COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Perindopril tosilate/Amlodipine Teva 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets (perindopril tosilate/amlodipine besilate)

NL/H/4995/001-004/DC

Date: 1 February 2022

This module reflects the scientific discussion for the approval of Perindopril tosilate/Amlodipine Teva 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets. The procedure was finalised on 29 June 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Perindopril tosilate/Amlodipine Teva 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets, from Teva B.V.

The products are indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Coveram 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets, which have been registered in France by Les Laboratoires Servier since 26 March 2008. In the Netherlands, the products have been registered since 14 May 2008 by mutual recognition procedure FR/H/0325/001-004.

The concerned member states (CMS) involved in this procedure were Belgium, Bulgaria, Czech Republic, Estonia, Croatia, Ireland, Italy, Lithuania (only for the 10 mg/5 mg and 10 mg/10 mg strengths), Latvia, Poland and Portugal.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The 5 mg/5 mg strength tablet is a white, oval, biconvex tablet, debossed “5/5” on one side and plain on the other side. Each tablet contains 5 mg perindopril tosilate equivalent to 3.408 mg perindopril converted in situ to perindopril sodium and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.

The 5 mg/10 mg strength tablet is a white, round, biconvex tablet, debossed “5/10” on one side and plain on the other side. Each tablet contains 5 mg perindopril tosilate equivalent to 3.408 mg perindopril converted in situ to perindopril sodium and 13.87 mg amlodipine besilate equivalent to 10 mg amlodipine.

The 10 mg/5 mg strength tablet is a white, oval, biconvex tablet, debossed “10/5” on one side and plain on the other side. Each tablet contains 10 mg perindopril tosilate equivalent

to 6.815 mg perindopril converted in situ to perindopril sodium and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.

The 10 mg/10 mg strength tablet is a white, round, biconvex tablet, debossed “10/10” on one side and plain on the other side. Each tablet contains 10 mg perindopril tosilate equivalent to 6.815 mg perindopril converted in situ to perindopril sodium and 13.87 mg amlodipine besilate equivalent to 10 mg amlodipine.

The tablets are packed in a white opaque PP tablet container and white opaque PE stopper with desiccant insert equipped with a tamper-evident PE flow reducer.

The excipients are: sodium hydrogen carbonate, povidone K 30, isomalt, cellulose microcrystalline, sodium starch glycolate (type A) and magnesium stearate.

II.2 Drug Substances

The active substances are perindopril tosilate and amlodipine besilate. Perindopril tosilate is not described in the European Pharmacopoeia (Ph.Eur.), but a different salt, perindopril tert-butylamine, is described. Amlodipine besilate is an established active substance described in the Ph.Eur.

II.2.1 Perindopril tosilate

Perindopril tosilate is a white to off-white powder very soluble in water, methanol, ethanol, dichloromethane and acetonitrile, freely soluble in ethyl acetate and practically insoluble in n-hexane. The substance is present in amorphous form and is hygroscopic. The perindopril tosilate corresponds to the S, S, S, S, S enantiomer.

The Active Substance Master File (ASMF) procedure is used for the active substance perindopril tosilate. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of a one-step synthesis. The amorphous form of the active substance is obtained. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The drug substance perindopril tosilate is controlled by an in-house specification. The drug substance specification of the ASMF-holder contains tests for description, identification,

specific optical rotation, water, sulphated ash, related substances, assay, content, stereochemical purity and residual solvents. The drug substance specification of the MAH contains additional requirements for particle size distribution, bulk and tapped density, and microbiological quality. Control of related substances and stereochemical purity is based on the Ph.Eur. monograph on perindopril tert-butylamine.

Batch analytical data demonstrating compliance with the drug substance specification were provided for three commercial scale batches.

Stability of drug substance

Stability data on the active substance perindopril tosilate have been provided for three commercial scale batches stored at 2 to 8°C up to 60 months and at 25°C/60% RH ((six months (three batches)), in accordance with applicable European guidelines. The batches were stored in polyethylene bags inside aluminium laminate bags containing a desiccant in a HDPE container. Apart from a slight decrease in water content, no specific trends or significant changes have been observed in the provided stability data.

Based on the data submitted, a retest period could be granted of 60 months when stored at 2-8 °C in the original storage package in order to protect from light and moisture.

II.2.2 Amlodipine besilate

Amlodipine besilate is a white or almost whiter powder, slightly soluble in water and 2-propanol, freely soluble in methanol and sparingly soluble in anhydrous ethanol.

The CEP procedure is used for the active substance amlodipine besilate. 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 Ph.Eur.

Manufacturing process

A CEP has been submitted for the active substance amlodipine besilate; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification of amlodipine besilate is in line with the Ph.Eur. and additional requirements of the CEP. Additional tests for particle size, density, and microbiological quality are included. The specification is acceptable in view of various European guidelines.

Batch analytical data demonstrating compliance with the all the drug substance specifications have been provided for three commercial scale batches.

Stability of drug substance
The assessment of stability studies was part of granting the CEP, the re-test period and storage conditions have been approved by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The products are established pharmaceutical forms and their development is adequately described in accordance with relevant European guidelines. The aim of the pharmaceutics development was to obtain immediate-release tablets containing qualitatively and quantitatively the same active substances as the innovator product. No novel or uncommon excipients have been used. The MAH has discussed all important functionality related characteristics. The MAH used a component assessment approach for the evaluation of elemental impurities and the content of elemental impurities in the final product from all the potential sources. Also other aspects (water, container closure, equipment) were considered.

The MAH adequately justified the selection of the Quality Control dissolution method. Discriminatory power is demonstrated at the proposed specification limit.

The solubility has been evaluated in the physiological pH range. The drug substance perindopril tosilate is a BCS Class III compound (high solubility and low permeability) and the drug substance amlodipine besilate is a BCS Class I (high solubility and high permeability).

For the 5/10 mg and 10/5 mg strengths, bioequivalence studies were performed. A biowaiver was requested for the 5/5 mg and 10/10 mg strengths. Both will be discussed in section IV on clinical aspects. To support the bioequivalence studies, results of *in vitro* dissolution tests at three different buffers and the media intended for drug product release are provided.

Manufacturing process
The manufacturing process consist of wet granulation, blending and compression. A flow chart and a comprehensive narrative description of the manufacturing process are provided by the MAH. The products are manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

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

Quality control of drug products
The finished products specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, dissolution, assay, impurities/degradation product and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The testing of microbiological quality is not routinely performed. Testing on the first three

production scale batches and then at least annually is proposed which is acceptable. A suitable risk evaluation concerning the presence of nitrosamine impurities in the products has been provided. Specific controls are not required.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug products

Stability data on the products have been provided for three batches of each strength stored at 25°C/60% RH (eighteen months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. No significant changes or trends have been detected in any of the tested batches. A photostability study was performed in conformity with ICH Q1B. Photostability testing reveals that the products are not photostable.

On basis of the data submitted, a shelf life was granted of 30 months. The labelled storage condition is: "Store in the original container in order to protect from light and moisture. Keep the container tightly closed".

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Perindopril tosilate/Amlodipine Teva have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Perindopril tosilate/Amlodipine Teva are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This products are generic formulations of Coveram which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Perindopril tosilate and amlodipine besilate are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profiles of the test products Perindopril tosilate/Amlodipine Teva 5 mg/10 mg and 10 mg/5 tablets (Teva B.V., The Netherlands) are compared with the pharmacokinetic profile of the reference products Coveram 5 mg/10 mg and 10 mg/5 mg (Les Laboratoires Servier, France). A biowaiver was requested for the additional 5/5 and 10/10 mg tablet strengths.

Biowaiver

The MAH requested a biowaiver for the additional 5/5 and 10/10 mg tablet strengths, which has been granted based on a bracketing approach.

According to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98Rev.1/Corr**), “Where bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition, a bracketing approach may be used. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, so that any differences in composition in the remaining strengths is covered by the two conducted studies.”

Although the four strengths are not fully dose-proportional, the biowaiver of strength for the 5/5 and 10/10 strengths are acceptable based on bracketing approach applied, where results of the strengths selected represent the extremes, so that any differences in composition in the remaining strengths is covered by the two conducted studies. Therefore, the results of the bioequivalence study with the 10/5 mg tablet can be extrapolated to the 10/10 mg tablet and the results of the bioequivalence study with the 5/10 mg tablet can be extrapolated to the 5/5 mg tablet.

Bioequivalence studies

The MAH performed two single-dose studies under fasted conditions. The choice of the reference products in the bioequivalence studies has been justified by comparison of dissolution results and compositions of test and reference products. The formula and preparation of the bioequivalence batches are identical to the formulas proposed for marketing.

According to the SmPC, the tablets should be preferably taken in the morning before a meal. As such, the fasting conditions are acceptable.

- **Study I: single dose study under fasted conditions (5/10 mg strength)**

Design

An open label, randomised, single dose, two way crossover, comparative bioequivalence study was carried out under fasted conditions in healthy male subjects, aged 19-44 years. Each subject received a single dose (1 x 5/10 mg tablet) of one of the two perindopril tosilate/amlodipine besilate formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 28 days.

For perindopril, blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, and 10.0 hours after administration.

For amlodipine, blood samples were collected pre-dose and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 24.0, 48.0 and 72.0 hours after administration.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

The pharmacokinetic variables of perindopril and amlodipine of the test and reference product are shown in table 1 and 2.

Four subjects were excluded form analyses. Two subjects did not report for period two check-in, one subject was withdrawn due to vomiting and one subject withdrew consent before being dose in period two. 38 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=38	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	142 ± 48	143 ± 48	103 ± 32	0.67 (0.33 – 1.5)	1.0 ± 0.2
Reference	140 ± 48	141 ± 48	100 ± 29	0.59 (0.33 – 1.5)	1.0 ± 0.2
***Ratio (90% CI)**	1.01 (0.98 – 1.05)	1.01 (0.98 – 1.05)	1.02 (0.95 – 1.09)	-	-
CV (%)	9.0	9.0	18.1	-	-

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

**ln-transformed values*

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

Treatment N=37	AUC_{0-72h} (*) (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	304 ± 64	7.8 ± 1.6	7.0 (5.0 – 12.0)
Reference	301 ± 66	7.5 ± 1.5	7.0 (5.0 – 12.0)
***Ratio (90% CI)**	1.02 (0.99 – 1.06)	1.06 (1.02 – 1.10)	-
CV (%)	7.5	9.8	-

$AUC_{0-\infty}$ 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
CV coefficient of variation
(*) n = 33

**ln-transformed values*

- **Study II: single dose study under fasted conditions (10/5 mg strength)**

An open label, randomised, single dose, two way crossover, comparative bioequivalence study was carried out under fasted conditions in 39 healthy male subjects, aged 21-45 years. Each subject received a single dose (1 x 10/5 mg tablet) of one of the two perindopril tosilate/amlodipine besilate formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 28 days.

For perindopril, blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, and 10.0 hours after administration.

For amlodipine, blood samples were collected pre-dose and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 24.0, 48.0 and 72.0 hours after administration.

The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
The pharmacokinetic variables of perindopril, perindoprilat and amlodipine of the test and the reference product are shown in table 3 and 4.

One subject was withdrawn from the study due to vomiting during the washout period. Another subject was withdrawn in period two due to vomiting. Two subjects withdrew consent during period two. 38 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=38	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	219 ± 76	220 ± 76	169 ± 52	0.67 (0.50 – 1.25)	1.0 ± 0.4
Reference	216 ± 65	218 ± 65	168 ± 51	0.67 (0.50 – 1.25)	1.0 ± 0.3
***Ratio (90% CI)**	1.00 (0.97 – 1.03)	1.00 (0.97 – 1.03)	1.01 (0.94 – 1.08)	-	-
CV (%)	8.3	8.3	17.7	-	-

$AUC_{0-\infty}$	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
CV	coefficient of variation

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amlodipine under fasted conditions.

Treatment N=38	**AUC_{0-72h} (*) (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	151 ± 32	3.8 ± 0.8	8.0 (5.0 – 12.0)
Reference	151 ± 29	3.7 ± 0.8	8.0 (5.0 – 12.0)
***Ratio (90% CI)**	1.02 (0.99 – 1.06)	1.04 (1.00 – 1.09)	-
CV (%)	7.8	10.8	-

AUC_{0-72}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation
(*)	n = 31

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Perindopril tosilate/Amlodipine Teva 5/10 mg and 10/5 mg tablets are considered bioequivalent with Coveram 5/10 mg and 10/5 mg tablets.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Perindopril tosilate/Amlodipine Teva.

Table 6. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Coveram. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profiles of the 5 mg/10 mg and 10 mg/5 products are similar to the pharmacokinetic profile of the respective reference product strengths. A biowaiver has been granted for the additional 5/5 and 10/10 mg tablet strengths. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

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 language used for the purpose of user testing the PL was English. The test consisted of: a pilot test with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Perindopril tosilate/Amlodipine Teva 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Coveram 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets. Coveram are well-known medicinal products with established favourable efficacy and safety profiles.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 essential similarity has been demonstrated for Perindopril tosilate/Amlodipine Teva with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 June 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4995/ 001-004/IA/001	Type B.II.b).2.1c) Change to importer, batch release arrangements and quality control testing of the finished product: Replacement or addition of a manufacturer responsible for importation and/or batch release, not including batch control/testing.	-	1 October 2021	Approved	
NL/H/4995/ /IB/002/G	Type A2.b) Change in the (invented) name of the medicinal product: for Nationally Authorised Products	-	5 November 2021	Approved	
NL/H/4995/ 1-4/IA/003	Type C.I.3.a) Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006: Implementation of wording agreed by the competent authority	SmPc, PL	1 December 2021	Approved	