

## PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Perindopril tert-butylamine 2 mg Ranbaxy, tablets  
Perindopril tert-butylamine 4 mg Ranbaxy, tablets  
Perindopril tert-butylamine 8 mg Ranbaxy, tablets  
Ranbaxy UK Ltd., United Kingdom

### perindopril tert-butylamine

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/0977/001-003/DC**  
**Registration number in the Netherlands: RVG 35208-35210**

**11 January 2010**

Pharmacotherapeutic group:	ACE inhibitors, plain
ATC code:	C09AA04
Route of administration:	oral
Therapeutic indication:	hypertension; symptomatic heart failure; stable coronary artery disease
Prescription status:	prescription only
Date of authorisation in NL:	12 September 2008
Concerned Member States:	Decentralised procedure with CZ, FI, HU, SK, UK, Only 4 and 8 mg: BE, EE, LT, LV, PL, Only 4 mg: ES, IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) and 10(3)

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 Perindopril tert-butylamine 2 mg, 4 mg and 8 mg Ranbaxy, tablets from Ranbaxy UK Ltd. The date of authorisation was on 12 September 2008 in the Netherlands.

The product is indicated for:

- treatment of hypertension
- treatment of symptomatic heart failure
- treatment of stable coronary artery disease; reduction of the risk of cardiac events in patients who have a history of myocardial infarction and/or revascularisation.

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

Perindopril inhibits the enzyme which converts angiotensin I into angiotensin II (angiotensin-converting enzyme (ACE)). The converting enzyme or kinase is an exopeptidase which converts angiotensin I into the vasoconstrictor angiotensin II and degrades the vasodilator bradykinin in to an inactive heptapeptide. Inhibition of the ACE results in a reduction in the plasma levels of angiotensin II, which leads to an increase in renin activity in the plasma (as a result of the inhibition of the negative feedback from the renin release) and a reduction in the secretion of aldosterone. As ACE inactivates bradykinin, the inhibition of ACE also results in the increased activity of the circulating and local kallikrein-kinin systems (and consequently also the activation of the prostaglandin system). It is possible that this mechanism contributes to the antihypertensive activity of the ACE inhibitors and is partly responsible for some of their side effects (e.g. cough).

Perindopril acts via its active metabolite, perindoprilate. The other metabolites do not show any inhibition of ACE activity *in vitro*.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Coversyl 2 mg, 4 mg and 8 mg tablets which have been registered in France by Les Laboratoires Servier since 22 June 1988. In the Netherlands, Coversyl 2 mg and 4 mg tablets have been registered since 17 July 1989, and Coversyl 8 mg tablets since 14 April 2003 (NL RVG 13635, 13636 and 27786 respectively). In addition, reference is made to Coversyl authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. In Hungary and Finland the marketing authorisation for the 2 mg tablet is granted according to Article 10(3) of Directive 2001/83/EC, hybrid application, as the 2 mg product is not authorised in these member states. The reference product is the 4 mg strength.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product. For one study the reference product was Coversyl 4 mg tablets, and for the other study Coversyl 8 mg tablets. Both reference products were registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a generic application.

## 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 active substance is perindopril tert-butylamine, an established active substance described in the European Pharmacopoeia (Ph.Eur.\*). The active substance is freely soluble in water.

The CEP procedure is used for the active substance. 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.

#### Quality control of drug substance

The chemical-pharmaceutical documentation on the active substance is of sufficient quality in view of the present European regulatory requirements. The MAH has submitted a copy of a valid CEP for the active substance perindopril tert-butylamine. The control tests and specifications for the drug substance are adequately drawn up. Batch analytical data demonstrating compliance with the drug substance specification have been provided.

#### Stability

The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

*\* 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

Perindopril tert-butylamine 2 mg Ranbaxy contains as active substance 2 mg of perindopril tert-butylamine, corresponding to 1.669 mg perindopril, and is a light pink to pink coloured capsule shaped tablet debossed with 'P9' on one side and a deep breakline on the other side.

Perindopril tert-butylamine 4 mg Ranbaxy contains as active substance 4 mg of perindopril tert-butylamine, corresponding to 3.338 mg perindopril, and is a white to off-white capsule shaped tablet debossed with 'P5' on one side and a deep breakline on other side.

Perindopril tert-butylamine 8 mg Ranbaxy contains as active substance 8 mg of perindopril tert-butylamine, corresponding to 6.676 mg perindopril, and is a white to off white coloured capsule shaped tablet debossed with 'P' and '6' on either side of the breakline on one side and a breakline on the other side.

The tablets are packed in a transparent PVC/Aluminium foil blister or in an opaque cold form/Aluminium foil blister.

The excipients are: lactose monohydrate, microcrystalline cellulose (E460), magnesium stearate (E470b), colloidal anhydrous silica (E551); *2 mg only*: red ferric oxide (E172).

The 4 mg and the 8 mg formulation are fully dose proportional; the 2 mg tablet contains the same amount of excipients as the 4 mg formulation with a minor difference in lactose to compensate for the difference in the content of the active substance.

#### Pharmaceutical development

The development of the product has been described, the choice of excipients is adequately justified and their functions explained. The excipients and packaging are usual for this type of dosage form. The dissolution profiles show that the test products and the reference products dissolve fast at three different pH conditions. The profiles are similar for all tablets strengths and are equivalent to the reference product. The pharmaceutical development of the product has been adequately performed.

#### Manufacturing process

The manufacturing process consists of blending the ingredients of the tablet core and granulating by compaction. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for 2 pilot scaled batches of 2 mg tablets and 2 batches of a common blend for 4 or 8 mg tablets. The tableting process is comparable for all strengths. The provided data are therefore deemed sufficient. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

#### Excipients

The excipients comply with Ph.Eur. These specifications are acceptable.

#### Quality control of drug product

The product specification includes tests for appearance, identity, assay, degradation, dissolution, disintegration, microbial limits, water, and uniformity of dosage units. For water content, related substances and assay separate shelf-life requirements have been set. The proposed limits are acceptable.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 2 pilot scaled batches of each strength, demonstrating compliance with the release specification.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis have been performed on 2 batches of each tablet strength. The available batch analysis results show that the tablets meet the proposed specifications.

#### Stability tests on the finished product

Stability data on the product have been provided on 2 pilot scaled batches of each strength stored at 25°C/60% RH (18 months) and 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/Al blisters and in OPA-Al-PVC/ Al blisters as proposed for marketing.

The available results are sufficient to grant the claimed shelf-life of 18 months, stored below 25°C, for the tablets packaged in PVC/Al blisters and in OPA-Al-PVC/ Al blisters.

Photostability studies show that the product is not sensitive to light. The substance and the product are however sensitive to moisture. The proposed storage conditions 'Store in the original packaging for protection against moisture' are therefore acceptable.

#### Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For lactose and magnesium stearate, scientific data and/or Certificates of suitability issued by the EDQM have been provided and 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

This products are generic formulations of Coversyl 2 mg, 4 mg and 8 mg tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

### Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of perindopril tert-butylamine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## II.3 Clinical aspects

Perindopril tert-butylamine is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Perindopril tert-butylamine 4 mg Ranbaxy is compared with the pharmacokinetic profile of the reference product Coversyl 4 mg tablets.

### *The choice of the reference product*

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

### Bioequivalence study with 4 mg

#### *Design*

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male Asian subjects, aged 20-37 years. Each subject received a single dose (4 mg) of one of the 2 perindopril tert-butylamine formulations. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of at least 5 weeks.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.58, 0.67, 0.83, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 48, 72, 120, 168, 216, 264, 312 and 360 hours after administration of the products.

#### *Analytical/statistical methods*

A high performance liquid chromatography mass spectrometric method (LCMS/MS) for the simultaneous determination of parent perindopril and its active metabolite perindoprilat in human plasma was developed and validated using ramipril and ramiprilat as internal standards. The bioanalytical methods have been validated.

Analysis of variance (ANOVA) has been performed on pharmacokinetic parameters ( $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$  for log (natural)- transformed data using appropriate procedure of SAS system. The 90% confidence intervals for the ratios of  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$  have been calculated. The mixed effect ANOVA model included sequence, formulation (treatment) and period as fixed effects and subject nested within sequence as a random effect.

#### *Results*

Out of the 32 included subjects, 26 subjects completed both periods of the study. A total of 6 subjects were withdrawn from the study for the following reasons:

- One subject was withdrawn from the study in Period I due to an adverse event of acarodermatitis (infected scabies).
- One subject was withdrawn from the study in Period I due to an adverse event of pyrexia.
- One subject was withdrawn from the study in Period II due to inadequate cooperation.
- One subject was withdrawn from the study in Period II due to an adverse event of furuncle over left cheek.
- One subject was withdrawn from the study in Period II due to an adverse event of vomiting.
- One subject was withdrawn from the study prior to Period II due to an adverse event of skin injury, experienced during the washout of Period I.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of perindopril under fasted conditions.

Treatment N=26	AUC <sub>0-t</sub> µg.h/l	AUC <sub>0-∞</sub> µg.h/l	C <sub>max</sub> µg/l	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	61 ± 15	61 ± 15	59 ± 15	0.58 (0.33-1.33)	0.78 ± 0.13
<b>Reference</b>	58 ± 14	59 ± 14	56 ± 14	0.58 (0.50-1.33)	0.78 ± 0.14
<b>*Ratio (90% CI)</b>	1.05 (1.00-1.10)	1.05 (1.00-1.09)	1.05 (0.98-1.13)	-	-
<b>CV (%)</b>	9.9	9.7	14.3	-	-
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of perindoprilat under fasted conditions.

Treatment N=26	AUC <sub>0-t</sub> µg.h/l	AUC <sub>0-∞</sub> µg.h/l	C <sub>max</sub> µg/l	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	303 ± 104	445 ± 163	6.0 ± 2.7	6.5 (0.67-16.0)	175 ± 88
<b>Reference</b>	299 ± 112	450 ± 176	6.1 ± 3.2	7.0 (0.83-16.0)	186 ± 95
<b>*Ratio (90% CI)</b>	1.05 (0.97-1.15)	1.02 (0.94-1.11)	1.02 (0.91-1.14)	-	-
<b>CV (%)</b>	18.5	17.9	24.4	-	-
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

The 90% confidence intervals calculated for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. The



extrapolation of the AUC of perindoprilat was more than 20% caused by the long half-life of perindoprilat of approximately 180 hours, which is according to literature. However, as sampling for perindoprilat took place for 360 hours the truncated AUC is sufficient. Based on the pharmacokinetic parameters of perindopril supported by the data of perindoprilat under fasted conditions, it can be concluded that Perindopril tert-butylamine 4 mg Ranbaxy and Coversyl 4 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. It is advice also for the innovator that perindopril should be used before the meals. Therefore no food interaction study is necessary.

*Extrapolation to other strengths*

The Perindopril tert-butylamine tablets fulfil the conditions for waiver of bioequivalence studies with 2 mg and 8 mg strengths of the product:

- The qualitative composition of the different strengths is the same (except for 2 mg where ferric oxide (red) is used as colorant).
- The excipients included in the composition of the formulation are well established and no interaction with the pharmacokinetics of the active substance is expected.
- The 4 mg and 8 mg Perindopril tert-butylamine tablets are “scale up - scale down” of the same formulation (the ratio of active ingredient to excipients is the same in both strengths). The 2 mg and 4 mg strengths are ‘look alike’ formulations, i.e, the ratio between the amounts of excipients (except diluent and colourant) is similar for both the strengths (the amount active ingredient differs, compensated by the amount of lactose, for the rest all amounts of excipients are equal).
- The therapeutic doses of perindopril show a linear and dose-proportional kinetic behaviour following both single oral dosing and at steady state during a once a day multiple dosing regimen.
- The dissolution profiles are similar. The *in vitro* test of dissolution characteristics demonstrates that dissolution profiles of the MAH’s perindopril tert-butylamine tablets and those of the Innovator’s in different member states are very similar.
- The results of comparative *in vitro* dissolution studies exhibit that the rate and extent of % drug dissolved from the MAH’s and Innovator’s formulations are comparable.

However, the ratio between the amounts of active substance and excipients is not the same for the 2 mg and 4 mg tablets. Furthermore, in both tablets the concentration of the active substance is not less than 5%, which is a requirement for the “look alike” approach according to the CHMP NfG on Investigation of Bioavailability and Bioequivalence (2001). However, based on the good solubility properties of the perindopril tablets and that perindopril is well and quickly absorbed, it is expected that the deviation from the guideline has no influence on the bioavailability/bioequivalence of the various perindopril strengths presented in this application. The results of the bioequivalence study performed with the 4 mg strength therefore apply also to the 2 mg strength.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

*Discussion on bioequivalence*

One of the CMS’s could not agree with the extrapolation of the results from the bioequivalence study with the 4 mg strength in support of the application for the 8 mg strength. According to this member state, evidence of bioequivalence of the 8 mg product has not been provided and the safety/efficacy of the 8 mg product has not been demonstrated.

This issue could not be resolved during the initial procedure, and therefore a CMD(h) referral was started for the 8 mg strength. The rationale provided by the CMS for referral was as follows:

The linearity/non-linearity of perindopril is not straightforward and the free:bound fraction increases with increasing the dose. If there is bioinequivalence, it is more likely to be shown with the higher dose (8 mg versus 4 mg), where the sensitivity to detect a difference between formulations may be greater.

As regards CHMP Note for Guidance (NfG), the arguments related to safety, pharmacokinetic and analytical grounds need to be addressed to the particular dose chosen for the bioequivalence study and not in general. There are no apparent safety or analytical issues with perindopril 8 mg being used in

bioequivalence study. For reasons given above, 8 mg might be more likely to detect any difference between these formulations and should have been the dose selected for the study.

CMD(h) referral

During the CMD(h) referral procedure, the MAH submitted a protocol of a bioequivalence study with Perindopril tert-butylamine 8 mg Ranbaxy tablets. In addition, a renewed literature overview was given, demonstrating that although perindopril dose linearity is not straightforward, due to a saturable protein / ACE binding, this is not translated into an observed nonlinearity in a clinical study setting. Concentration dependent perindoprilat protein binding, mainly to ACE, is only about 20% estimated from the 8 mg dose, which explains why despite a theoretical ceiling in perindopril protein binding dose linear pharmacokinetics are observed in the clinical dose range. The choice of the 4 mg dose-strength for the bioequivalence study would then be justified on the CHMP NfG requirements, safety and analytical considerations.

Despite these justifications, consensus could not be reached on the main question whether the results from the bioequivalence study with the 4 mg strength could be extrapolated to the 8 mg in support of the application for the 8 mg strength. As the MAH had already started a bioequivalence study with the 8 mg strength, it was decided to await the results.

Bioequivalence study with 8 mg

*Design*

An open label, balanced, randomized, two treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male Asian subjects, aged 21-32 years. The study was carried out with Perindopril tert-butylamine 8 mg Ranbaxy tablets and the reference product Coversyl 8 mg tablets from the French market. The test product is identical to the product to be marketed. The generic product has the same qualitative composition as the originator product with regard to the active ingredient. Each subject received a single dose (8 mg) of one of the 2 perindopril tert-butylamine formulations. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of at least 35 days.

Blood samples were collected pre-dose and at 0.083, 0.167, 0.25, 0.333, 0.417, 0.5, 0.583, 0.667, 0.75, 0.833, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

*Analytical/statistical methods*

A high performance liquid chromatography mass spectrometric method (LCMS/MS) for the simultaneous determination of the parent perindopril and the active metabolite perindoprilat in human plasma was developed and validated using ramipril and ramiprilat as internal standards.

Analysis of variance (ANOVA) has been performed on pharmacokinetic parameters ( $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$  for log (natural)- transformed data using appropriate procedure of SAS system. The 90% confidence intervals for the ratios of  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$  have been calculated. The mixed effect ANOVA model included sequence, formulation (treatment) and period as fixed effects and subject nested within sequence as a random effect.

*Results*

All 26 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of perindopril under fasted conditions.

Treatment N=26	$AUC_{0-t}$ $\mu\text{g.h/l}$	$AUC_{0-\infty}$ $\mu\text{g.h/l}$	$C_{max}$ $\mu\text{g/l}$	$t_{max}$ h	$t_{1/2}$ h
<b>Test</b>	94 $\pm$ 21	95 $\pm$ 21	98 $\pm$ 32	0.58 (0.33-1.25)	0.78 $\pm$ 0.22
<b>Reference</b>	92 $\pm$ 26	92 $\pm$ 26	96 $\pm$ 26	0.58 (0.25-1.00)	0.78 $\pm$ 0.15



<b>*Ratio (90% CI)</b>	1.03 (0.96-1.11)	1.03 (0.96-1.11)	1.00 (0.90-1.11)	-	-
<b>CV (%)</b>	16	16	22	-	-
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t<sub>max</sub> (median, range)) of perindoprilat under fasted conditions.

<b>Treatment N=26</b>	<b>AUC<sub>0-t</sub> µg.h/l</b>	<b>AUC<sub>0-∞</sub> µg.h/l</b>	<b>C<sub>max</sub> µg/l</b>	<b>t<sub>max</sub> h</b>	<b>t<sub>1/2</sub> h</b>
<b>Test</b>	233 ± 34	-	12 ± 4	6.0 (4.0-10.0)	-
<b>Reference</b>	222 ± 52	-	11 ± 5	6.0 (4.0-12.0)	-
<b>*Ratio (90% CI)</b>	1.07 (1.01-1.12)	-	1.10 (1.00-1.20)	-	-
<b>CV (%)</b>	10	-	19	-	-
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

The 90% confidence intervals calculated for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> of perindopril and AUC<sub>0-t</sub> and C<sub>max</sub> of perindoprilat are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. It is acceptable that for the metabolite only the AUC<sub>0-t</sub> is reported, because of the long half-life of perindoprilat (approximately 180 hours) and as after 72 hours absorption is assumed to be complete. Based on the pharmacokinetic parameters of perindopril supported by the data of perindoprilat under fasted conditions, it can be concluded that Perindopril tert-butylamine 8 mg Ranbaxy and Coversyl 8 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

#### *CMD(h) conclusion*

Bioequivalence has been demonstrated for the 8 mg product. Therefore, agreement could be reached and the 8 mg strength was found approvable.

#### Risk management plan

Perindopril tert-butylamine was first approved in 1988, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of perindopril tert-butylamine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

## Product information

### Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. A preliminary test was performed with 2 participants, which led to some revisions to the leaflet e.g. addition of examples of ACE inhibitors in section 1 and several changes in section 2 '*Do not take Perindopril tablets if any of the following apply to you*'. Subsequently a test with 10 participants was performed. This led to the following main results:

- The correct section was traced to answer the question on average 98.75% of the time.
- A similar result was achieved that, on average, each question was answered correctly 98.13% of the time.

Due to the high score no changes to the leaflet have been done. A second round with an additional 10 participants gave a similar outcome and also after this round the leaflet has not been modified.

The readability test itself and the evaluation report are of acceptable quality. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability.

### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Perindopril tert-butylamine 2 mg, 4 mg and 8 mg Ranbaxy, tablets have a proven chemical-pharmaceutical quality and are generic forms of Coversyl 2 mg, 4 mg and 8 mg tablets. Coversyl tablets is a well-known medicinal product with an established favourable efficacy and safety profile.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other perindopril tert-butylamine containing products.

The Board followed the advice of the assessors.

Agreement between member states was reached during a written procedure on the 2 mg and 4 mg tablets. Bioequivalence was shown to be in compliance with the requirements of European guidance documents.

Regarding the 8 mg tablets, an unresolved issue remained regarding demonstration of bioequivalence. Therefore, a CMD(h) referral was started. Agreement could still not be reached on whether the 4 mg bioequivalence results could be extrapolated to the 8 mg strength. Subsequently, the MAH submitted a newly performed bioequivalence study with the 8 mg tablet, demonstrating bioequivalence. Herewith agreement could be reached, and the issue regarding bioequivalence was resolved.

The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Perindopril tert-butylamine 2 mg, 4 mg and 8 mg Ranbaxy, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 January 2008 for the 2 mg and 4 mg strengths, and on 1 May 2008 for the 8 mg product. Perindopril tert-butylamine 2 mg, 4 mg and 8 mg Ranbaxy, tablets were authorised in the Netherlands on 12 September 2008.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from January 2008 to January 2011.

The date for the first renewal will be: 23 January 2013

There were no post-approval commitments made during the procedure.

## List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C <sub>max</sub>	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
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
NfG	Note for Guidance
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 <sub>1/2</sub>	Half-life
t <sub>max</sub>	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
Insertion of text in section 5.1 of SmPC after Heart Failure Indication	NL/H/0977/001-002/II/001	II	2-9-2008	1-11-2008	Approval	Y, Annex I
Change in batch size of the finished product; up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation	NL/H/0977/002/IA/002	IA	23-7-2008	6-8-2008	Approval	N

## ANNEX I – Type II variation NL/H/0977/001-002/II/001

### INTRODUCTION

The MAH proposes two type II variations to include the results of the EUROPE study in the SPC. Perindopril is indicated for the treatment of essential hypertension, symptomatic heart failure and reduction of the risk of cardiac events in stable coronary artery disease.

The Netherlands is the RMS in this procedure with the following CMSs: BE, CZ, EE, ES, FI, HU, IT, LT, LV, PL, SK, UK.

### ASSESSMENT

The MAH proposes to implement a text in section 5.1 of the SPC. This variation considers adjustment of the SPC in section 5.1 after Heart Failure indication to include the results of the EUROPE study.

The following text has been added:

#### Patients with stable coronary artery disease

*The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.*

*Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108).*

*The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure.*

*Overall, 90% of the patients had a previous myocardial infarction and/or revascularisation.*

*Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.*

*The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001). In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.*

The text proposal is in harmonisation with the text in the SPC of the innovators product. Furthermore, the text has already been implemented in the SPC of Perindopril tert-butylamine 8 mg Ranbaxy (NL/H/0977/003/MR) during the CMD(h) referral procedure of this strength. The variation at issue has been submitted to include the same text in the SPC of the other strengths (2 and 4 mg) and for the registration (NL/H/0978).

### CONCLUSION

The variations were mutually recognised and ended positively on 1 November (day 60 of the procedure).