

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

**Flutensif 1.5 mg/5 mg and 1.5 mg/10 mg modified-release tablets  
Les Laboratoires Servier, France**

**indapamide/amlodipine**

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/2639/001-002/DC  
Registration number in the Netherlands: RVG 112321-112322**

**18 February 2014**

Pharmacotherapeutic group:	calcium channel blockers and diuretics
ATC code:	C08GA02
Route of administration:	oral
Therapeutic indication:	substitution therapy for treatment of essential hypertension in patients already controlled with indapamide and amlodipine given concurrently at the same dose level
Prescription status:	prescription only
Date of authorisation in NL:	11 November 2013
Concerned Member States:	Decentralised recognition procedure with AT, BG, DE, EE, EL, ES, FI, FR, HU, IT, LT, LV, PT, RO, SK
Application type/legal basis:	Directive 2001/83/EC, Article 10b

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), 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 Flutensif 1.5 mg/5 mg and 1.5 mg/10 mg modified-release tablets from Les Laboratoires Servier. The date of authorisation was on 11 November 2013 in the Netherlands.

Flutensif is indicated as substitution therapy for treatment of essential hypertension in patients already controlled with indapamide and amlodipine given concurrently at the same dose level.

A comprehensive description of the indication and posology is given in the SmPC.

Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to thiazide diuretics, which acts by inhibiting the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle.

This decentralised procedure concerns a fixed dose application. Fixed dose combinations contain active substances from medicinal products already authorised in the EEA but not hitherto used in combination for therapeutic purposes. In these kinds of applications the results of new pre-clinical tests or new clinical trials relating to that combination are provided. However, it is not necessary to provide pre-clinical and clinical data relating to each individual active substance.

Flutensif is a fixed combination of a thiazide-like diuretic (indapamide SR) and a calcium antagonist (amlodipine, besilate salt) formulated as a modified-release tablet to be given once daily.

This dual association is proposed as substitution therapy for the treatment of essential hypertension, in patients already controlled with the combination of indapamide and amlodipine, given concurrently at the same dose level. This is the first fixed dose combination of a diuretic and a calcium antagonist in line with one of the recommended combinations by the current European and American guidelines for the management of hypertension.

The innovator product containing indapamide, Fludex SR 1.5 mg tablets (NL License RVG 19206), was first registered in the Netherlands by Les Laboratoires Servier in December 1995 for the indication of essential hypertension. The product was approved through a Mutual Recognition Procedure (FR/H/0100/001).

The Dutch amlodipine innovator product Norvasc 5 mg and 10 tablets (NL RVG 13348-13349) has been registered by Pfizer since June 1990 for the indications hypertension, chronic stable angina pectoris and vasospastic (Prinzmetal's) angina.

The MAH gave the following argumentation for this fixed dose combination:

In line with the requirements stated in the document CHMP/EWP/191583/05 entitled *Questions and answers on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardio-vascular treatment and prevention*:

- indapamide SR and amlodipine are well known (therapeutic experience of 18 years and 23 years, respectively) for the treatment of hypertension,
- the joint application of the components already in widespread use at the proposed dosage strengths, has proven to be efficacious and safe and thus clinically useful,
- the pharmacological rationale for the use of indapamide and amlodipine in combination is adequately justified in literature; in this respect a bibliographical data analysis is presented in this application,
- the present application is based on pharmacokinetic data: interaction and bioequivalence studies.

The marketing authorisation is granted based on article 10b of Directive 2001/83/EC.

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

A total of 4 studies have been performed which were designed to compare bioavailability to the reference formulations and to assess pharmacokinetic interaction between the two compounds.

Interaction was assessed in a study with administration of a single administration of indapamide SR at the highest strength and a single administration of amlodipine.

For the bioavailability a comparison was made with one tablet of the proposed fixed dose combination to the reference products, administered as one tablet of indapamide SR plus one tablet of amlodipine. The bioequivalence studies were a single dose study under fasted conditions, a single dose study under fed conditions and a multiple dose study under fasted conditions. The studies were conducted with Flutensif 1.5 mg/10 mg modified-release tablets. The MAH applied for a biowaiver for the lower strength. The study results are briefly presented in this report under section II.3 'Clinical aspects'.

No scientific advice has been given to the MAH with respect to these products.

The RMS checked Paediatric Investigation Plan (PIP) compliance. On 27 August 2010 the EMA adopted a product-specific waiver for indapamide/amlodipine besilate for all subsets of the paediatric population from birth to less than 18 years of age (EMA-000896-PIP01-01).

## 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 this product type 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 substances

The active substances are indapamide and amlodipine, established active substances described in the European and/or United States Pharmacopoeia (Ph.Eur, USP\*). Indapamide is a white or almost white powder, which is practically insoluble in water and soluble in ethanol (96%). Amlodipine is a white or almost white powder, which is freely soluble in methanol, sparingly soluble in ethanol and slightly soluble in purified water and 2-propanol.

*\*Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA, respectively.*

The CEP procedure is used for the suppliers of both active substances. 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 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.

#### Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

#### Quality control of drug substance


Limits and tests as per proposed specification are in line with the respective Ph.Eur. monographs on indapamide and amlodipine. For indapamide requirements of the CEP are adopted and appropriate additional tests are included. The specification is acceptable in view of the route of synthesis and the various European guidelines. For amlodipine, requirements of the CEP are adopted. Appropriate additional tests are included. This specification is acceptable as well. The limits for particle size for both substances were discussed in relation to the drug product and found acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches of each supplier.


#### Stability of drug substance

The retest periods for indapamide and amlodipine are 3 years and 5 years respectively, when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

### **Medicinal Product**

#### Composition

Flutensif 1.5 mg/5 mg is a white, round, film-coated, bilayered, modified-release tablet engraved with \* on one face. One tablet contains 1.5 mg indapamide and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.

Flutensif 1.5 mg/10 mg is a pink, round, film-coated, bilayered, modified-release tablet engraved with \* on one face. One tablet contains 1.5 mg indapamide and 13.87 mg amlodipine besilate equivalent to 10 mg amlodipine.

The modified-release tablets are packed in PVC/Aluminium blisters and HDPE bottles equipped with a screw tamper evident polypropylene cap.

The excipients are:

#### *Tablet core*

Hypromellose 4000m Pa.s (E464), lactose monohydrate, magnesium stearate (E572), povidone K30 (E1201), silica colloidal anhydrous, calcium hydrogen phosphate dihydrate, microcrystalline cellulose (E460), croscarmellose sodium (E468), pregelatinized maize starch.

#### *Tablet film-coating*

Glycerol (E422), hypromellose 6 mPa.s (E464), macrogol 6000, magnesium stearate (E572), titanium dioxide (E171), iron oxide red (E172 – 1.5 mg/10 mg only)

The composition of the amlodipine layer is not quantitatively proportional for the two dosage strengths. The amount of cellulose varies to compensate the lower drug load.

#### Pharmaceutical development

For the pharmaceutical development the Quality by Design (QbD) approach was applied. It is used as a support in the choice of the excipients as well as showing the robustness of the manufacturing process. The development of the product has been adequately described, the choice of excipients is justified and their functions explained, the development of the process is supported by the QbD data. In the bioequivalence studies, the MAH uses two single products for comparison, *i.e.* indapamide as registered by the MAH itself (Fludex® SR 1.5 mg) and amlodipine from Pfizer (Norvasc® 5 mg and 10 mg tablets). Drug load is low for both active substances (<2% for indapamide and <5% for amlodipine). The drug product is not dose-proportional with respect to the amlodipine layer, since the amount of cellulose varies to compensate the lower drug load. The 1.5 mg/10 mg product contains iron oxide red for colouring of the tablet. However, the conditions for granting a biowaiver for the lower strength are fulfilled.

Overall, the pharmaceutical development data is considered sufficient. The products used in the bioequivalence are considered acceptable. In some European countries amlodipine is not registered as a tablet, but only as a capsule. Since the product used in the bioequivalence studies (tablet) is recognised

as an acceptable European reference product, the conclusions on bioequivalence apply to these countries as well.

#### Manufacturing process

The manufacturing process is not a standard process. It consists of mixing and granulation of the two layers, compression of the layers and coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches of each strength.

Compliance to the Note for Guidance on the start of shelf-life is stated.

#### Control of excipients

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

#### Quality control of drug product

The product specification includes tests for appearance, average mass, dissolution of both active substances, identification of amlodipine and indapamide, assay of both active substances, uniformity of dosage units, purity and microbiological quality. The drug product specification is acceptable. The analytical methods have been adequately validated. Batch analytical data from the proposed production sites have been provided on three pilot-scale and on four full-scale batches for both strengths, demonstrating compliance with the release specification.

#### Stability of drug product

Stability data on the product has been provided for each strength on pilot-scale batches for PVC/aluminium blister and on pilot-scale batches and industrial-scale batches for HDPE bottle. The batches were stored at 25°C/60% RH (up to 18 months), 30°/65% (up to 18 months), 30°C/75%RH (up to 18 months for HDPE bottle only) and 40°C/75% RH (up to 6 months). The conditions used in the stability studies are according to the stability guideline.

For the blister pack decreases were observed in assay of amlodipine at accelerated and intermediate conditions and at long term conditions slight decreases were observed. For the HDPE bottle decreases in assay of amlodipine were only observed at accelerated conditions. However, all results remained within specification limits.

A photostability study was conducted. The results demonstrate that the product is photostable. Dose dispensing for the HDPE bottle has been studied. The claimed shelf-life of 18 months for the product in blisters and HDPE bottles can be granted given the data available. The claimed storage conditions of 'store below 30°C' (blister) and none (HDPE bottle) are considered acceptable.

The in-use storage showed that the product remains stable in an open bottle for 90 days. The proposed pack size (100 tablets) is considered to be covered by these results, no specific information has to be stated for the in-use storage.

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

A declaration with respect to the TSE safety of lactose monohydrate has been included. The lactose used can be considered to be of no risk with respect to transmitting TSE. Magnesium stearate and glycerol are of vegetable origin.

## **II.2 Non-clinical aspects**

### **Pharmacology and pharmacokinetics**

For this fixed dose application, no new data regarding pharmacology or pharmacokinetics have been provided. No new studies have been performed and none are considered necessary. This is acceptable, as both active substances are well known.

### **Toxicology**

The toxicological profile of indapamide and amlodipine is also well known, and the substances have been used in combination for many years. There are therefore no safety concerns. New studies have been performed on several impurities. The established specification limits are considered qualified.

### Environmental risk assessment

Since Flutensif is intended for substitution of both active ingredients used in separate tablets, this will not lead to an increased exposure to the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal. An environmental risk assessment is therefore not deemed necessary

## II.3 Clinical aspects

### Pharmacokinetics

The pharmacokinetic properties of indapamide and amlodipine are well known. A total of 4 pharmacokinetic studies have been performed, study no. PKH-05520-001/002/003/004. For all studies analytical methods have been described and pharmacokinetic and statistical analyses were acceptable.

#### PKH-05520-001

This study investigated the potential pharmacokinetic interaction between indapamide SR 1.5 mg and amlodipine 10 mg, after single oral dose, in healthy volunteers under fasting conditions. This was an open-label randomized three-period cross-over study.

The following treatments were administered as indicated per period:

- One tablet of indapamide SR 1.5 mg co-administered with one tablet of amlodipine 10 mg, oral single dose (treatment T).
- One tablet of indapamide SR 1.5 mg, oral single dose (treatment R);
- One tablet of amlodipine 10 mg, oral single dose (treatment S).

The initial protocol was designed for a total of 30 subjects included; drop-out subjects were replaced by subjects assigned to the same treatment sequence in order to have 30 completed subjects.

All included subjects were excluded from the study after period 1 due to a major sample collection deviation. The withdrawn subjects were replaced by 31 new subjects aged between 18-40 years of the Caucasian race (19 male, 12 female). There was a drop-out due to personal reasons, thus the number of subjects for which pharmacokinetic and statistical analysis was performed was 30.

Each treatment period was separated by a washout of 2 weeks. The study design is an acceptable approach for this type of investigation.

Table 4.2.1 Indapamide pharmacokinetic parameters  
(indapamide co-administered with amlodipine *versus* indapamide)

Indapamide			
Parameter	Unit	geom Mean (geom %CV) Treatment T (n=30)	geom Mean (geom %CV) Treatment R (n=30)
AUC <sub>last</sub>	ng*h/mL	290.4 (31.8%)	294.7 (33.9%)
AUC	ng*h/mL	325.7 (28.7%) n=28**	322.9 (28.7%) n=29**
C <sub>max</sub>	ng/mL	8.094 (31.4%)	8.090 (31.3%)
t <sub>max</sub>	h	12.0 (4.0 – 36.0)*	12.0 (4.0 – 24.0)*

\* : median and range

\*\* : if percentage of AUC extrapolated from AUC<sub>last</sub> is greater than 20%, the AUC value is not reported and not taken into account in statistics calculations. Additional AUC values with AUC<sub>ext</sub>>20 % are reported as AUC<sub>all</sub>.

T: One tablet of indapamide SR 1.5 mg co-administered with one tablet of amlodipine 10 mg

R: One tablet of indapamide SR 1.5 mg

Table 4.2.2 Amlodipine pharmacokinetic parameters  
(amlodipine co-administered with indapamide *versus* amlodipine)

<b>Amlodipine</b>			
Parameter	Unit	geom Mean (geom %CV) Treatment T (n=30)	Geom. Mean (geom %CV) Treatment S (n=30)
AUC <sub>last</sub>	ng*h/mL	265.7 (32.5%)	264.0 (32.9%)
AUC	ng*h/mL	278.4 (33.3%)	277.7 (33.3%)
C <sub>max</sub>	ng/mL	5.52 (28.0%)	5.56 (29.3%)
t <sub>max</sub>	h	6.0 (3.0 – 8.0)*	6.0 (2.0 – 8.0)*

\* : median and range

T: One tablet of indapamide SR 1.5 mg co-administered with one tablet of amlodipine 10 mg

S: One tablet of amlodipine 10 mg

Table 4.3.1 Geometric mean ratios (treatment T / treatment R for indapamide and treatment T / treatment S for amlodipine, respectively) and 90% Confidence Intervals for pharmacokinetic parameters of indapamide and amlodipine

Parameter	Indapamide (n=30)	Amlodipine (n=30)
	Ratio T/R (90% CI)	Ratio T/S (90% CI)
AUC <sub>last</sub>	98.56% (92.32%,105.20%)	100.67% (97.38%,104.07%)
AUC	100.35% (93.64%,107.53%), n=28**	100.22% (96.87%,103.69%)
C <sub>max</sub>	100.05% (93.69%,106.83%)	99.23% (95.94%,102.63%)
	Difference T-R <sup>+</sup> (CI)*	Difference T-S <sup>+</sup> (CI)*
t <sub>max</sub>	0h <sup>+</sup> (-2h,+3h)*	0h <sup>+</sup> (-1h,+0.5h)*

\*\* : if percentage of AUC extrapolated from AUC<sub>last</sub> is greater than 20%, the AUC value is not reported and not taken into account in statistical calculations. Additional AUC values with AUC<sub>ext</sub>>20% are reported as AUC<sub>all</sub> in listings 12.2.3.1. to 12.2.3.2.

\* : nonparametric evaluation; <sup>+</sup> : between treatment difference (median of time differences);

T: One tablet of indapamide SR 1.5 mg co-administered with one tablet of amlodipine 10 mg

R: One tablet of indapamide SR 1.5 mg

S: One tablet of amlodipine 10 mg

For indapamide and amlodipine the pharmacokinetic parameters are comparable and 90% confidence intervals are within 80 to 125% interval range. The results of study PKH-05520-001 demonstrate the absence of a significant interaction between both co-administered components of the applied combination product indapamide and amlodipine.

#### PKH-05520-002

This was a bioequivalence study of one tablet of the fixed combination of indapamide sustained release (SR) 1.5 mg/amlodipine 10 mg versus one tablet of indapamide SR 1.5 mg plus one tablet of amlodipine 10 mg, after single oral dose in fasted conditions. This was an open-label randomized, two-period, two-way crossover study in 32 healthy male subjects of Caucasian origin, aged 19 to 46 years.

The treatment administered were:

- fixed combination of indapamide sustained release (SR) 1.5 mg/amlodipine 10 mg
- one tablet of indapamide SR 1.5 mg plus one tablet of amlodipine 10 mg

There was a wash-out period of 2 weeks between treatments. The blood samples were collected pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours post dose.

All 32 subjects completed the study and were included in the pharmacokinetic analysis. There were no relevant protocol deviations.

**Table (4.2) 1 - Indapamide pharmacokinetic parameters**

<b>Indapamide</b>			
Parameter	Unit	Geom. Mean (geom. %CV)	
		Treatment T (n=32)	Treatment R (n=32)
AUC <sub>72</sub>	ng* <sup>h</sup> /mL	256.6 (24.3 %) n=29	261.5 (25.2 %)
AUC <sub>last</sub>	ng* <sup>h</sup> /mL	240.4 (29.0 %)	257.1 (27.3 %)
C <sub>max</sub>	ng/mL	6.826 (21.9 %)	7.431 (29.7 %)
t <sub>max</sub>	h	12.02 (4.0 – 24.0)#	16.0 (6.0 – 24.05)#

# : median and range

T: One tablet of S 05520: indapamide SR 1.5 mg/amlopidine 10 mg  
R: One tablet of indapamide SR 1.5 mg plus one tablet of amlopidine 10 mg  
Refer to table 10.2

**Table (4.2) 2 - Amlodipine pharmacokinetic parameters**

<b>Amlodipine</b>			
Parameter	Unit	Geom. Mean (geom. %CV)	
		Treatment T (n=32)	Treatment R (n=32)
AUC <sub>72</sub>	ng* <sup>h</sup> /mL	176.6 (18.3 %)	166.8 (33.2 %)
AUC <sub>last</sub>	ng* <sup>h</sup> /mL	176.6 (18.3 %)	166.8 (33.2 %)
C <sub>max</sub>	ng/mL	5.643 (19.7 %)	5.287 (32.8 %)
t <sub>max</sub>	h	6.0 (3.0 – 8.0)#	6.0 (2.0 – 8.0)#

# : median and range

T: One tablet of S 05520: indapamide SR 1.5 mg/amlopidine 10 mg  
R: One tablet of indapamide SR 1.5 mg plus one tablet of amlopidine 10 mg  
Refer to table 10.2

**Table (4.3) 1 - Geometric mean ratios (treatment T / treatment R) and 90 % Confidence Intervals for pharmacokinetic parameters of indapamide and amlodipine**

Parameter	Least Squares Geometric Mean Ratio T/R (90% CI)	
	Indapamide	Amlodipine
	(n=32)	(n=32)
AUC <sub>72</sub>	95.85 % (91.26 %, 100.66 %), n=29	105.90 % (99.36 %, 112.87 %)
AUC <sub>last</sub>	93.54 % (88.96 %, 98.34 %)	-
C <sub>max</sub>	91.86 % (86.92 %, 97.06 %)	106.73 % (99.22 %, 114.80 %)

T: One tablet of S 05520: indapamide SR 1.5 mg/amlopidine 10 mg  
R: One tablet of indapamide SR 1.5 mg plus one tablet of amlopidine 10 mg  
Refer to table 10.3

Pharmacokinetic parameters for both indapamide and amlodipine demonstrate comparable results. The 90% confidence intervals of AUC values and C<sub>max</sub> were within the pre-specified acceptance criteria of 80-125%. Statistical evaluation of the pharmacokinetic parameters resulted in possible treatment effects for indapamide AUC<sub>last</sub> and C<sub>max</sub> and a period effect for amlodipine C<sub>max</sub>.

For amlodipine AUC<sub>last</sub> equals AUC<sub>72</sub> which explains the identical results depicted in the table. For a total of 3 subject for indapamide the AUC<sub>72</sub> was not determined as the terminal rate constant could not reliably be estimated.

The values of t<sub>max</sub> for indapamide differ between the test and the reference treatment. Median (range) values for the test treatment were 12 (4-24) and for the reference 16 (6-24) hours. However, no statistically significant difference was demonstrated. C<sub>max</sub> values were not above the validated range for



amlodipine or indapamide. The guideline criteria for the conclusion of bioequivalence have been met as 90% confidence intervals are within pre-specified limits of 80-125%.

**PKH-05520-003**

This was a bioequivalence study of the fixed combination of indapamide SR 1.5 mg/amlodipine 10 mg versus indapamide SR 1.5 mg plus amlodipine 10 mg, after repeated oral administration under fasted conditions. This was an open-label, randomized, two-period, two-way crossover study in 33 healthy males aged 20 to 44 of Caucasian origin.

A 7-day consecutive dosing was administered of:

- one tablet of the fixed combination of indapamide SR 1.5 mg/amlodipine 10 mg
- one tablet of indapamide SR 1.5 mg plus one tablet of amlodipine 10 mg

The study periods were separated by a wash-out of one week and each period consisted of a 7-day consecutive administration. Blood samples were drawn pre-dose at days 4, 5, 6 and 7 of each period. Furthermore blood sample were drawn 1, 2,3, 4, 6, 8, 10, 12, 16 and 24 hours post dose on day 7.

A total of 33 subjects were included in the study and due to 2 drop-outs (adverse event skin eruption, personal reason) a total of 31 subjects finished the study phase and were included in the pharmacokinetic set. The analytical range of amlodipine was extended in order to account for the higher expected C<sub>max</sub> values.

**Table (4.2) 1 - Indapamide pharmacokinetic parameters**

<b>Indapamide</b>			
Parameter	Unit	Geom. Mean (geom. %CV)	
		Treatment T (n=31)	Treatment R (n=31)
AUC <sub>t</sub>	ng*h/mL	267.6 (27.3 %)	270.2 (33.6 %)
C <sub>max</sub>	ng/mL	13.7 (28.5 %)	14.1 (29.3 %)
C <sub>min</sub>	ng/mL	8.54 (33.2 %)	8.28 (40.2 %)
t <sub>max</sub>	h	4.0 (2.0 – 12.0)#	8.0 (2.0 – 16.0)#

# : median and range

T: One tablet of S 05520: indapamide SR 1.5 mg/amlodipine 10 mg

R: One tablet of indapamide SR 1.5 mg plus one tablet of amlodipine 10 mg

Refer to table 10.2

**Table (4.2) 2 - Amlodipine pharmacokinetic parameters**

<b>Amlodipine</b>			
Parameter	Unit	Geom. Mean (geom. %CV)	
		Treatment T (n=31)	Treatment R (n=31)
AUC <sub>t</sub>	ng*h/mL	266.5 (26.7 %)	278.5 (31.2 %)
C <sub>max</sub>	ng/mL	14.4 (26.7 %)	15.4 (27.2 %)
C <sub>min</sub>	ng/mL	7.71 (32.1 %)	8.21 (34.1 %)
t <sub>max</sub>	h	6.0 (4.0 – 10.0)#	6.0 (3.0 – 16.0)#

# : median and range

T: One tablet of S 05520: indapamide SR 1.5 mg/amlodipine 10 mg

R: One tablet of indapamide SR 1.5 mg plus one tablet of amlodipine 10 mg

Refer to table 10.2

**Table (4.3) 1 - Geometric mean ratios (treatment T / treatment R) and 90 % Confidence Intervals for pharmacokinetic parameters of indapamide and amlodipine**

Parameter	Least Squares Geometric Mean Ratio T/R (90% CI)	
	Indapamide (n=31)	Amlodipine (n=31)
AUC <sub>T</sub>	99.17 % (90.74 %, 108.38 %)	95.86 % (92.94 %, 98.87 %)
C <sub>max</sub>	97.28 % (90.88 %, 104.13 %)	94.12 % (89.90 %, 98.53 %)
C <sub>min</sub>	103.12 % (91.13 %, 116.68 %)	94.12 % (90.35 %, 98.04 %)

T: One tablet of S 05520: indapamide SR 1.5 mg/amlodipine 10 mg  
R: One tablet of indapamide SR 1.5 mg plus one tablet of amlodipine 10 mg  
Refer to table 10.3

Results of mean pre-dose levels at day 4, 5, 6 and 7 demonstrate the establishing of a steady state. Pharmacokinetic parameters for both compounds are comparable for both the test and the reference formulation, with the exception of t<sub>max</sub> for indapamide. The median value of t<sub>max</sub> for the indapamide test formulation is 4 hours (range 2-12), for the reference formulation 8 hours (2-16). This has been sufficiently explained by the flat concentration time curve of one subject. C<sub>max</sub> was not observed outside the validated range of both analytical methods.

The 90% confidence intervals for the main pharmacokinetic parameters AUC<sub>T</sub>, C<sub>max</sub> and C<sub>min</sub> of both compounds are within pre-specified acceptance criteria of 80-125%.

For amlodipine a significant period effect was reported for AUC<sub>T</sub> and C<sub>min</sub> and a treatment effect for AUC<sub>T</sub>, C<sub>max</sub> and C<sub>min</sub>. The guideline criteria for the conclusion of bioequivalence have been met as 90% confidence intervals are within pre-specified limits of 80-125%.

#### PKH-05520-004

This was a bioequivalence study of one tablet of the fixed combination of indapamide SR 1.5 mg/amlodipine 10 mg versus one tablet of indapamide SR 1.5 mg plus one tablet of amlodipine 10 mg, after administration of a single oral dose under fed conditions. This was an open-label randomized two-period, two-way cross-over study in 32 healthy male Caucasian participants aged between 18 to 42 years. The breakfast was a high fat high calorie breakfast, containing approximately 168 g, 630 g, 232 g of proteins, fat and carbohydrates, respectively.

The following treatments were administered:

- one tablet of the fixed combination of indapamide SR 1.5 mg/amlodipine 10 mg
- one tablet of indapamide SR 1.5 mg plus one tablet of amlodipine 10 mg

The dosing periods were separated by a 2 week wash-out. The blood samples were collected at pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours post dose.

As a total of 32 subjects were included, but 1 dropped-out (personal reason), the total pharmacokinetic set was 31 subjects.

**Table (4.2) 1 - Indapamide pharmacokinetic parameters**

<b>Indapamide</b>			
Parameter	Unit	Geom. Mean (geom. %CV)	
		Treatment T (n=31)	Treatment R (n=31)
AUC <sub>72</sub>	ng*h/mL	246.0 (20.4 %)	248.5 (21.0 %)
AUC <sub>last</sub>	ng*h/mL	238.6 (22.8 %)	243.5 (23.3 %)
C <sub>max</sub>	ng/mL	10.77 (31.2 %)	9.55 (31.8 %)
t <sub>max</sub>	h	6.0 (3.0 – 12.0)#	8.0 (3.0 – 12.0)#

# : median and range

T: One tablet of S 05520: indapamide SR 1.5 mg/amlodipine 10 mg

R: One tablet of indapamide SR 1.5 mg plus one tablet of amlodipine 10 mg

Refer to table 10.2

**Table (4.2) 2 - Amlodipine pharmacokinetic parameters**

<b>Amlodipine</b>			
Parameter	Unit	Geom. Mean (geom. %CV)	
		Treatment T (n=31)	Treatment R (n=31)
AUC <sub>72</sub>	ng*h/mL	206.3 (19.5 %) n=30	214.5 (19.8 %)
AUC <sub>last</sub>	ng*h/mL	205.0 (19.5 %)	214.5 (19.8 %)
C <sub>max</sub>	ng/mL	5.97 (19.5 %)	6.13 (18.0 %)
t <sub>max</sub>	h	6.0 (3.0 – 16.0)#	6.0 (3.0 – 16.0)#

# : median and range

T: One tablet of S 05520: indapamide SR 1.5 mg/amlodipine 10 mg

R: One tablet of indapamide SR 1.5 mg plus one tablet of amlodipine 10 mg

Refer to table 10.2

**Table (4.3) 1 - Geometric mean ratios (treatment T / treatment R) and 90 % Confidence Intervals for pharmacokinetic parameters of indapamide and amlodipine**

Parameter	Least Squares Geometric Mean Ratio T/R (90% CI)	
	<b>Indapamide</b>	<b>Amlodipine</b>
	(n=31)	(n=31)
AUC <sub>72</sub>	99.03 % (94.87 %, 103.36 %)	95.82 % (92.69 %, 99.04 %), n=30
AUC <sub>last</sub>	98.05 % (93.34 %, 102.99 %)	95.43 % (92.34 %, 98.61 %)
C <sub>max</sub>	112.74 % (101.87 %, 124.76 %)	97.29 % (93.12 %, 101.64 %)

T: One tablet of S 05520: indapamide SR 1.5 mg/amlodipine 10 mg

R: One tablet of indapamide SR 1.5 mg plus one tablet of amlodipine 10 mg

Refer to table 10.3

The guideline criteria for the conclusion of bioequivalence have been met as 90% confidence intervals are within pre-specified limits of 80-125%. The influence of food on the pharmacokinetic behaviour of the compounds was assessed by comparing pharmacokinetic parameters of this study with study PKH-05520-002. In comparison, the food intake slightly lowered the t<sub>max</sub> of indapamide which is according to the SmPC.

### Safety

Safety data from the 158 healthy volunteers included in the pharmacokinetic studies showed that the fixed combination indapamide/amlodipine was well tolerated, whether it was administered at single or repeated dose, under fed or fasted conditions.

No serious adverse event was observed with the fixed combination, no death or other significant event occurred. The number of participants having reported at least one emergent adverse event was similar in the different treatment groups in all studies. The adverse events were, as expected, mainly related to the nervous system, gastrointestinal disorders and to vascular disorders. Headache (listed event in the

indapamide and amlodipine SmPCs), flushing (listed event in the amlodipine SmPC) and orthostatic hypotension (listed event in the indapamide and amlodipine SmPCs) were the most frequently observed adverse events.

#### Biowaiver

The MAH applied for a biowaiver for Flutensif 1.5 mg/5 mg. The waiver was granted, since the following guideline criteria were fulfilled for the 2 formulations:

- the different strengths are manufactured by the same manufacturer using the same manufacturing process.
- the qualitative composition is identical for indapamide 1.5 mg/amlodipine 5 mg and indapamide 1.5 mg/amlodipine 10 mg tablets. The quantitative composition of the modified-release indapamide layer is identical for the 1.5 mg/5 mg and 1.5 mg/10 mg strengths.
- the quantitative composition of the amlodipine layer is not proportional between both strengths, but waiver criteria of the guideline are fulfilled:
  - the amount of the active substance(s) is less than 5% of the tablet core weight,
  - the amount of the filler is changed to account for the change in amount of active substance. The amounts of other core excipients are the same for the concerned strengths;
- the dissolution profiles of indapamide SR and amlodipine are similar for both strengths.

#### **Conclusion on pharmacokinetics**

From the four studies it is concluded that there is no pharmacokinetic interaction between the individual compounds of this fixed-dose combination product. As all 90% confidence intervals for important pharmacokinetic parameters are within 80.00 – 125.00%, the proposed combination product is considered bioequivalent with co-administration of the separate reference products Fludex® SR 1.5 mg and Norvasc®.

The pharmacokinetic studies have been performed administrating the highest strength applied for, indapamide SR 1.5 mg/amlodipine 10 mg. A biowaiver for studies with the lower strength, indapamide SR 1.5/ amlodipine 5 mg, is acceptable as all criteria have been fulfilled.

The influence of food on the pharmacokinetic behavior of both compounds has been assessed by comparing pharmacokinetic parameters after intake of a high-fat high calorie meal. The food intake slightly lowered the  $t_{max}$  of indapamide, which is also stated in the SmPC.

#### **Clinical efficacy**

Both indapamide and amlodipine have been marketed for many years as monotherapies (indapamide SR since 1994 and amlodipine since 1990), and are freely combined by practitioners in the treatment of hypertension. Although not considered pivotal for this application, the MAH provided further clinical data to justify the use of the fixed dose combination. The current ESH/ESC guideline recommends certain combinations of antihypertensive drugs when combination therapy is indicated. These include the combination of a calcium antagonist and a thiazide diuretic; including chlorthalidone and indapamide. These would provide a synergistic effect based on their pharmacologic mode of action. In addition, the MA provided prescription and co-prescription data of the combination of a diuretic and a calcium antagonist, and more precisely of indapamide and amlodipine in Europe based on a drug utilization study.

Overall, these data and the argumentation of the MAH are considered sufficient to justify established combined use of both substances.

#### **Clinical safety**

Both components are well known with respect to their safety profile. Safety of the combination has been assessed in one pharmacokinetic study, a company driven study for the development of a new FDC, and data from clinical practice. These data do not suggest any substantial different safety profile from what has been known from both monocomponents.

#### Risk management plan

The MAH submitted a statement regarding the absence of a Risk Management Plan. This is acceptable, since the product contains indapamide and amlodipine which have been authorised for 18 and 23 years, respectively and have a well known safety profile. The member states consider that the

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

### **Product information**

#### SmPC

The content of the SmPC approved during the decentralised procedure is acceptable, as it contains all relevant information for each of the active substances.

#### Readability test

The package leaflet (PL) 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. The testing process involved one pilot test with two participants, followed by two main test rounds with ten participants each.

Fifteen questions about the most critical parts of the package leaflet and four general questions about the package leaflet were used. There were sufficient questions about the critical sections.

The conclusions are clear, concise and clearly presented. Each question met the criterion that more than 90 % of the participants found the right section and were able to answer the question correctly.

The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The PL did not need to be adapted in view of the results of the tests. The readability test has been sufficiently performed.

### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Flutensif 1.5 mg/5 mg and 1.5 mg/10 mg modified-release tablets have a proven chemical-pharmaceutical quality and are considered an approvable fixed dose combination. Both indapamide and amlodipine are well known, established substances, which are used as a combination in clinical practice.

Four bioequivalence studies, under fasted, fed, single- and multiple dose conditions, showed that there is no pharmacokinetic interaction between the individual compounds of this fixed-dose combination product. The proposed combination product is considered bioequivalent with co-administration of the separate reference products Fludex® SR 1.5 mg and Norvasc®. The efficacy and safety profile is considered the same as for the monocomponents.

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

The SmPC is consistent with those of Fludex® SR 1.5 mg and Norvasc®. The SmPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that this fixed dose combination is approvable, since bioequivalence has been demonstrated with the innovator products of the individual components. The decentralised procedure was finalised on 5 September 2013. Flutensif 1.5 mg/5 mg and 1.5 mg/10 mg modified-release tablets were authorised in the Netherlands on 11 November 2013.

The PSUR submission cycle is 3 years, as published in the EURD list on the EMA website.

The date for the first renewal will be: 5 September 2018.

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
EEA	European Economic Area
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EU	European Union
EURD	European Union Reference Date
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
LPD	Longitudinal Patient Databases
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
QbD	Quality by Design
SD	Standard Deviation
SmPC	Summary of Product Characteristics
t <sub>½</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