proportions of patients achieving DBP response and SBP response, and proportions of patients with optimal, normal, high-normal and high BP. Further secondary endpoints were proportion of patients requiring additional antihypertensive therapy to achieve DBP control, the additional reduction in BP by the use of additional antihypertensive therapy and time to starting additional hypertensive therapy. The efficacy endpoints were assessed after 6 months of treatment (i.e. last trough observation carried forward). Baseline was defined as baseline of the preceding trial (mean DBP and SBP, response endpoints) or end of the preceding trial (mean DBP and SBP).

The safety and tolerability of T80/H25 over 6 months were assessed by physical examination findings, measuring heart rate and laboratory parameters, 12-lead ECG data and reported adverse events.

RESULTS

During the preceding trial 502.480, 48.1% had been treated with the FDC T80/H12.5 and 51.9% had been treated with the FDC T80/H25. Overall, 92.8% completed the trial and 7.2% discontinued the trial prematurely. The majority of the trial population was male (55.6%) and white (90.0%); 6.9% were Asian and 3.0% were black. The mean age of the patients was 57.6 years and the mean duration of hypertension was 7.7 years. The proportion of patients taking additional antihypertensive medication at some stage during this open-label trial was 17.4%.

By the end of the preceding trial (502.480), 50.8% of the patients entering trial 502.491 had achieved DBP control; based on previous treatment in trial 502.480, 206 (50.0%) patients treated with the FDC T80/H12.5 and 220 (51.6%) patients treated with the FDC T80/H25 had achieved DBP control. At the end of trial 502.491, the proportion of patients achieving DBP control increased to 71.6%.

The proportions of patients with DBP control at the end of the preceding study and during the present study are summarised in the following table 3.

Table 3

Visit	Trough DBP control, N (%)	
	No (DBP ≥90 mmHg)	Yes (DBP <90 mmHg)
End of study 502.480 (N=421)	207 (49.2)	214 (50.8)
Month 1 (N=414)	126 (30.4)	288 (69.6)
Month 3 (N=416)	118 (28.4)	298 (71.6)
End of this study (N=426)	121 (28.4)	305 (71.6)

At the end of the preceding trial, the mean trough SBP/DBP was 142.3/89.1 mmHg for patients entering trial 502.491. After 6 months of treatment with the FDC T80/H25, the mean trough SBP/DBP decreased further by 5.2/.3.7 mmHg to 137.0/85.4 mmHg.

Mean trough seated DBP and SBP with mean changes from the end of study 502.480 are shown in table 4 below.

Table 4

Visit	Trough DBP [mmHg]		Trough SBP [mmHg]	
	Actual mean (SD)	Mean change (SD)	Actual mean (SD)	Mean change (SD)
End of study 502.480	89.1 (7.2)		142.3 (12.7)	
Month 1	86.6 (7.4)	−2.7 (6.2)	138.9 (13.3)	−3.7 (10.2)
Month 3	85.9 (7.6)	−3.2 (6.6)	137.2 (12.5)	−5.0 (10.3)
End of this study	85.4 (7.6)	−3.7 (7.3)	137.0 (12.4)	−5.2 (10.7)

The SBP/DBP changes from the last visit of the run-in period of trial 502.480 to the end of trial 502.491 were ─11.3/─9.6 mmHg. The DBP and SBP response rate was analysed with respect to the baseline of the preceding trial.

Table 5

Visit	Response, N (%)	
	No	Yes
Trough DBP response[1]		
End of study 502.480 (N=416)	194 (46.6)	222 (53.4)
Month 1 (N=409)	114 (27.9)	295 (72.1)
Month 3 (N=411)	105 (25.5)	306 (74.5)
End of this study (N=421)	111 (26.4)	310 (73.6)
Trough SBP 140/10 response[2]		
End of study 502.480 (N=416)	185 (44.5)	231 (55.5)
Month 1 (N=409)	132 (32.3)	277 (67.7)
Month 3 (N=411)	102 (24.8)	309 (75.2)
End of this study (N=421)	99 (23.5)	322 (76.5)
Trough SBP 140/20 response[3]		
End of study 502.480 (N=416)	221 (53.1)	195 (46.9)
Month 1 (N=409)	168 (41.1)	241 (58.9)
Month 3 (N=411)	140 (34.1)	271 (65.9)
End of this study (N=421)	141 (33.5)	280 (66.5)

Source data: Tables 15.2.4: 1, 5 and 9

The response rate increased from 53.4% to 73.6% for DBP and from 55.5% to 76.5% (140/10 mmHg) and 46.9% to 66.5% (140/20 mmHg) for SBP by the end of this trial. Most of the BP response was achieved within the first 3 months.

By the end of trial 502.480, 9.7% of the patients had achieved an 'optimal' or 'normal' BP and a further 20.9% had moved into the 'high-normal' BP category. Further improvements were observed during trial 502.491 with 18.5% of patients achieving 'optimal' or 'normal' BP, and a further 33.8% achieving 'high-normal' BP at the end of the study. The mean exposure was 170.2 days (24.3 weeks) with 84.5% of the patients being exposed for at least 24 weeks and 31.7% for at least 26 weeks.

Of the 426 patients who completed the study 74 (17.4%) took additional antihypertensives during the treatment phase. Of the 74 patients 39 had been treated with T80/H12.5 and 35 with T80/H25 in the preceding trial. The proportion of patients with DBP control increased from 20.5% prior to the intake of the new therapy to 63.0% at the end of the study.

Table 6

	DBP [mmHg]		SBP [mmHg]	
	Actual Mean (SD)	Change Mean (SD)	Actual Mean (SD)	Change Mean (SD)
Pre-antihypertensive[1]	93.7 (5.9)		148.4 (14.0)	
Post-antihypertensive[2]	86.7 (7.1)	-7.0 (7.7)	140.0 (12.0)	-8.3 (12.5)

- Supportive studies

Double-blind placebo-controlled forced-titration trials

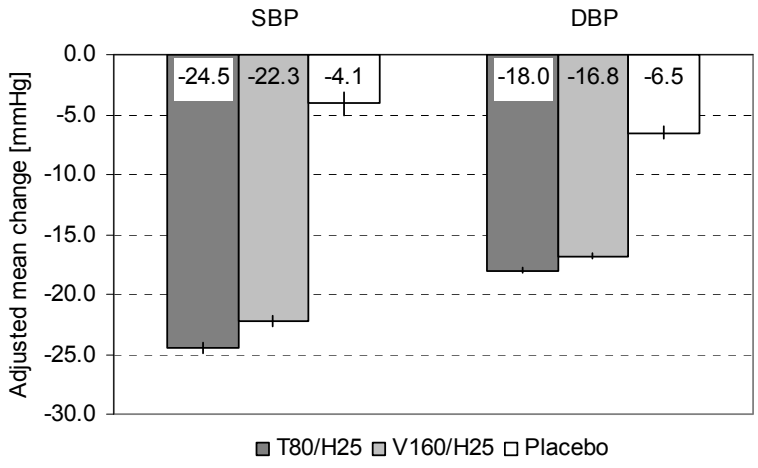
Trials 502.421 and 502.476 were two large, double-blind, forced-titration studies performed in USA of identical design, entry criteria, and endpoints. These studies supplied short-term efficacy data for T80/H25 in comparison with placebo and valsartan (V) 160/H25. Patients were randomised in a 4:4:1 ratio to telmisartan, valsartan, or placebo. After a 2-week initial monotherapy period, patients were treated with the combination therapies (or placebo) for 6 weeks. Additional antihypertensives were not allowed. In study 502.421, the daily dose in the T arm was taken as 2 tablets of the approved FDC T40/H12.5, whereas trial 502.476 used the to-be-marketed FDC T80/H25. Therefore, these 2 trials also serve to demonstrate the clinical equivalence of the 2 posologies.

2121 patients were evaluated for efficacy (942 on T80/H25, 952 on V160/H25, 227 on placebo). Overall, 3.9% of the patients discontinued the studies prematurely. The higher discontinuation rate in the placebo group (12.8%) was mainly due to AEs (worsening of disease under study) and lack of efficacy.

The objective of these trials was to show that telmisartan 80 mg /hydrochlorothiazide 25 mg (T80/H25) is superior to placebo in lowering seated trough cuff blood DBP and SBP, and possibly superior to V160/H25 in lowering DBP and SBP in patients with mild to moderate hypertension..

As regard the 502.421 study, for the primary endpoint, the adjusted mean changes from baseline in seated trough SBP/DBP were −24.0/−17.6 mmHg for T80/H25 compared with −4.4/−6.8 mmHg for placebo (both p-values <0.0001). The mean changes in the reductions of SBP/DBP for T80/H25 in comparison with the FDC V160/H25 were −24.0/−17.6 mmHg for T80/H25 compared with −21.2/−16.1 mmHg (with the adjusted mean differences being -1.5 mmHg for DBP (p=0.0096) and -2.8 mmHg for SBP (p=0.0026), DBP control was achieved by 70.9% of patients treated with T80/H25, 67.0% of patients treated with V160/H25, and 28.3% of patients treated with placebo.
The results of study 502.476 for the primary endpoint, were −24.6/−18.2 mmHg for the FDC T80/H25 compared with −4.1/−6.1 mmHg for placebo (both p-values <0.0001). The mean changes in the reductions of SBP/DBP for the FDC T80/H25 was −22.5 mmHg while for the FDC V160/H25 was -17.0 mmHg (DBP p-value=0.0254 and SBP p-value=0.0174) as shown in figure 3 below.

Figure 3



DBP control was achieved by 77.3% of patients treated with T80/H25, 71.1% of patients treated with V160/H25, and 32.8% of patients treated with placebo. DBP and SBP response was achieved by 86.5% and 91.0% of patients treated with T80/H25, by 81.9% and 86.9% of patients treated with V160/H25, and by 40.3% and 38.7% of patients treated with placebo.

In both studies the most frequently reported AEs during the randomised treatment period were headache and dizziness. During study 502.421, two patients, both randomised toT80/H25, had SAEs that were considered possibly drug-related; one patient experienced diverticulitis and hypokalaemia (initial potassium level was 2.6 mEq/L with repeat levels of 2.6 and 3.1 mEq/L following treatment with a potassium supplement) and another patient was admitted to hospital with uncontrolled hypertension and chest pain. Two patients died during the study 502.476; one 75-year old woman died of myocardial infarction during the placebo run-in phase, and another woman, aged 63 years, died in the post-study period of unknown causes, 6 days after completing the trial. Both deaths were not considered to be drug-related.

The *studies 502.210, 502.214, and 502.216* were 3 long-term dose-titration trials comparing telmisartan with enalapril, lisinopril and with atenolol, respectively, with and without the add-on therapy with hydrochlorothiazide.

Titration was started with low doses of the monotherapies, which were to be increased with subsequent addition of H12.5 and H25. Medication was to be up-titrated at pre-defined time points and only if the target BP (<90 mmHg DBP) had not been achieved. No additional antihypertensive medications were allowed.

The pooled analysis of these studies was descriptive and evaluated only patients who had stayed at least 14 days on T80/H25 or T80/H12.5 as final treatment. The mean age was 63.6 years and was substantially higher than in the other analysis sets because of trial 502.210 that was performed in patients of at least 65 years of age.

In these titration-to-response trials, the proportion of patients who received T80/H25 increased over time. Of the patients treated with a combination of T/H as final treatment, 35.9% took T80/H25 as their final treatment. The mean time on the final treatment was 84.3 days for T80/H25 and 103.8 days for T80/H12.5. Over the complete treatment periods, i.e. from study start to end of treatment, patients with final treatment T80/H25 achieved somewhat smaller BP reductions (20.3/13.2 mmHg) than the patients on T80/H12.5 as final treatment (23.7/14.9 mmHg). This was to be expected, since patients receiving T80/H25 were a negative selection, i.e. those who failed to achieve BP control on monotherapy or lower dose diuretic combinations. In these patients the incremental effect of the up-titration from T80/H12.5 to T80/H25 was a BP reduction of 7.0/4.8 mmHg from last value on T80/H12.5 to last value on T80/H25; this is shown in the following table 8.

Table 7. Incremental effect of up-titration from T80/H12.5 to T80/H25 on seated BP in patients with T80/H25 as final treatment (EFF-4)

Change from baseline	Last on T80/H12.5	Last on T80/H25
Number of patients	34	34
Seated DBP, mean (SD) [mmHg]	96.6 (7.4)	−4.8 (6.9)
Seated SBP, mean (SD) [mmHg]	164.9 (26.3)	−7.0 (15.1)

- Analysis performed across trials (pooled analyses and meta-analysis)

The primary source of evidence for the positive benefit risk balance of this line extension comes from studies 502.480 and 502.491. Two double-blind, forced-titration trials (502.421 and 502.476, EFF-3) add efficacy data for T80/H25 in comparison with placebo and V160/H25. Further supportive evidence was obtained in 8 titration-to-response trials, either in a double-blind, active-controlled fashion (502.210, 502.214, 502.216; EFF-4) or in open-label, uncontrolled, long-term trials (502.219, 502.220, 502.221, 502.228, 502.260; EFF-5).

All 12 trials used comparable inclusion and exclusion criteria that included a representative population of patients with mild to moderate hypertension but with limited comorbidities. Patients had to be at

least 18 years of age and had to have a diagnosis of mild to moderate essential hypertension. The requirement of DBP ≥90 mmHg or DBP ≥95 mmHg to 114 mmHg was used in most of the studies. Furthermore, an upper limit for systolic BP (SBP) was defined, e.g. 200 mmHg.

Women who were pregnant or breast feeding, or not using adequate contraception were excluded as were those with severe renal or hepatic impairment, hypo- or hyperkalaemia, angioedema, hypertrophic obstructive cardiomyopathy or haemodynamically relevant stenosis of the aortic or mitral valve, drug or alcohol dependency, or intolerance to any ingredient of the trial medications.

The pooled analysis included 3591 patients with a mean age of 55.0 years. Approximately 80% of the patients were younger than 65 years of age and 57.1% of the patients were male. The majority of the patients were non-black (81.8%) and the mean body mass index (BMI) was 30.8 kg/m^2. The mean duration of hypertension was about 8 years.

BP was measured using a standard sphygmomanometer and was determined 20 to 30 hours after the last administration of trial medication to be considered as 'trough' measurement. Trial medication was to be administered once daily in the morning. In all trials, DBP and/or SBP at trough levels were the main efficacy variables, either as absolute changes from baseline or based on several DBP and/or SBP response criteria.

Primary endpoints were specified in the protocols of the controlled trials 502.480, 502.421, 502.476, 502.210, 502.214, and 502.216, and for the uncontrolled trial 502.491 but not in the open-label titration-to-response trials (EFF-5).

In the randomised, double-blind, controlled studies 502.480 (EFF-1), 502.421 and 502.476 (EFF-3), the primary endpoint was the change from baseline in trough seated DBP (and SBP for 502.421 and 502.476) after 8 weeks of randomised treatment.

Studies 502.421 and 502.476 employed a hierarchical testing procedure. First the superiority of T80/H25 against placebo in the reduction of trough seated DBP and then SBP was tested and thereafter, assuming superiority was established, the non-inferiority in DBP and then superiority in DBP and SBP against V160/H25 was evaluated.

The double-blind, randomised, titration-to-response trials (502.210, 502.214, 502.216; EFF-4) compared the efficacy of 2 titration regimens, based on either T/H or a comparator/H. The definition of primary endpoints in these studies varied considerably. In the 502.210 trial, the primary endpoint was the change from baseline in trough supine DBP and SBP. The primary endpoint of trial 502.214 was the proportion of patients who, after 12 weeks of titration, entered the maintenance period and whose final trough supine DBP after 60 weeks of randomised treatment was <90 mmHg without the use of H. In trial 502.216, the primary efficacy endpoint was DBP response after 26 weeks based on a 3-level rating scale with categories 'full', 'partial', and 'minimal/no' DBP response, using a proportional odds model.

In the uncontrolled trial 502.491, the primary endpoint was the proportion of patients achieving trough seated DBP control (DBP <90 mmHg) at the end of the 6-month treatment period, analysed by descriptive statistics.

Overall, the results for the primary endpoints showed either clear clinical benefits for a T80/H25-based treatment compared with T80/H12.5, V160/H25, and placebo or demonstrated similar efficacy for a T/H-based treatment regimen (including T80/H25) and active comparator-based treatment regimens (ACE-inhibitors or beta-blockers).

Clinical safety

Safety data from 12 clinical trials investigating T80/H25 or T80/H12.5, as previously listed in Table 1 were submitted.

The main objective of these safety analyses was to provide information for an adequate understanding of the safety profile of T80/H25 when used in patients with mild to moderate hypertension. Comparative data from 2 studies with T80/H25, V160/H25, and placebo were also included. Additionally, the safety profile of the FDC T80/H25 was compared with the free combination T80/H25. The evaluation was based upon all available information relevant to patient safety.

On 19 July 2004 the applicant requested scientific advice for the development of the FDC T80/H25. EMEA suggested that the following specific information be provided:

- Is there a higher incidence of hypokalaemia, palpitations, cardiac arrhythmias including tachycardia and bradycardia, and erectile dysfunction including impotence on treatment with T80/H25 compared with T80/H12.5?

- Does treatment with T80/H25 result in an increased occurrence of laboratory abnormalities and possibly clinically significant laboratory abnormalities compared with T80/H12.5? Laboratory parameters of special interest were plasma potassium, uric acid, and triglycerides

Based on the review of data presented, no clinically meaningful differences in the adverse event profiles of T80/H25 and T80/H12.5 were detected. No specific increased incidence was identified for all adverse events, in particular for those effects indicated by EMEA. No additional safety issues were identified during the assessment of this application.

Discussion on the clinical aspects
Overall, the results for the primary endpoints showed clear clinical benefits for a T80/H25-based treatment compared with T80/H12.5, V160/H25, and placebo or demonstrated similar efficacy for a T/H-based treatment regimen (including T80/H25) and active comparator-based treatment regimens (ACE-inhibitors or beta-blockers).

Based on the review of data presented, no clinically meaningful differences in the adverse event profiles of T80/H25 and T80/H12.5 were detected. No specific increased incidence was identified for all adverse events, in particular for those effects indicated by EMEA. No additional safety issues were identified during the assessment of this application.

The SPC for the T80/H25 strength in section 4.1 and 4.2 was revised in order to reflect the patient population studied in the pivotal clinical trials (study 502.480 and 6-month follow up study 502.491). The main results of these pivotal clinical trials as well as the pooled analysis of two studies comparing T80/H25 with placebo and V160/H25 were included in section 5.1 of the SPC accordingly.
Section 4.8 of the SPC was amended with the information that the overall incidence and pattern of adverse events reported with the new strength T80/H25 was comparable with the approved strength T80/H12.5.

5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan

After evaluation and assessment of all information presented in this Risk Management Plan, the CHMP considered that for telmisartan/ HCTZ currently no important safety risk could be identified. With regard to the highlighted hepatic adverse events (hepatic function abnormal, jaundice and liver disorder; all MedDRA PTs), these are not regarded as important safety risks because these events are already listed as side effects in the Company Core Data Sheet. The frequencies of occurrence in Japanese and/ or Asian patients are the focus for these events. Nevertheless, in the section below a summary of actions considered necessary to resolve this safety finding is given.

The evaluation for important potential safety risks did not result in any notable finding. Based on the evaluation and assessment of the information available the applicant concludes that no new safety studies for telmisartan/ HCTZ are required.

Summary of actions for specific safety concerns

The evaluation of identified and potential risk did not lead to any medically relevant findings. However, a higher reporting of hepatic adverse events such as "hepatic function abnormal", "jaundice" and "liver disorder" have been observed in one clinical trial (502.516) performed with telmisartan in Japan. Although these hepatic adverse events are already listed as side effects in the Company Core Data Sheet, they are identified as a medically relevant finding due to the potentially increased frequency. In order to address this finding adequately, the applicant included it as an action item in the Risk Management Plan (see the summary below).

Safety concern	**Potential increase of frequency of the following listed side effects in Japanese patients: "hepatic function abnormal", "jaundice" and "liver disorder"**
Action(s) proposed	After completion of the Japanese study (502.516) the results will be compared with those found in other populations including those in other Asian patients who were enrolled into clinical trials.
Objective of proposed action(s)	In order to allow a conclusive assessment of the results, the ongoing clinical trial (502.516) should be completed and, thereafter comparisons with pooled data from other clinical trials should be performed. The focus of these evaluations should be the comparison of Japanese versus non-Asian patients.
Rationale for proposed action(s)	All concerned events are already listed in the Company Core Data Sheet. The concern to be resolved focuses on the evaluation of different frequencies of the events between ethnic groups.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Dependent on the results of the analysis of the relevant clinical trials the following scenarios may be followed: 1. If the results of the Japanese study are not statistically significant different from those from pooled analysis of other clinical trials the Company Core Datasheet will not be updated and the issue is considered resolved. 2. If the results will show statis tically significant differences the Company Core Data Sheet will be adapted accordingly.
Milestones for evaluation and reporting including justification for choice of milestones After complication of the Japanese study the relevant analyses will be performed.	After complication of the Japanese study the relevant analyses will be performed.
Titles of protocols (Annex full study protocols and provide cross reference to position in annex 5)	All studies listed in Table 1:11 Relevant studies performed with telmisartan including Japanese study 502.516

No identified or potential safety risks are included in this EU-RMP. Therefore no outstanding action items or milestones are listed. With regard to the hepatic safety finding the following timelines are given:

Actions	**Milestones/ exposure**	**Milestones/ calendar time**	**Study status**
Analysis of frequencies of hepatic adverse events in Japanese patients	After completion of the Japanese clinical trial (502.516) further analyses taken all relevant clinical studies with telmisartan and telmisartan/ HCTZ into account will be performed.	After completion of the clinical trial 502.516	ongoing

A Risk Minimisation Plan for telmisartan/ HCTZ based on the presented and discussed data is considered not necessary. However, the company will monitor the drug in question and in case any new safety risk is identified will re-evaluate the necessity of a Risk Minimisation Plan.

6 Overall conclusions, risk/benefit assessment and recommendation

Quality

Telmisartan/hydrochlorothiazide (80/25 mg) has been developed based on the already authorised 80/12.5 mg and 40/12.5 mg strengths. The composition of the new strength is similar to the 80/12.5 mg strength. There are only minor differences between the compositions of the hydrochlorothiazide layers.

The results of tests carried out indicate satisfactory consistency and uniformity of product quality characteristics, as already demonstrated for the approved strengths, and these in turn lead to the conclusion that the new strength should have a satisfactory and uniform performance in the clinic.

Non-clinical pharmacology and toxicology

The pivotal clinical trials (non-responder study 502.480 and 6 month follow up study 502.491) for this line extension project were conducted with the production scale commercial products, therefore there was no need to add new biopharmaceutical data for this submission. In particular no pivotal BE studies were required.

Efficacy

For the establishment of the clinical efficacy and safety of the fixed dose combination (FDC) T80/H25, data of 12 clinical trials performed in patients with mild to moderate hypertension were used. The pivotal clinical trials for this extension application were study 502.480 and 6 month follow up study 502.491
Overall, the results for the primary endpoints showed clear clinical benefits for a T80/H25-based treatment compared with T80/H12.5, V160/H25, and placebo or demonstrated similar efficacy for a T/H-based treatment regimen (including T80/H25) and active comparator-based treatment regimens (ACE-inhibitors or beta-blockers).

Safety

No clinically meaningful differences in the adverse event profiles of T80/H25 and T80/H12.5 were detected. No specific increased incidence was identified for all adverse events. No additional specific safety issues have been identified.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Product Information

The conclusions drawn for the readability of PritorPlus 80mg/25mg tablets are considered applicable to the package leaflets of the other strengths. Also the QRD comments provided during the procedure were taken into account for the other approved strengths.

- User consultation

A report on the outcome of the consultation with users to review the readability of the package leaflet was submitted during this procedure.

Review of Protocol
The user testing of the English language package leaflet was performed in two waves of 10 interviews. In addition, a preliminary examination of the package leaflet was carried out in order to identify potential problematic sections of the package leaflet. Furthermore, 3 pilot interviews were concluded to ensure that the questions in the questionnaire were appropriate for their intended purpose.

A maximum of 45 minutes was planned for each interview, normally lasting between 20 and 30 minutes. The participants had 7 to 10 minute to familiarise themselves and read the PL before the actual review. The interviewer asked to find each item of information and to explain it in the participant's own word

20 adult participants were recruited in two rounds: the mean age was 55 years with a range of 33-80 ($6 < 45$ years, $14 \geq 45$ years). The target patient group consisted of persons suffering from hypertension but not taking the active substance. Focus was laid on elderly persons with lower educations, thus reflecting well the patient target group. Gender distribution was well balanced. None of the participants had experience with telmisartan or hydrochlorothiazide.

Questionnaire
21 questions were asked. The first two questions served as an introduction to the interview and were not included in the evaluation. The following 14 questions which were evaluated addressed the relevant issues of the package leaflet. The last 5 questions asked the respondents on their overall impression of the leaflet, i.e. the design and layout.

Evaluation of the results
More than 99% of the information of the PIL was found and 100% of the information was understood by all participants, from which 96.8% was understood in detail or good. At least 18 out of 20 participants found and comprehended the information necessary to answer each individual question.
The final result of the readability testing is well over the demanded value of 81% requested by the EC guideline.

The CHMP considered that the user testing provided was adherent to the EC Guideline and the results reported met the readability success criteria.

Risk-benefit assessment

The applicant has submitted an extension application to the marketing authorisation for a new strength (80mg telmisartan/25mg hydrochlorothiazide) of PritorPlus for the treatment of essential hypertension indicated in patients whose blood pressure is not adequately controlled on PritorPlus 80mg/12.5mg or patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

Based on the provided data on quality, non-clinical and clinical aspects, the benefit risk assessment is considered favourable. The overall Benefit/Risk ratio of the new strength of the fixed dose combination is positive provided that the commitments with regard to the qulity aspects will be performed accordingly.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product. A Risk Minimisation Plan for telmisartan/ hydrochlorothiazide based on the presented and discussed data is considered not necessary. However, the applicant will monitor the drug in question and in case any new safety risk would be identified will re-evaluate the necessity of a Risk Minimisation Plan.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of the new strength (80mg telmisartan/25mg hydrochlorothiazide) of the PritorPlus fixed dose combination in the treatment of essential hypertension indicated in patients whose blood pressure is not adequately controlled on PritorPlus 80mg/12.5mg or patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately was favourable and therefore recommended the granting of an extension to the marketing authorisation of PritorPlus.