CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ramipril-HCT 2.5/12.5 mg tablets
Ramipril-HCT 5/25 mg tablets

Alfred E. Tiefenbacher (GmbH & Co. KG), Germany

ramipril and hydrochlorothiazide

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/721/01-02/MR
Registration number in the Netherlands: RVG 30670, 30671

21 May 2008

Pharmacotherapeutic group:	ACE inhibitors and diuretics
ATC code:	C09BA05
Route of administration:	oral
Therapeutic indication:	Treatment of essential hypertension. Ramipril/Hydrochlorothiazide fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on ramipril alone or hydrochlorothiazide alone.
Prescription status:	prescription only
Date of authorisation in NL:	26 July 2005
Concerned Member States:	Mutual recognition procedure with DE and IT
Application type/legal basis:	Directive 2001/83/EC, Articles 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 concerned member states have granted a marketing authorisation for Ramipril-HCT 2.5/12.5 mg and Ramipril-HCT 5/25 mg tablets, from Alfred E. Tiefenbacher (GmbH & Co. KG). The first date of authorisation was on 26 July 2005 in the Netherlands. The product is indicated for treatment of essential hypertension. Ramipril/Hydrochlorothiazide fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on ramipril alone or hydrochlorothiazide alone.

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

Ramipril/Hyrochlorothiazide tablets have an antihypertensive and diuretic effect. Ramipril is a long acting angiotensin converting enzyme (ACE) inhibitor, which exhibits similar pharmacodynamic properties as benazepril, lisinopril, and quinapril. Ramipril is hydrolysed after absorption to form its major active metabolite ramiprilat. Hydrochlorothiazide is a widely prescribed diuretic belonging to the class of thiazides. Ramipril and hydrochlorothiazide are used alone or in combination in antihypertensive therapy. The antihypertensive effects of both substances are supplementing each other. The antihypertensive effects of both substances are almost additive, whereas the potassium loss caused by hydrochlorothiazide is reduced by ramipril.

This application concerns a generic application claiming essential similarity with the innovator product Tritazide (NL License RVG 15551), a fixed dose combination tablet containing ramipril and hydrochlorothiazide, which has been registered in the Netherlands by Sanofi-Aventis since 22 June 1994. In addition, reference is made to Tritazide authorisations in the individual member states.

The marketing authorisation is granted based on article 10(1) or 10(3) of Directive 2001/83/EC, depending on the strength of the reference product in the member state where the application is made.

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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Delix® 5 plus, registered in Germany. 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. This generic product can be used instead of its reference product.

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.

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 and excipients
The active substances are ramipril and hydrochlorothiazide, both established active substances described in the European Pharmacopoeia (Ph.Eur.). Ph.Eur. is an official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU. The active substance specification for ramipril is based on the Ph.Eur. and in-house specifications for amounts of residual solvents, bulk density and particle size. Also the active substance specification for hydrochlorothiazide is based on the Ph.Eur. specifications, with additional specifications for particle size. The active substance specifications are considered adequate to control the quality. Batch analytical data demonstrating compliance with these specifications have been provided for 5 batches for the active substance ramipril and 5 batches for the active substance hydrochlorothiazide.

The CEP procedure is used for the suppliers of the active substances ramipril and hydrochlorothiazide. 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, and 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.

For the active substance ramipril stability data have been provided for 9 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 2 years when stored at a temperature below 25°C in a well-closed container, protected from light. The active substance hydrochlorothiazide is stable for 4 years when stored in double polyethylene bags placed in fibre drums, without further storage conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

The excipients are well-known pharmacopoeial substances and usual for tablet cores. All excipients comply with the requirements in their Ph.Eur. monographs.

Medicinal Product

Composition
Ramipril-HCT 2.5/12.5 tablets contain as active ingredients 2.5 mg ramipril and 12.5 mg hydrochlorothiazide and are white, modified capsule-shaped tablets. The tablets are embossed with a score on both sides, with “2.5” and "12.5” on each side of the score on one side.
Ramipril-HCT 5/25 tablets contain as active ingredients 5 mg ramipril and 25 mg hydrochlorothiazide and are white, modified capsule-shaped tablets. The tablets are embossed with a score on both sides, with “5” and "25” on each side of the score on one side.

The tablets are supplied in PVC/PCTFE/Aluminium blister packaging. The blister material was chosen on the fact that hydrochlorothiazide is sensitive to light.

The excipients are standard excipients for tablet cores: lactose monohydrate, hypromellose (E 464), crospovidone (E 1202), microcrystalline cellulose, and sodium stearyl fumarate.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be bioequivalent with the innovator product Tritazide, 5 mg/25 mg tablets (Aventis, The Netherlands).

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 2 pilot batches for both tablet strengths in accordance with the relevant European guidelines. The MAH committed to provide process validation data of the first three production scale batches.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications are based on the monograph for tablets Ph.Eur. and include tests for appearance, identity, assay, dissolution, uniformity of mass of halved tablets, degradation products, moisture, microbial purity and disintegration. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches for each strength in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. Based on the data submitted, a shelf life was granted of 2 years with the labelled storage condition: “Do not store above 25°C. Store in the original package in order to protect from moisture.”. After marketing authorisation the shelf life was changed by a type IB variation from 2 to 3 years (see table Steps taken after finalisation of the initial procedure at Page 10).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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 product is a generic formulation of Tritazide, which is 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 ramipril and hydrochlorothiazide released into the environment. It does not contain any components which result in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Ramipril and hydrochlorothiazide are well-known active substances with established efficacy and tolerability.

The content of the SPC approved during the mutual recognition procedure is identical to the outcome of the mutual recognition repeat use procedure DK/H/532/01-02/E01.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Ramipril-HCT 5/25 mg tablets is compared with the pharmacokinetic profile of the German reference product Delix 5 plus.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different Member states <or with the EU reference product.

A single-dose, randomised, 2-way crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 19-53 years. Each subject received daily a single dose (5 mg ramipril and 25 mg hydrochlorothiazide) of one of the 2 Ramipril/Hydrochlorothiazide 5/25 mg formulations. The wash-out period was at least 40 days. The tablet was orally administered with 240 ml water after an overnight fast. Six subjects withdrew from the study (reason not recorded), one subject was withdrawn because of vomiting, and one subject was withdrawn because of a positive result for HbsAg hepatitis B. A total of 24 subjects completed the study. The bioavailability of the test Ramipril-HCT 5/25, 5 mg ramipril and 25 mg hydrochlorothiazide, tablet (Alfred E. Tiefenbacher (GmbH & Co. KG, Germany), was compared to the reference product Delix 5 plus, 5 mg ramipril and 25 mg hydrochlorothiazide, tablet (Aventis Pharma, Germany).

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

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng.h	**t_{max}** h	**$t_{1/2}$** h
Test	15.4 ± 7.9	16.0 ± 8.0	14.0 ± 6.9	3.0 (1.3-8.0)	2.8 ± 1.2
Reference	14.6 ± 7.6	15.2 ± 7.6	13.8 ± 7.9	3.0 (1.3-4.5)	2.8 ± 1.0
***Ratio (90% CI)**	1.06 (0.99-1.14)	1.05 (0.98-1.13)	1.04 (0.93-1.15)	--	--
CV (%)	14.3 %	14.4 %	22 %	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

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

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng.h	**t_{max}** h	**$t_{1/2}$** h
Test	280 ± 7.9	393 ± 149	7.6 ± 4.4	0.50 (0.33-1.30)	282 ± 57
Reference	292 ± 103	420 ± 181	7.9 ± 5.2	0.50 (0.33-1.50)	291 ± 98
***Ratio (90% CI)**	0.96 (0.93-1.00)	0.95 (0.90-1.00)	0.97 (0.87-1.07)	--	--
CV (%)	8.0 %	10.5 %	21 %	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

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

Treatment N=32	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng.h	**t_{max}** h	**$t_{1/2}$** h
Test	874 ± 230	919 ± 231	121 ± 37	2.5 (1.3-4.5)	9.5 ± 1.7
Reference	855 ± 211	902 ± 209	121 ± 43	2.0 (0.9-4.5)	9.8 ± 2.4
***Ratio (90% CI)**	1.02 (0.94-1.10)	1.01 (0.94-1.09)	1.01 (0.90-1.13)	--	--
CV (%)	16.1 %	15.0 %	23 %	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} of ramipril, ramiprilat and hydrochlorothiazide are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. The other pharmacokinetic variables were comparable. Based on the pharmacokinetic parameters under fasting conditions, it can be concluded that test Ramipril-HCT 5/25 mg tablet and the reference Delix 5 plus tablet are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. From the literature it is known that concomitant food intake has no influence on the absorption of both active substances. Therefore a food interaction study was not deemed necessary.

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

The 2.5/12.5 mg and the 5.0/25.0 mg tablets are dose-proportional. The pharmacokinetics of ramipril and hydrochlorothiazide is linear in the range 5-10 mg. The results of the bioequivalence study performed with the 10 mg tablet therefore apply to the other tablet 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).

During the procedure a potential serious risk to public health was raised by two member states regarding the proposed indication in the SPC: *'Treatment of essential hypertension. Ramipril/Hydrochlorothiazide fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on ramipril alone or hydrochlorothiazide alone'*. For some concerned member states only the indication *'Essential hypertension in patients that cannot be adequately controlled with ramipril alone'* was approvable. The add-on indication for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide alone could not be granted, because of the lack of an add-on study in non-responders to hydrochlorothiazide
Following the discussion in the CMD(h) of 11-12 December 2006, all concerned member states were of the opinion that the add-on effects of ramipril to non-responders to hydrochlorothiazide have been adequately demonstrated by results from appropriately designed parallel group comparative studies of the combination with the individual components as extensively described in the literature. Therefore the proposed indication *'Treatment of essential hypertension. Ramipril/Hydrochlorothiazide fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on ramipril alone or hydrochlorothiazide alone'* was granted.

Risk management plan
The combination of ramipril and hydrochlorothiazide was first approved in 1992, and there is now more than 10 years post-authorisation experience with this combination of active substances. The safety profile of ramipril and hydrochlorothiazide 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.

Readability test
The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of 20 participants and the questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ramipril-HCT 2.5/12.5 mg tablets and Ramipril-HCT 5/25 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Tritazide. Tritazide is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the European guidance documents. The SPC is consistent with that of the outcome of the mutual recognition repeat use procedure DK/H/532/01-02/E01.

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. Braille conditions are met by the MAH.

The Board followed the advice of the assessors.

In the CMD meeting of 11-12 December 2006, the following was discussed:
A concern was raised with regard to granting of the add-on indication for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide alone, because of the lack of an add-on study in non-responders to hydrochlorothiazide. All concerned member states are in agreement that the add-on effects of ramipril to non-responders to hydrochlorothiazide have been adequately demonstrated by results from appropriately designed parallel group comparative studies of the combination with the individual components. Therefore, the indication *'Treatment of essential hypertension. Ramipril/Hydrochlorothiazide fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on ramipril alone or hydrochlorothiazide alone'* was approvable.

The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Ramipril-HCT 2.5/12.5 mg and 5/25 mg tablets, with the reference product, and have therefore granted a marketing authorisation.

The PSUR submission cycle is 3 years. The 1st PSUR will cover the period from September 2006 until September 2009.

The date for the first renewal will be: 7 September 2011.

The following post approval commitment was made during the procedure:

<u>Quality – Medicinal Product</u>
The MAH committed to provide process validation data of the first three production scale batches.

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_{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
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCT	Hydrochlorothiazide
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
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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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 procedure	Approval/non approval	Assessment report attached
Based on the review of the process validation data of the first three production scale batches, the concerned member states considered the post-approval commitment fulfilled.	NL/H/0721/01-02/MR	Post-approval commitment	NA	NA	Y	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product "All other manufacturing operations except batch release"	NL/H/0721/001-02/IB/001	type IB	26-1-2007	25-2-2007	Y	N
Change in the shelf life of the finished product, as packaged for sale, from 2 to 3 years	NL/H/721/01-02/IB/002	type IB	26-1-2007	25-2-2007	Y	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product "Secondary packaging site for all types of pharmaceutical forms"	NL/H/721/01-02/IA/004	type IA	25-10-2007	8-11-2007	Y	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product "Secondary packaging site for all types of pharmaceutical forms"	NL/H/721/02/IA/005	type IA	25-10-2007	8-11-2007	Y	N