COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fentanyl Sandoz 100, 200, 300, 400, 600 and 800 microgram, sublingual tablets (fentanyl citrate)

NL/H/4557/001-006/DC

Date: 25 May 2023

This module reflects the scientific discussion for the approval of Fentanyl Sandoz 100, 200, 300, 400, 600 and 800 microgram, sublingual tablets. The procedure was finalised on 20 October 2019. 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
CQAs	Critical Quality Attributes
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
FRCs	Functional-related characteristics
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PASS	Post-authorisation safety studies
PSURs	Periodic safety update reports
PDE	Permitted Daily Exposure
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
µg	Microgram

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fentanyl Sandoz 100, 200, 300, 400, 600 and 800 microgram, sublingual tablets, from Sandoz B.V.

The product is indicated for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain. Breakthrough pain is a transient exacerbation of otherwise controlled chronic background pain.

The active substance of this product is fentanyl (as citrate) and belongs to the pharmaco-therapeutic group of Analgesics; Opioids; Phenylpiperidine derivatives. Fentanyl is a potent μ-opioid analgesic with rapid onset of analgesia and short duration of action. Fentanyl is approximately 100-fold more potent than morphine as an analgesic. Special precautions for disposal and other handling include: Waste material should be disposed of safely. Patients/carers should be encouraged to return any unused product to the Pharmacy, where it should be disposed of in accordance with national and local requirements.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Abstral sublingual tablets (SE/H/0575/001-007; 50, 100, 200, 300, 400, 600 and 800 microgram) which has been registered in Sweden by Kyowa Kirin Limited since 29 February 2008 (original product). In the Netherlands, Abstral (100 – 800 microgram) has been registered since 2011 by the procedure RVG 108843-8.

The concerned member states (CMS) involved in this procedure were France, Germany, Greece, Italy.

II. QUALITY ASPECTS

II.1 Introduction

Fentanyl Sandoz are sublingual tablets, administered directly under the tongue at the deepest part, and contain as active substance fentanyl citrate. The sublingual tablets of the different strengths can be distinguished by different shapes and are as follows:

- The 100 microgram strength are white, round tablets.
- The 200 microgram strength are white, oval-shaped tablets.
- The 300 microgram strength are white, triangle-shaped tablets.
- The 400 microgram strength are white, diamond-shaped tablets.
- The 600 microgram strength are white, D-shaped tablets.
- The 800 microgram strength are white, capsule-shaped tablets.

The excipients are: mannitol (E 421), microcrystalline silicified cellulose, sodium croscarmellose and magnesium stearate.

The 300, 400, 600 and 800 µg (microgram) sublingual tablets are dose/weight proportional. The 100, 200 and 300 µg strengths have similar quantitative composition of excipients and the same tablet core weight and therefore, the composition of these strengths is not quantitatively proportional.

The sublingual tablets are packed in child-resistant perforated unit-dose blisters of PA/AL/PVC//AL/PET (Polyamide Aluminum/Polyvinyl chloride/Aluminum/Polyethylene terephthalate) and enclosed in a cardboard box.

II.2 Drug Substance

The active substance is fentanyl citrate, is an established active substance described in the European Pharmacopoeia (Ph.Eur.). Fentanyl citrate is a white or almost white powder which is soluble in water, freely soluble in methanol, sparingly soluble in ethanol (96%) and very slightly soluble in methylene chloride. It presents no chirality or polymorphism. The manufacturer consistently produced the same crystalline form. Taking into account that the pharmaceutical form is a sublingual tablet with a very low content of active substance and dissolves within a few minutes, the crystalline form rapidly disappears. Therefore, no impact on the quality of the finished product is expected and the polymorphic form has not been included in the specification of the finished product. This is acceptable.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the 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; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Additionally, the particle size of the drug substance is controlled. The limits for the particle size test are justified based on the active substance batch used in the bio-batch. The proposed specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three commercial batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The composition, strengths, posology and method of administration are in line with the reference product. Formulation studies during development have identified critical Functional-related characteristics (FRCs) such as the particle size of mannitol and microcrystalline silicified cellulose. The formulations of the product are developed based on: the initial risk evaluation of the impact of the drug substance characteristics, the formulation composition and the manufacturing process on the identified Critical Quality Attributes (CQAs). Overall, the formulation development studies were carried out adequately and addressed the identified high risks in the initial risk assessment. An updated risk assessment was provided to justify how these high risks were mitigated.

Manufacturing process
The sublingual tablets are manufactured by direct compression with a series of steps of sieving and mixing of excipients, followed by compression. In-process controls test methods, limits, frequency of testing and number of units tested per parameter have been described for the final blend, uncoated tablets and the blister packed tablets. All six tablet strengths contain <2% of active substance (approximately 0.32%). Therefore, the manufacture of the finished product is considered as non-standard and production-scale validation data is provided. The validation covered all manufactured strengths for production of the marketed product. However, a bracketing approach was used for the dose-proportional strengths of 300, 400, 600 and 800 µg sublingual tablets. This is acceptable. The validation data demonstrates that the manufacturing process of all strengths consistently produces a finished product that meets all in-process and finished product specifications.

Control of excipients

The choice of excipients is similar to reference product. Brief descriptions of the functions of all excipients are provided. All the excipients used are well-known pharmaceutical ingredients that comply with the requirements of the Ph. Eur. except for microcrystalline silicified cellulose which complies with the USP requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, uniformity of dosage units, degradation products (including impurity A, any unknown degradation product and total degradation products), assay, disintegration and microbial purity. The release and shelf-life limits are identical except for impurity A and total degradation products. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The risk assessment for elemental impurities provided is acceptable according to ICH Q3D. In addition, batch analysis data has been provided showing levels of elemental impurities below 30% of Permitted Daily Exposure (PDE) established by ICH.

Satisfactory validation data for non-compendial analytical methods have been provided.

Batch analytical data (from three batches of strengths 100, 200, 300 and 800 µg and one batch of 400 and 600 µg) from the proposed production site have been provided, demonstrating compliance with the specification. The batches tested are the same used for process validation, bioequivalence study (300 µg strength) and for stability studies.

Stability of drug product

Stability data on the product have been provided, two batches per strength stored at 25°C/ 60% RH (12 months) one batch per strength stored at 30°C/ 60% RH (6 months) and three batches per strength stored at 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations. The results indicate that there were no out of specification results for the parameters tested in samples directly exposed. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: “Do not store above 25°C. Store in the original package in order to protect from moisture”.

Stability was also tested for the bulk product, two batches were stored for 12 months at long term conditions and one batch for 6 months at long-term conditions. All results are within specification limits and no specific trends were observed. The proposed holding time of 6 months for the bulk product stored at the proposed conditions and packaging is acceptable.

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 Fentanyl Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Fentanyl Sandoz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Abstral which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Fentanyl citrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Fentanyl Sandoz, sublingual tablets Sandoz B.V. was compared with the pharmacokinetic profile of the reference product Abstral (Kyowa Kirin Limited, Sweden). The bioequivalence study was performed with the 300 µg strength of the test and reference product. A bio-waiver was requested for the other strengths based on *In vitro* dissolution data. The choice of the reference product in the bioequivalence study has been justified by

comparison of the dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing. The batches used for the additional strengths are the production scale batches also used for validation and stability studies.

Biowaiver

The dissolution studies were performed according to the Guideline On The Investigation Of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1, with the following general requirements for the test and reference products:

- The pharmaceutical products are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same:

  there was some deviation regarding this criterium; however, according the guideline this condition is still considered fulfilled based on the fact that the amount of the active substance is less than 5 % of the tablet core weight, the weight of the capsule content. For this product, the 100 and 200 µg strengths are dose proportional based upon the 5% rule with the 300 µg strength used in the bioequivalence study. The 400, 600 and 800 µg strengths are (normal) dose proportional with the 300 µg strength.
- The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule).
- Appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing.

The dissolution tests at pH 1.2, 4.5 and 6.8 show that more than 85% of the active is released within 5 minutes for the 300 µg bio-batch strength and the additional strengths of the test product. Therefore, the profiles can be considered as similar. All other conditions for the biowaiver criteria are met.

Bioequivalence study, fasted conditions

Design

A open label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male and female subjects, aged 18-46 years. Each subject received a single dose (300 µg) of one of the two fentanyl citrate formulations. The sublingual tablet was orally administered after fasting for at least 10 hours. The subjects wet the mouth with 20 mL water before placing the table under the tongue, at the deepest part, and allowed it to dissolve completely in the sublingual cavity without chewing or sucking. Fluid intake was not allowed one hour before

and until three hours after drug administration. Food intake was not allowed for at least 5 hours post-dose.

There were two dosing periods, separated by a washout period of 7 days. During each treatment period, subjects received a total of three oral doses of naltrexone 50 mg (an opioid antagonist, reverses an opioid overdose) at the following time points:

- Day 0; in the evening, approximately 12 hours before study medication administration.
- Day 1; approximately 30 minutes before study medication administration.
- Day 1; 12 hours after administration.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24 and 32 hours after administration of the products.

According to the SmPC, patients should be advised not to eat or drink anything until the sublingual tablet is completely dissolved. As such, the fasting condition applied in the study is considered adequate. Wetting the mouth before placing the tablet is acceptable. Fentanyl is a potent μ-opioid analgesic and it is approximately 100-fold more potent than morphine as an analgesic. For safety reasons, the tablet strength of 300 μg (instead of the highest strength of 800 μg) was used in the bioequivalence study, which is acceptable, as fentanyl shows linear pharmacokinetics. Furthermore, the antagonist naltrexone was used. Overall, 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 36 subjects that participated in the study completed both periods and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of fentanyl 300 μg, under fasted conditions.

Treatment N=36	**AUC_{0-t}** (pg.h/mL)	**$AUC_{0-\infty}$** (pg.h/mL)	**C_{max}** (pg/mL)	**t_{max}** (h)
Test	3358 ± 1631	4058 ± 2356	641 ± 209	1.0 (0.33 – 2.5)
Reference	3399 ± 1658	3982 ± 2202	664 ± 213	1.0 (0.33 – 2.0)
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	-	0.97 0.90 - 1.05	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t=32 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC0-t, AUC0-∞ and Cmax are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Fentanyl Sandoz 300 µg is considered bioequivalent with Abstral 300 µg. Furthermore, the results of the bioequivalence studies with the 300 µg formulation can be extrapolated to the other Fentanyl Sandoz strengths, 100, 200, 400, 600 and 800 µg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr, section 4.1.6.

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 Fentanyl Sandoz.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Respiratory depression • Local tolerability • Misuse • Medication errors • Drug dependence • Drug abuse • Off-label use • Drug diversion • Overdose
Important potential risks	• Brain lesion • Cardiovascular depression • Accidental exposure • Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs
Missing information	• Use in children and adolescents • Use in fertility, pregnancy and lactation • Use in patients with cardiac, renal or hepatic impairment • Long-term use

At the time of approval of this product, it was considered that additional risk minimisation measures (including educational material) were necessary for the safe and effective use of the product. The educational material should be submitted by the MAH to the competent authorities of the Member States and its content and implementation should be agreed with the competent authorities prior to launch.

The educational material should contain the following key elements:

- Information about background pain in cancer patients
  - medication
- Information about breakthrough pain in cancer patients
  - definition, diagnosis and treatment
- Introduction to the product
  - product overview, selection of patients and way of administration
- Titration
  - need, dose, maintenance treatment, switch of medication, referral patients
- Important consideration
  - important adverse reactions (including respiratory depression)
- Guidelines for patients and carers
  - correct administration of medication and treatment adherence (with special attention for serotonin syndrome), monitoring efficacy and adverse reactions, actions taken in case of accidental overdose, misuse and abuse, pharmacovigilance, safe handling and more information).

To inform patients/carers about the Fentanyl Sandoz sublingual tablets, the patients guide should contain the following key-elements, which should replace the key-elements as currently proposed by applicant:

- Breakthrough cancer pain
- Information about the fentanyl sublingual formulation (including contraindications)
- Initiation and administration of the product
- Correct and safe use of the product and therapy adherence
- Special precautions for safe storage and disposal
- Important adverse reactions, including:
  - Respiratory depression
  - Overdose
  - Risk of misuse and dependence
  - Accidental exposure
- Which actions to take in case of adverse reactions.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Abstral. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to reference product Abstral. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fentanyl Sandoz 100, 200, 300, 400, 600 and 800 microgram, sublingual tablets has a proven chemical-pharmaceutical quality and is a generic form of Abstral sublingual tablets. Abstral 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 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 Fentanyl Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 October 2019.

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/4557/ IB/001/G (100-800 µg)	- Change in the (invented) name of the medicinal product ○ For Nationally Authorised Products. - 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 Nee	20-03-2020	Approved	N/A
NL/H/4557/ 1-6/IA/002 (100-800 µg)	- 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 1901/2006SmPCSmPC. ○ Implementation of wording agreed by the competent authority.	Yes	08-06-2020	Approved	N/A
NL/H/4557/ 1-6/IB/003 (100-800 µg)	- Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar. ○ Implementation of change(s) for which no new additional data are submitted by the MAH.	Yes	19-06-2020	Approved	N/A
NL/H/4557/ IA/004/G (100-800 µg)	- Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. ○ Secondary packaging site.	No	13-07-2020	Approved	N/A

	- 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			
NL/H/4557/ IA/006/G (100-800 µg)	- Change in pack size of the finished product. ○ Change in the number of units (e.g. tablets, ampoules, etc.) in a pack. Change within the range of the currently approved pack sizes.	Yes	02-09-2020	Approved	N/A
NL/H/4557/ 1-6/IB/005 (100-800 µg)	- Change in the (invented) name of the medicinal product ○ For Nationally Authorised Products.	Yes	25-09-2020	Approved	N/A
NL/H/4557/ IA/007/G (100-800 µg)	- Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. ○ Secondary packaging site. - Change in immediate packaging of the finished product. ○ Qualitative and quantitative composition. Solid pharmaceutical forms.	No Yes	26-01-2021	Approved	N/A
NL/H/4557/ 1-6/P/001 (100-800 µg)	- To amend the route of administration on the outer packaging to 'Sublingual use', in line with the SmPC. ○ Changes in section 5 of the labelling.	Yes	26-01-2021	Approved	N/A
NL/H/4557/ 1-6/ IA/007/G	- Change in immediate packaging of the finished product.	Yes	26-01-2021	Approved	N/A

(600-800 µg)	○ Qualitative and quantitative composition. Solid pharmaceutical forms				
NL/H/4557/ 5-6/IB/008 (600-800 µg)	- Change in pack size of the finished product. ○ Change in the number of units (e.g. tablets, ampoules, etc.) in a pack. Change outside the range of the currently approved pack sizes.	Yes	02-06-2021	Approved	N/A
NL/H/4557/ 1-6/IA/010 (100-800 µg)	- 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 1901/2006SmPCSmPC. ○ Implementation of wording agreed by the competent authority.	Yes	29-07-2021	Approved	N/A
NL/H/4557/ 1-6/IB/011 (100-800 µg)	- 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	20-10-2021	Approved	N/A
NL/H/4557/ 1-6/IB/013 (100-800 µg)	- Change in the shelf-life or storage conditions of the finished product. ○ Change in storage conditions of the finished product or the	Yes	12-11-2021	Approved	N/A

	diluted/reconstituted product.				
DE/H/xxxx/IA/1233/G (100-800 µg)	- Change in the name and/or address of the marketing authorisation holder.	Yes	29-03-2022	Approved	N/A
NL/H/4557/1-6/IB/015 (100-800 µg)	- 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 1901/2006SmPCSmPC. o Other variation (to align SPC and PIL in accordance with PSUSA/00001370/202104).	Yes	19-05-2022	Approved	N/A
NL/H/xxxx/WS/543 (100-800 µg)	- Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan. o Other variation.	No	01-07-2022	Approved	N/A
NL/H/4557/1-6/IB/009 (100-800 µg)	- 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 SmPC. o Other variation.	Yes	21-07-2022	Approved	N/A