COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Atorvastatine Xiromed 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets (atorvastatin calcium trihydrate)

NL/H/6661/001-004/DC

Date: 28 April 2026

This report reflects the scientific discussion for the approval of Atorvastatine Xiromed 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets. The procedure was finalised on 14 November 2016 in Denmark (DK/H/2592/001-004/DC). After a transfer on 24 March 2026, the current RMS is the Netherlands. As a result, the product name, procedure number and layout have been updated in this report. For information on other changes after the finalisation 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Atorvastatine Xiromed, film-coated tablets in the strengths 10 mg, 20 mg, 40 mg and 80 mg from Medical Valley Invest AB.

The product is indicated for:

Hypercholesterolaemia
The product is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C),LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.

The product is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Prevention of cardiovascular disease
Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

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

The active substance Atorvastatin is a synthetic lipid-lowering agent; it is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

The active substance is considered to be a well-known active substance.

This decentralised application for a marketing authorisation with Denmark as Reference Member State (RMS) and DE, ES, IS, NL, NO, SE, UK as Concerned Member States, concerns a generic application according to article 10(1) of Directive 2001/83/EC. The applicant is claiming essential similarity with the original product (brand leader) Lipitor 10 mg film-coated tablets. The reference product marketed in Denmark is Zarator film-coated tablets registered since 1997. The brand leader product (also known as Sortis and other associated names) with Pfizer as marketing authorisation holder is authorised via the MR procedure DE/H/0109/001-004/MR.

The applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Sortis (80 mg film-coated tablets), registered in Germany.

This generic product can be used instead of its reference product.

II. QUALITY ASPECTS

II.1 Introduction

The film-coated tablets are presented in the strengths 10, 20, 40 or 80 mg. Each tablet contains atorvastatin calcium trihydrate to obtain a quantity corresponding to the declared amount atorvastatin (free base). The tablets are round, biconvex, film-coated tablets with bisection line on one side and debossed 10, 20, 40 or 80.

Atorvastatine Xiromed is approved to be packed in two different blister presentations:

PVC-TE layer-PVdC/Hard aluminium foil blister strips (the TE (thermoelastic) layer is an aqueous polyurethane dispersion connecting the PVC and PVDC foils in a single foil).
Pack sizes: 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 90, 98 and 100 film-coated tablets.

Or

Oriented PVC / aluminium foil blister.
Pack sizes: 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 90, 98 and 100 film-coated tablets.

However, not all pack-sizes may be marketed.

Excipients:
The excipients in the tablet core are:
Lactose monohydrate, microcrystalline cellulose (E460), calcium carbonate (E170), copovidone, crospovidone type B, croscarmellose sodium, sodium laurilsulfate, silica (colloidal anhydrous), talc and magnesium stearate.

The coating contains: Hypromellose (E464), titanium dioxide (E171) and macrogol (400).

Compliance wih Good Manufacturing Practice
The RMS 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 manufacture and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The CEP procedure is used for the active substance atorvastatin calcium trihydrate.
Stability of drug substance
An appropriate re-test period when stored in double polyethylene bags in a triple laminated polybag, placed in a polyethylene container has been set.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented.

Quality control of drug product
Batch analysis has been performed on 3 batches from each manufacturing site. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

Atorvastatine Xiromed film-coated tablets are packed in PVC/thermoeleastic layer (polyurethane)/PVdC hard - aluminium foil blisters or oriented polyamide/aluminium/PVC - aluminium foil blisters.

The proposed shelf-life/storage condition: 36 month, do not store above 30°C.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since the product Atorvastatine Xiromed is 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

Pharmacodynamic, pharmacokinetic and toxicological properties of atorvastatin calcium trihydrate are well known. As atorvastatin calcium trihydrate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview reports refers 130 publications up to year 2013.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Atorvastatin calcium is a well-known active substance with established efficacy and tolerability.

As atorvastatin calcium is a widely used, well-known active substance, the applicant has not provided additional studies (apart from a supportive bioequivalence study referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical report refers 228 publications up to year 2014. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Atorvastatine Xiromed, 80 mg is compared with the pharmacokinetic profile of the reference product Sortis (also know as Lipitor and Zarator) from Parke-Davis GmbH/Pfizer Pharma GmbH (80 mg film-coated tablets), registered in Germany.

The application concerns the strengths 10, 20, 40 and 80 mg. The bioequivalence study was carried out with the 80 mg strength and biowaiver is applied for the remaining 10, 20 and 40 mg strengths. The conditions for biowaiver are considered fulfilled.

Bioequivalence study

The study was an open-label, randomized, two-treatment, two-sequence, three-period crossover, reference-replicate, single-dose bioavailability study conducted under fasting conditions with a wash out period of 14 days between each of the three administrations. One film-coated tablet of 80 mg was administered in each period.
45 healthy Caucasian male subjects (19-49 years) participated in the study. 44 subjects completed all three periods of the study and were included in the pharmacokinetic and statistical analysis (one drop-out for personal reasons).

The chosen primary and secondary variables:
The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, residual area, t_{max}, K_{el} and $t_{½\ el}$.
Primary variables: AUC_{0-t} and C_{max}

Statistical methods – criteria for conclusion of bioequivalence:

ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
The ANOVA model included sequence, period and treatment as fixed effects and subject nested within sequence as random effect.
Nonparametric test (Wilcoxon's Signed-Rank test) was carried out on t_{max}.

The geometric mean ratio (GMR) should lie within the conventional acceptance range 80.00-125.00%. If the within-subject coefficients of variation of the reference product (CV_{WR}) is ≤ 30%, 90% geometric confidence intervals of the ratio (A/B) of least-squares means from the mixed model analysis of the ln-transformed AUC_{0-t} and C_{max} should be within 80.00% to 125.00%.

Results

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

A randomised, single-dose, three-period, crossover reference-replicate bioavailability study to compare the pharmacokinetics of the test product Atorvastatin 80 mg film-coated tablets (Alkaloid –INT.d.o.o) versus the reference product Sortis 80 mg film-coated tablets (Parke-Davis GmbH/Pfizer Pharma GmbH) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 80 mg tablet administered after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The washout period between treatment periods was at least 14 days.

The pharmacokinetic results for atorvastatin are presented below [mean, standard deviation (SD) and % confidence intervals):

					Reference (SORTIS® (B))					
		Test (ATORVASTATIN (A))			First Administration			Second Administration		
Parameters		Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC_{0-t}	(pg·h/mL)	186343.54	85903.74	46.10	192476.44	90406.55	46.97	182585.52	76768.26	42.05
AUC_{0-inf}	(pg·h/mL)	190600.14	86941.22	45.61	196911.71	91799.05	46.62	187453.46	79177.19	42.24
C_{max}	(pg/mL)	45044.57	28458.05	63.18	49334.61	31603.85	64.06	47713.06	22042.75	46.20
Residual area	(%)	2.41	2.33	96.81	2.44	1.86	76.14	2.51	1.61	63.91
T_{max}	(h)	1.30	0.92	70.84	0.962	0.593	61.68	0.974	0.802	82.39
T_{max}*	(h)	1.00	1.12	-	0.667	0.750	-	0.667	0.563	-
K_{el}	(h^{-1})	0.0738	0.0128	17.37	0.0717	0.0107	14.95	0.0718	0.0121	16.81
$T_{½ el}$	(h)	9.75	2.22	22.77	9.93	1.93	19.40	9.97	1.97	19.81

* Medians and interquartile ranges are presented.

AUC_{0-inf}	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
Tmax	time at which peak concentration is achieved
K_{el}	% of the total amount of drug in body eliminated per unit of time
$T_{½el}$	elimination half life

The treatment comparisons for atorvastatin are presented below: (ratio of least-squares means, 90% Confidence Interval):

Statistical Analysis	Ratio of LS Means [1]	90 % Geometric C.I. [2]		CV_{WR}
		Lower	Upper	
AUC_{0-t}	98.89%	93.80%	104.26%	17.09%
AUC_{0-inf}	98.83%	93.87%	104.06%	16.66%
C_{max}	92.70%	82.42%	104.28%	34.06%

[1] Calculated using least-squares means (ln-transformed data)

[2] 90% Geometric Confidence Interval using ln-transformed data

AUC_{0-inf}	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
CV_{WR}	within-subject variability

The 90% confidence intervals for AUC and C_{max} for test versus reference product for atorvastatin are within predefined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 10 mg, 20 mg and 40 mg and 80 mg strengths of the product meet the criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 80 mg strength can be extrapolated to the 10 mg, 20 mg and 40 mg strengths.

Pharmacokinetic conclusion

Bioequivalence studies:
Based on the submitted bioequivalence study, bioequivalence between the test product Atorvastatine Xiromed and the reference product Sortis is considered demonstrated (under fasting conditions) and therefore, bioequivalent.

Biowaiver:
The results of study (100283) with 80 mg formulation can be extrapolated to other strengths (10, 20 and 40 mg), according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.
The justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

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 Atorvastatine Xiromed.

The following summary list of safety concerns has been agreed with no additional pharmacovigilance measures:

Table 1

Summary of safety concerns	
Important identified risks	• Hepatotoxicity (increased transaminases, hepatitis, jaundice) • Haemorrhagic stroke • Rhabdomyolysis, myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia • Interaction with CYP3A4 inhibitors / OATP1B1 inhibitors • Diabetes mellitus • Severe skin reactions • Interstitial lung disease
Important potential risks	• Use during pregnancy and breastfeeding
Missing information	• Use in paediatric patients <10 years of age

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The test was conducted through one-to-one structured interviews with a Test Administrator. The test consisted of a pilot round with 4 participants, followed by two rounds with 10 participants each. The target demographic group was men and women (well-chosen regarding gender, education and age) who could imagine having to receive a medicine for the treatment of hypercholesterolaemia and prevention of cardiovascular diseases. The questions covered the following areas: traceability, comprehensibility and applicability; 17 questions specific to atorvastatin and 3 specific to the format of the package leaflet and 1 question re the overall impression of the PL.

The results show that the package leaflet 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

Atorvastatine Xiromed, film-coated tablets in the strengths 10 mg, 20 mg, 40 mg and 80 mg from Medical Valley Invest AB has a proven chemical-pharmaceutical quality and is a generic form of Sortis. Sortis (and other associated names) is a well-known medicinal product with an established favourable efficacy and safety profile.

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

The MAH presented a risk management plan summarising the safety concerns. There are no additional pharmacovigilance or risk minimisation measures.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Atorvastatine Xiromed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 14 November, 2016.

Atorvastatine Xiromed was authorised in Denmark on 14 November, 2016

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), no routine PSURs are required for this product.

The date for the first renewal will be: 14 November, 2021.

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

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
DK/H/2592/001-4/IB/001/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Primary packaging site	No	12-7-2017	Approved	N.A.
	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place	No			
	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.	No			
	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the	No			

	finished product - Secondary packaging site 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 - Including batch control/testing	 Yes			
DK/H/2592/001-4/IB/002/G	Change in the (invented) name of the medicinal product - for Nationally Authorised products Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use - Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	Yes No	8-9-2017	Approved	N.A.
DK/H/2592/001-4/IB/003	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active	No	8-12-2017	Approved	N.A.

	substance, For a starting material/reagent/ intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)				
DK/H/2592/001-4/IA/004	Change in the shape or dimensions of the pharmaceutical form - Immediate release tablets, capsules, suppositories and pessaries	Yes	7-2-2018	Approved	N.A.
DK/H/2592/001-4/IA/007	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	Yes	17-3-2018	Approved	N.A.
DK/H/2592/001-4/IB/006/G	Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use - Introduction of a	No	4-4-2018	Approved	N.A.

	summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location Change in the (invented) name of the medicinal product - for Nationally Authorised products	 Yes			
DK/H/2592/IB/005	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/ biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	12-7-2018	Approved	N.A.
DK/H/2592/001-4/IA/008	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	Yes	6-11-2018	Approved	N.A.

	Articles 45 or 46 of Regulation 1901/2006SmPCS mPC - Implementation of wording agreed by the competent authority				
DK/H/2592/001-4/IA/009/G	Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Minor change in the manufacturing process. Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	No No Yes	28-11-2018	Approved	N.A.
DK/H/2592/001-4/IA/011/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/ intermediate used in the	No	15-3-2019	Approved	N.A.

	manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
DK/H/2592/001-4/IB/012	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 1901/2006SmPCS mPC - Other variation	Yes	17-4-2019	Approved	N.A.
DK/H/2592/001-4/IB/010/G	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Other variation Change in the shelf-life or storage conditions of the finished product - Change in storage conditions of the finished	No Yes	24-4-2019	Approved	N.A.

	product or the diluted/ reconstituted product				
DK/H/2592/001-4/IB/013	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 1901/2006SmPCS mPC - Other variation	Yes	23-5-2019	Approved	N.A.
DK/H/2592/001/IA/014	Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	No	21-6-2019	Approved	N.A.
DK/H/2592/001-4/IB/015	Changes in the manufacturing process of the active substance - Minor change to the restricted part of an Active Substance Master File.	No	21-8-2019	Approved	N.A.
DK/H/2592/001-4/IA/016	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure	Yes	11-10-2019	Approved	N.A.

	concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCS mPC - Implementation of wording agreed by the competent authority				
DK/H/2592/001-4/IA/017	Change in the name and/or address of the marketing authorisation holder	Yes	2-12-2019	Approved	N.A.
DK/H/2592/001-4/IA/018	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/ intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	No	29-7-2020	Approved	N.A.
DK/H/2592/001-4/IB/020/G	Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use	No	10-1-2021	Approved	N.A.

	- Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location Change in the (invented) name of the medicinal product - for Nationally Authorised products	 Yes			
DK/H/2592/001-4/IA/021/G	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)). Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place Submission of a new or updated Ph. Eur. certificate	Yes No No	11-6-2021	Approved	N.A.

	of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/ intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
DK/H/2592/001-4/IA/022	Change in the shape or dimensions of the pharmaceutical form - Immediate release tablets, capsules, suppositories and pessaries	No	29-7-2021	Approved	N.A.
DK/H/2592/001-4/IA/024	Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	No	15-8-2021	Approved	N.A.
DK/H/2592/001-4/IB/019	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/ biosimilar medicinal products following assessment of the same change for	Yes	22-9-2021	Approved	N.A.

	the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH				
DK/H/2592/001-4/IB/023	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/ intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	No	7-11-2021	Approved	N.A.
DK/H/2592/001-4/R/001	Renewal	No	17-12-2021	Approved	N.A.
DK/H/2592/001-4/IA/028	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/ intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial	No	8-5-2022	Approved	N.A.

	Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer				
DK/H/2592/001-4/IB/025	Change in the re-test period/ storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier. - Re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	No	2-6-2022	Approved	N.A.
DK/H/2592/001-4/IB/026	Change in immediate packaging of the finished product - Change in type of container or addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms	Yes	2-6-2022	Approved	N.A.
DK/H/2592/001-4/IA/029/G	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place	No	5-10-2022	Approved	N.A.

	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/ intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
DK/H/2592/001-4/IA/031	Change in test procedure for the finished product - Minor changes to an approved test procedure	No	19-2-2023	Approved	N.A.
DK/H/2592/001-4/IA/033	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/ intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph	No	30-4-2023	Approved	N.A.

	- Updated certificate from an already approved manufacturer				
DK/H/2592/001-4/IA/032	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation	Yes	24-5-2023	Approved	N.A.
DK/H/2592/001-4/IA/034/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Secondary packaging site - Primary packaging site	No	2-7-2023	Approved	N.A.
DK/H/2592/001-4/IB/027	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan - Other variation: RMP update.	No	5-10-2023	Approved	N.A.
DK/H/2592/001-4/IA/035	Change in the shape or dimensions of the pharmaceutical form - Immediate release tablets, capsules, suppositories and pessaries	Yes	1-2-2024	Approved	N.A.
DK/H/2592/001-4/IB/030	Change in the re-test period/ storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier. - Re-test	No	8-2-2024	Approved	N.A.

	period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
DK/H/2592/001-4/IA/036/G	Change in test procedure for the finished product - Minor changes to an approved test procedure Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/ intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	No	15-3-2024	Approved	N.A.
DK/H/2592/001-4/IA/038	Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition, deletion or replacement	Yes	3-6-2024	Approved	N.A.
DK/H/2592/001-4/IB/037	Change in the manufacturing process of the	No	20-9-2024	Refused	Unavailable

	finished product, including an intermediate used in the manufacture of the finished product - Other variation				
DK/H/2592/001-4/IA/039	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 1901/2006SmPCS mPC - Implementation of wording agreed by the competent authority	Yes	13-11-2024	Approved	N.A.
DK/H/2592/001-4/IA/041/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph	No	12-6-2025	Approved	N.A.

	- Deletion of certificates (in case multiple certificates exist per material) - Updated certificate from an already approved manufacturer				
DK/H/2592/001-4/WS/042	Changes in the composition (excipients) of the finished product - Other excipients - Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level	Yes	15-10-2025	Approved	N.A.
DK/H/2592/001-4/IA/043/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/ intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	No	28-10-2025	Approved	N.A.
DK/H/2592/001-4/II/040	Changes in the composition (excipients) of the finished product - Other excipients - Qualitative or quantitative	Yes	27-11-2025	Approved	N.A.

	changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product.				