

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Tarka 240 mg/2 mg modified release tablets
Tarka 240 mg/4 mg modified release tablets
Abbott B.V., the Netherlands

trandolapril/verapamil hydrochloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/107/05-06/MR
Registration number in the Netherlands: RVG 29700, 31430

20 May 2010

Pharmacotherapeutic group:	Phenylalkylamine derivatives, Verapamil, combinations
ATC code:	C08DA51
Route of administration:	oral
Therapeutic indication:	240 mg/2 mg: treatment of essential hypertension in patients whose blood pressure is not controlled on verapamil SR 240 mg alone, or in patients whose blood pressure has been normalised on the individual components in the same proportion of doses. 240 mg/4 mg: essential hypertension in patients whose blood pressure has been normalised on the individual components in the same proportion of doses.
Prescription status:	prescription only
Date of first authorisation in NL:	22 September 2005
Concerned Member States:	Mutual recognition procedure with DE, DK and IT
Application type/legal basis:	Directive 2001/83/EC, Article 10.1 (b) (iii)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Tarka 240 mg/2 mg and 240 mg/4 mg modified-release tablets, from Abbott B.V. The date of authorisation was on 22 September 2005 in the Netherlands. The products have the following indications:

Tarka 240 mg/2 mg: treatment of essential hypertension in patients whose blood pressure is not controlled on verapamil SR 240 mg alone, or in patients whose blood pressure has been normalised on the individual components in the same proportion of doses.

Tarka 240 mg/4 mg: treatment of essential hypertension in patients whose blood pressure has been normalised on the individual components in the same proportion of doses.

A comprehensive description of the indications and posology is given in the SPC.

The mutual recognition procedure for Tarka 240 mg/2 mg tablet and Tarka 240 mg/4 mg tablet concern line extensions of Tarka 180 mg/2 mg tablet, for which in the Netherlands a marketing authorization was granted on 20 April 1999 (NL/H/107/04, NL licence RVG 22638).

Pharmacodynamic properties

Tarka is a fixed combination of the phenylalkylamine calcium antagonist verapamil and the ACE inhibitor trandolapril.

Verapamil

The pharmacologic action of verapamil is due to inhibition of the influx of calcium ions through the slow channels of the cell membrane of vascular smooth muscle cells and of the conductile and contractile cells in the heart. Verapamil does not interfere with sympathetic regulation of the heart because it does not block the beta-adrenergic receptors. The mechanism of action of verapamil results in arterial vasodilation and reduction of myocardial contractility.

Trandolapril

Trandolapril suppresses the plasma renin-angiotensin-aldosterone system (RAS). Renin is an endogenous enzyme synthesized by the kidneys and released into the circulation where it converts angiotensinogen to angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme, a peptidyl dipeptidase, to angiotensin II. Angiotensin II is a potent vasoconstrictor responsible for arterial vasoconstriction and increased blood pressure, as well as for stimulation of the adrenal gland to secrete aldosterone. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to reduced aldosterone secretion. Although the latter decrease is small, small increase in serum potassium concentrations may occur, along with sodium and fluid loss. The cessation of the negative feedback of angiotensin II on the renin secretion results in an increase of the plasma renin activity.

Another function of the converting enzyme is to degrade the potent vasodilating kinin peptide bradykinin to inactive metabolites. Therefore inhibition of ACE results in an increased activity of circulating and local kallikrein-kinin system which contributes to peripheral vasodilation by activating the prostaglandin system. It is possible that this mechanism is involved in the hypotensive effects of ACE inhibitors and is responsible for certain adverse reactions. In patients with hypertension administration of ACE inhibitors results in a reduction of supine and standing blood pressure to about the same extent with no compensatory increase of the heart rate. Peripheral arterial resistance is reduced with either no change or an increase in cardiac output.

Tarka

Neither animal studies nor healthy volunteer studies could demonstrate pharmacokinetic or RAS interactions between verapamil and trandolapril. The observed synergistic activity of these two active substances must therefore be due to their complementary pharmacodynamic actions. In clinical trials Tarka was more effective in reducing high blood pressure than either active substance alone.

Regulatory history of Tarka

In 1995, the capsule formulation of Tarka 180 mg/2 mg was registered in the Netherlands for the therapeutic indication *'essential hypertension inadequately controlled by either of the two component drugs.'* This procedure was followed by a request for registration in other EU countries using the MRP procedure (NL/H/107/03). During the first round of the MRP objections were raised by CMS, noting that a specific study for demonstrating an add-on effect of the individual components had not been performed for this dosage, precluding registration in the EU member states under the aforementioned therapeutic indication. Eventually, the therapeutic indication was changed in *'essential hypertension, in patients whose blood pressure has been normalised with the individual components in the same proportion of doses'*, hence a substitution indication.

The procedure ended on 27 June 1996. The concerned member states who recognized the Dutch marketing authorization were: AT, BE, DE, DK, EL, ES, FI, IE, IT, LU, PT and UK. The marketing authorizations for capsules in AT, BE, DE, FI, IE, and LU were withdrawn post tablet launch due to marketing/commercial reasons.

The second renewal for Tarka 180 mg/2 mg capsule ended on 11 August 2006.

On 20 April 1999 Tarka 180 mg/2 mg tablet obtained a marketing authorisation in The Netherlands. This was a line-extension of Tarka 180/2 capsules. The indication was the same as for the capsules.

The MRP for Tarka 180 mg/2 mg tablets ended on 28 July 2004 (NL/H/107/04). The concerned member states who recognized the Dutch marketing authorization were: AT, BE, DE, DK, FI, IE, IT, LU. On 30 December 2005 the marketing authorisation has been withdrawn in AT and on 25 October 2005 in BE and FI. The first renewal for Tarka 180 mg/2 mg tablet ended on 14 July 2005.

At the end of 2003, the MAH submitted a dossier for the registration of Tarka 240 mg/4 mg only, for the treatment of patients with essential hypertension whose blood pressure cannot be adequately controlled with verapamil alone. A marketing authorisation was not granted at that time, since major objections were identified. The principal clinical issue was that the trandolapril dose of the fixed combination tablet (4 mg) was considered too high, in view of a usual trandolapril maintenance dose of 2 mg and a maximal recommended dosage of 4 mg. The MAH subsequently submitted a dossier for the registration of both Tarka 240 mg/4 mg and Tarka 240 mg/2 mg, to allow for a more gradual dose titration. According to the MAH, these Tarka dose combinations serve a clear unmet medical need as current guidelines define stricter (ie., lower) blood pressure goals for special populations of patients with essential hypertension, such as patients with diabetes and renal disease. There is much experience with both Tarka 240 mg/2 mg and 240 mg/4 mg, which have been on the market since 1997 in the United States of America, with Tarka 240 mg/4 mg as the most commonly used fixed combination dose level.

The marketing authorisation was granted based on article 10.1 (b) (iii) of Directive 2001/83/EC.

No paediatric development programme was submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The product contains two active substances: verapamil hydrochloride and trandolapril. Verapamil is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Trandolapril is also an active substance described in the Ph.Eur. Full documentation on the active substance has been included in the dossier. Trandolapril is levorotary with 5 chiral centres, and is utilized as the 2S, 3aR, 7aS, S, S isomer. Two crystalline forms were mentioned by the registration holder.

The CEP procedure is used for the active substance verapamil. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture

The manufacturing process of verapamil hydrochloride is covered by the CEP.

Trandolapril is manufactured in three steps. All starting materials are defined sufficiently. For all other materials used in synthesis, acceptable quality requirements have been laid down as well. Full details of the manufacturing process are included in the dossier.

Quality control of drug substance

The specification for verapamil is in line with the Ph.Eur. monograph, with additional tests for particle size. The specification for trandolapril is in line with the Ph.Eur., with additional requirements for residual solvents, specific surface area and particle size. The specifications are acceptable in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches from both substances.

Stability

The active substance verapamil hydrochloride is stable for three years when adequately stored. Assessment thereof was part of granting the CEP and has been granted by the EDQM. Stability data for verapamil hydrochloride were updated ('stable for years when adequately stored') by a post-approval variation (NL/H/0107/005-006/IA/028), according to the current CEP for verapamil.

Stability data on trandolapril have been provided to substantiate a retest period of 5 years, stored below 30°C. This claim is in line with the approved retest period for trandolapril substance for Tarka 180/2 of which this product is a line extension.

* Ph.Eur., is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition

The products concerned are bilayer film-coated tablets and they consist of an immediate release trandolapril outerlayer (2 mg/ 4 mg) and a prolonged-release verapamil hydrochloride innerlayer (240 mg). The following excipients are used: maize starch, lactose, povidone, hypromellose, sodium stearyl fumarate, water, microcrystalline cellulose, sodium alginate, magnesium stearate and film coating ingredients including hypromellose, hydroxypropylcellulose, macrogol, talc, colloidal silica, docusate sodium, titanium dioxide and ferric oxides.

The tablets are packed in colourless, transparent PVC/PVDC-aluminium blisters. The excipients and packaging are usual for this type of dosage form.

For the verapamil part the tablet is dose proportional to the 180mg/2mg formulation. The qualitative composition is the same for the trandolapril part but there are minor changes in excipients compensating the different amount of active substance. The weight of the trandolapril layer of the tablet formulation is the same.

Pharmaceutical development

The products are line-extensions, addition of new strengths, of Tarka 180/2 mg capsules and the bilayer tablets Tarka 180/2 mg, registered by MRP's already, with NL as RMS (NL/H/107/003 and NL/H/107/004 respectively). The development of the products has been described, the choice of excipients is justified and their functions explained in relation to the line extension. Sufficient information has been provided. The pharmaceutical development of the products has been adequately performed.

Excipients

The excipients comply with Ph.Eur. requirements where applicable. Titanium dioxide E171, as well as, the ferric oxides and hydroxides E172 comply with EC Directives 78/25/EEC and 95/45/EC. These specifications are acceptable.

Manufacturing process

Trandolapril granules and verapamil granules are manufactured separately, tableting is performed using a tablet press, and finally, the tablets are film-coated. The manufacturing process has been adequately validated according to relevant European guidelines. Data on twelve recent commercial batches were presented to confirm suitability and consistency of the manufacturing process. These data comprised results of in-process controls and release tests. The mixing process has been validated with regard to the homogeneous distribution of trandolapril over the whole batch.

Quality control of drug product

The product specification includes tests for appearance, identity, assay, degradation, dissolution (both substances), hardness, uniformity of mass and uniformity of content and microbiological purity. Separate shelf-life specifications have been set for assay trandolapril and related substances derived from trandolapril. Related substances derived from verapamil are also limited wider at the end of the shelf-life than at release. The acceptance criteria for verapamil drug release are also slightly widened for shelf-life testing. The proposed test parameters and limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on at least three full-scaled batches, demonstrating compliance with the release specification.

Stability tests on the finished product

Stability data on the product has been provided on

- Three batches of 240 mg/4 mg tablets were stored in the approved packaging (36 months at 25°C/60% RH; 24 months at 30°C/70% RH; 6 months at 40°C/75% RH)
- Three batches of 240 mg/2 mg tablets were stored in the approved packaging (3 months at 25°C/60% RH; 3 months at 30°C/70% RH; 3 months at 40°C/75% RH).

- Three batches of 180/2 mg tablets were stored in the approved packaging (36 months at 25°C/60% RH; 36 months at 30°C/70% RH; 6 months at 40°C/75% RH). These data were considered as supportive.

The conditions used in the stability studies are according to the ICH stability guideline. An increase is seen in the levels of individual impurities, which is more pronounced at 30°C/70% RH and 40°C/75% RH. However, all results remain within the shelf-life specification. The results support the claimed shelf-life of 3 years, with additional storage condition 'Do not store above 25°C'.

The MAH committed to review the shelf-life specification for the related substances of trandolapril when additional stability results become available in PVC/PVDC. The MAH also agreed to tighten the trandolapril assay shelf-life limit to 90-105%.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate and sodium stearyl fumarate used are of vegetable origin. Lactose is made from milk retrieved from healthy animals under the same conditions as milk for human consumption. Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

No new preclinical data have been submitted as these are the same as in the dossier of the lower tablet strength and capsules (procedure NL/H/107/04, NL licence RVG 22638). This is considered acceptable.

Environmental risk assessment

The active ingredients have been on the market since 1960 (verapamil) and 1992 (trandolapril). From the experience in the past the MAH justifies that these products do not contribute to an increase in the exposure of the active drug substances. Therefore an Environmental Risk Assessment is not deemed necessary.

II.3 Clinical aspects

GCP aspects

The MAH states that there were no unusual aspects of the research approaches used in the clinical development program and that all studies were conducted in accordance with Good Clinical Practice guidelines.

Pharmacokinetics

A bioequivalence study (TV-4-CP) was submitted to demonstrate bioequivalence under fasting conditions after multiple-dosing with the individual components, verapamil and trandolapril, for both fixed-dose combinations (FDC). The Tarka® FDC tablets contain a slow-release formulation of the verapamil component. Two fixed dose combinations at both ends of the dosing spectrum (240/4 mg and 120/0.5 mg verapamil/trandolapril) were tested in this cross over design study.

The dissolution-profiles of the 240 mg/2 mg FDC formulation compared to the 240/4 formulations are considered similar. Thus, study TV-4-CP bridges over the 240 mg/2 mg strength, as it also included the assessment of the lowest dose level of verapamil 120 mg and trandolapril 0.5 mg. Two CHMP Notes for Guidance apply: Note for guidance on the investigation on bioavailability and bioequivalence (CHMP/EWP/QWP/1401/98) and Note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation) (CHMP/EWP/QWP/280/96). The AUC and C_{max} of trandolapril was about ten times increased after an 8 times increased dose and the AUC and C_{max} of trandolaprilat is only 2-4 times increased after an 8 times increased dose. This was recognised by the MAH as an indication for non-linearity.

Statistical analysis of the critical pharmacokinetic parameters for proving bioequivalence is shown for days 7 and 8 separately.

240/4 mg

Data for the inactive prodrug trandolapril on day 7 do not show bioequivalence, but bioequivalence for the active metabolite trandolaprilat is shown for both days. The critical component here is the active metabolite. Therefore the RMS concludes that bioequivalence is shown for the ACE-inhibitor component of the FDC which is consistent with the bioequivalence guidance (CPMP/EWP/QWP/1401/98). For verapamil, the second component of the FDC, $C_{\max}$ on day 7 barely falls outside the acceptance range with an upper limit of the confidence interval of 1.254. Bioequivalence is again shown on day 8, and for both days of the active norverapamil metabolite. Hence, no clinically significant implications are expected for the verapamil compound of the FDC.

Thus, both FDC dose-strengths, 240/4 and 240/2, can be considered bioequivalent to the individual components.

Both verapamil and norverapamil rate and extent of absorption were affected by food. The AUC of verapamil was decreased by 15 %, $C_{\max}$ by 42 % and $t_{\max}$ increased from 6 to 13 hours. Food did not affect the pharmacokinetics of trandoprilat.

Clinical efficacy

Five clinical studies have been submitted. An overview is presented in the table below:

Table 1. Overview of the five clinical studies.

Protocol	Countries	Study design Duration	Treatment regimen	Subject numbers
TV-50-HTN Double-blind, randomised, placebo-controlled, factorial study to evaluate the safety and efficacy of oral trandolapril in combination with verapamil (Isoptin® SR) in subjects with mild to moderate essential hypertension.	US (multicentre)	Double-blind, randomised, placebo-controlled, 4x4 factorial 6 weeks	Placebo T 0.5 mg QD T 2 mg QD T 8 mg QD V 120 mg QD V 180 mg QD V 240 mg QD V 120/T 0.5 mg QD V 120/T 2 mg QD V 120/T 8 mg QD V 180/ T 0.5 mg QD V 180/T 2 mg QD V 180/T 8 mg QD V 240/T 0.5 mg QD V 240/T 2 mg QD V 240/T 8 mg QD	53 41 67 43 35 57 48 45 38 37 37 66 38 35 43 40
TV-51-HTN Double-blind, randomised, placebo-controlled, study to evaluate the safety and efficacy of oral trandolapril in combination with verapamil (Isoptin® SR) in subjects with mild to moderate essential hypertension.	US (multicentre)	Double-blind, randomised, placebo-controlled, parallel group 2 x2 factorial 6 weeks	Placebo T 4 mg QD V 240 mg QD V 240 mg/T 4 mg QD	152 159 157 163
INVEST (INternational VErapamil SR/trandolapril Study) Randomised controlled clinical trial comparing a calcium antagonist treatment strategy (Isoptin® SR) with a non calcium antagonist treatment strategy for the control of hypertension in a primary care coronary artery disease patient population	US, Puerto Rico, Canada, Cuba, Mexico, Caribbean, Turkey, Hungary, Germany, Italy, Australia, and New Zealand (multicentre)	Open-label, randomised, prospective, blinded endpoint evaluation mean 2.7 years	Tarka® 180/2 mg QD ^a Tarka® 240/4 mg QD ^a V 240 mg QD followed by Tarka® 240/4 mg ^b V 240 mg QD followed by Tarka 240/2 mg ^c V240/T2 mg QD followed by Tarka 240/4 mg ^d .	2686 1498 734 1848 433
VT020 Antihypertensive efficacy and safety of verapamil SR 240 mg/trandolapril 2 mg in patients insufficiently pretreated with single-blind verapamil SR 240 mg monotherapy. A double-blind randomised parallel-group comparison to verapamil SR 240 mg	Czech Republic, United Kingdom, Hungary, the Netherlands, and Poland (multicentre)	Double-blind, randomised, active-controlled, add-on. 20 weeks (8 single-blind, 12 double-blind)	V 240 mg QD V 240/T 2 mg QD	282 291
VT082 Verapamil SR 240 mg, trandolapril 2 mg and the fixed combination of both drugs for treatment of essential hypertension	Israel (multicentre)	Double-blind, randomised, placebo-controlled, parallel group, 2x2 factorial, 12 weeks	Placebo T 2 mg QD V 240 mg QD V 240 mg/T 2 mg QD	91 92 90 184

a. All subjects who received at least one prescription for Tarka® 180/2 mg QD and/or Tarka® 240/4 mg QD, or the exact subcomponents of either fixed dose combination as separate prescriptions of verapamil SR and trandolapril, were included in the safety analyses.

b. All subjects who received at least one prescription for verapamil 240 mg QD with no trandolapril, followed at some later date by Tarka® 240/4 mg QD or its exact subcomponents, were included in the efficacy analysis.

c. All subjects who received at least one prescription for verapamil 240 mg QD with no trandolapril, followed at some later date by Tarka® 240/2 mg QD or its exact subcomponents, were included in the efficacy analysis.

d. All subjects who received at least one prescription for Tarka 240/2 mg, followed at some later date by Tarka® 240/4 mg QD or its exact subcomponents, were included in the efficacy analysis.

V: verapamil; T: trandolapril

Three factorial design studies were conducted to investigate blood pressure (BP) lowering responses with verapamil/ trandolapril combination therapies relative to component monotherapies. In the first factorial design study (TV-50), a statistically significantly larger sitting DBP reduction of 3 mmHg with verapamil/ trandolapril 240 mg/2 mg compared to verapamil SR 240 mg monotherapy was observed. A larger BP reduction with verapamil/trandolapril 240 mg/2 mg compared to verapamil SR 240 mg monotherapy was also observed in the second factorial design study (VT-082), but this did not reach statistical significance presumably due to a relatively large BP lowering effect in the verapamil SR 240 mg monotherapy group. The third factorial design study (TV-51), demonstrated a statistically significant larger reduction in trough sitting DBP of 4 mmHg with verapamil/trandolapril 240 mg/4 mg compared to verapamil SR 240 mg alone. Overall, these three factorial design studies showed that a larger BP reduction can be achieved with verapamil/trandolapril 240 mg/2 mg or 240 mg/4 mg relative to verapamil SR 240 mg monotherapy, as a consequence of additive BP lowering effects.

Importantly, clinical evidence for an additive effect also in patients with an insufficient treatment response to verapamil alone was obtained in study VT-020. This large add-on study showed a statistically significant further reduction in both sitting SBP/DBP of 4/2 mmHg with verapamil/ trandolapril 240 mg/2 mg in patients insufficiently treated with verapamil SR 240 mg monotherapy, in accordance with requirements in the regulatory guideline on fixed combination drugs. Further confirmative evidence for the efficacy of verapamil/trandolapril 240 mg/2 mg relative to verapamil SR 240 mg in patients with an insufficient treatment response to monotherapy was obtained in post-hoc analysis B on data from the large outcome INVEST study in which patients were uptitrated according to BP lowering response. In INVEST a differential BP lowering strategy was chosen for various racial groups that are common in the US society. Specifically African Americans are known to respond poorer to ACE inhibition and these were therefore immediately uptitrated to a 240/4 mg dose level. Ultimately, compared to a EU population a much larger representation of African Americans with a different dosing regimen was thus included in the trial population. Subgroup analyses of the benefit/risk in a more representative EU population were therefore performed. Furthermore, in INVEST also sizeable populations had been gradually uptitrated from 240 mg verapamil to 240mg/2 mg V/trandolapril and ultimately 240/4mg. Post hoc analyses of the additional BP lowering efficacy between these dosing steps were considered vary valuable in support of a clear dosing recommendation in the SPC. The following post hoc analyses (including the above mentioned post hoc analysis B) were therefore performed on request of the MEB:

- A. Repeat analysis of the original INVEST subanalysis in group 1 for Caucasians only.
- B. Analysis of BP response in subjects treated with verapamil SR 240 mg followed by Tarka 240/2 mg at some later date.
- C. Analysis of BP response in subjects treated with Tarka 240/2 mg followed by Tarka 240/4 mg at some later date.
- D. Analysis of BP response in Caucasian subjects who received Tarka 240/4 mg once daily (or its exact subcomponents) as their first prescription of trandolapril after Tarka 240/2 mg once daily.
- E. Analysis of BP response in Caucasian subjects who received Tarka 240/4 mg once daily (or its exact subcomponents) as their first prescription of trandolapril after Tarka 240/2 mg once daily without concomitant HCTZ.

Regarding the higher fixed dose combination (240 mg/4 mg), the initial INVEST post-hoc analysis showed that the addition of trandolapril 4 mg after inadequate response to verapamil SR 240 mg monotherapy resulted in a further reduction in SBP/DBP of approximately 9/4 mmHg across the three analysis groups, and thereby provided confirmation for the additive effects observed in factorial design study TV-51. Analysis C showed a clinically relevant further SBP/DBP reduction of approximately 8/4 mmHg in both the overall population as well as Caucasians that were titrated from Tarka 240 mg/2 mg to Tarka 240 mg/4 mg at some later date. For both the overall population and the Caucasian subset who received Tarka 240 mg/2 mg followed by Tarka 240 mg/4 mg, the proportion of patients with BP control improved from 10% to approximately 35~%. Results on Caucasian subjects that received Tarka 240 mg/4 mg as their first prescription after Tarka 240 mg/2 mg confirmed these findings, showing a further SBP/DBP reduction of 7/4 mmHg (analysis D).

Overall, these additional post-hoc INVEST analyses indicate that a further BP reduction can be obtained with Tarka 240 mg/2 mg as compared to verapamil SR 240 mg, thereby being consistent with the results obtained in the pivotal add-on study TV-020 and factorial design study TV-50. The INVEST study results also indicate that titration from Tarka 240 mg/2 mg to Tarka 240/4 mg results in a clinically relevant further BP reduction in Caucasian patients with an insufficient response to Tarka 240 mg/2 mg.

Clinical safety

With respect to safety, results on studies TV-50, TV-51, VT-082 and VT-020 on the combination of verapamil 240 mg and trandolapril 2 or 4 mg did not suggest a significant additional safety risk compared to its already registered individual drug components. The most frequently observed adverse events were the well known AE headache and cough of the individual components. Within the limitations posed by the difference in cardiovascular risk profile between the two treatment groups, the INVEST study post-hoc analysis comprising a large number of patients with coronary artery disease and hypertension showed a safety profile of Tarka 240 mg/4 mg that appeared to be comparable to the already registered Tarka 180 mg/2 mg.

Overall conclusion on clinical aspects

In view of these clinical efficacy and safety findings, the line-extension with Tarka 240 mg/2 and 240 mg/4 mg is considered approvable by the MEB.

CMD(h)-referral

During the procedure, one of the member states was of the opinion that the clinical program submitted could not support the following indications which were claimed at the start of the procedure,

240 mg/2 mg: Treatment of essential hypertension; Tarka 240 mg/2 mg is indicated in patients whose blood pressure is not adequately controlled on verapamil alone.

240 mg/4 mg: Treatment of essential hypertension; Tarka 240 mg/4 mg is indicated in patients whose blood pressure is not adequately controlled on Tarka 240 mg/2 mg alone.

Because demonstration of a superior blood pressure lowering of the 240 mg/2 mg and 240 mg/4 mg dose strengths compared to the approved 180 mg/2 mg dose strength had not been demonstrated. Therefore, a referral to the CMD(h) was started.

In the CMD(h) meeting of 16-18 October 2006 the following was discussed:

It was noted that the NfG on clinical investigation of medicinal products in the treatment of hypertension – Fixed combinations, does not address line extensions of fixed-combinations and does not require demonstration of a superior blood lowering pressure effect to the approved fixed combination. The clinical studies performed demonstrated superiority of the fixed combination over placebo and the individual compounds. This is reflected in a new wording of the indication for both strengths, as shown in the introduction of this PAR (see also Page 2), by which agreement was reached.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Tarka 240 mg/2 mg and 240 mg/4 mg modified-release tablets have a proven chemical-pharmaceutical quality. Two points remain that can be solved post-approval.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

No new preclinical data have been submitted as these are the same as in the dossier of the lower tablet strength and capsules (procedure NL/H/107/04, NL licence RVG 22638). This is considered acceptable.

During the procedure, one of the member states was of the opinion that the clinical program submitted could not support the indications which were claimed at the start of the procedure, because demonstration of a superior blood pressure lowering of the 240 mg/2 and 240 mg/4 mg dose strengths compared to the approved 180/ 2 mg dose strength was not demonstrated. Therefore, a referral to the CMD(h) was started.

Following the discussion held in the CMD(h) meeting of 16-18 October 2006, agreement was reached by means of a new wording of the indication for both the 240 mg/2 mg and the 240 mg/4 mg strength. It was noted that the NfG on clinical investigation of medicinal products in the treatment of hypertension – Fixed combinations, does not address line extensions of fixed-combinations and does not require demonstration of a superior blood lowering pressure effect to the approved fixed combination. The clinical studies performed demonstrated superiority of the fixed combination over placebo and the individual compounds.

Tarka was discussed during the board meeting of 27 November 2003.

The MEB, on the basis of the data submitted, considered that Tarka 240 mg/2 mg and 240 mg/4 mg modified release tablets demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation on 22 September 2005. The other member states mutually recognised the Dutch evaluation for the marketing authorisation. The CMD(h) referral procedure was finished on 25 September 2006.

The SPC, package leaflet and labelling are in the agreed templates.

The following PSUR-cycle has been agreed:

First	6-month PSUR (following launch – 15 March 2007)
2nd	6-month PSUR (16 March 2007 – 15 September 2007)
3rd	6-month PSUR (16 September 2007 – 15 March 2008)
4th	6-month PSUR (16 March 2008 – 15 September 2008)
First annual PSUR [actually 10-months of data] (16 September 2008 – 18 July 2009) to support the renewal.	
Second Annual PSUR (19 July 2009 – 15 March 2010)	
Subsequent 3-year intervals to follow.	

The date for the first renewal will be 16 March 2010.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to review the shelf-life specification for the related substances of Trandolapril when additional stability results become available in PVC/PVDC.
- The MAH agreed to tighten the trandolapril assay shelf-life limit to 90-105%.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	Blood Pressure (DBP = diastolic BP, SBP = systolic BP)
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FDC	Fixed Dose Combinations
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in module 1, 2 and 3.	NL/H/0107/005-006/II/012	II	29-1-2007	30-3-2007	Approval	N
Change in the immediate packaging blister material	NL/H/0107/005-006/IB/025	IB	22-2-2007	26-3-2007	Approval	N
Addition of a new manufacturing site for drug substance trandolapril.	NL/H/0107/005-006/II/026	II	30-5-2007	29-7-2007	Approval	N
Change of specification(s) of a former non-European pharmacopoeial substance to comply with Ph. Eur. Or with the national pharmacopoeia of a member state. Active substance.	NL/H/0107/005-006/IB/027	IB	12-4-2007	12-5-2007	Approval	N
Submission of a new or updated PH. Eur Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved.	NL/H/0107/005-006/IA/028	IA	15-1-2008	29-1-2008	Approval	N
Change in the name and/or address of the marketing authorization holder.	NL/H/0107/005-006/IA/029	IA	16-1-2008	30-1-2008	Approval	N
Change in the name and/or address of the marketing authorization holder.	NL/H/0107/005-006/IA/030	IA	11-2-2008	25-2-2008	Approval	N