COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nurofen Retard 300 mg prolonged-release tablets (ibuprofen)

NL/H/5350/001/DC

Date: 27 May 2026

This module reflects the scientific discussion for the approval of Nurofen Retard 300 mg prolonged-release tablets. The procedure was finalised on 11 April 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AEs	Adverse Events
ASMF	Active Substance Master File
BA	Bioavailability
b.i.d.	Bis in die, twice daily administration
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
IR	Immediate release
MAH	Marketing Authorisation Holder
MEC	Minimum effective concentration
PDE	Permitted Daily Exposure
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PR	Prolonged-Release
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
t.i.d.	Three times a day
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 Nurofen Retard 300 mg prolonged-release tablets, from Reckitt Benckiser Healthcare B.V.

The product is indicated in adults only, for the short-term treatment of mild to moderate pain expected to last longer than 6-8 hours, such as backache, muscular pain, joint pain, period pain and dental pain.

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(3) of Directive 2001/83/EC, which concerns a hybrid application.

This decentralised procedure concerns a hybrid application using as reference the innovator product Nurofen 200 mg coated tablets (NL RVG 10674), which has been registered in the Netherlands through a national procedure by Reckitt Benckiser Healthcare B.V since 24 January 1985. The current product differs from the reference product in strength (ibuprofen 300 mg instead of 200 mg) and in pharmaceutical form (prolonged release tablet instead of immediate release film coated tablet). Because of the distinctive drug-release profile of this new PR tablet formulation, bioavailability (BA) studies cannot be used to demonstrate bioequivalence with the reference product. To investigate relative bioavailability two pivotal studies have been submitted, a single dose trial and a multiple dose trial where the new product is compared to the reference. In addition, three supportive BA studies were provided. To support the efficacy, one pivotal study and one supportive study have been submitted.

The formulation is based on modified matrix technologies resulting in a simple monolithic tablet that releases ibuprofen in a bi-modal fashion via a combination of diffusion and erosion. The release rate of ibuprofen is controlled via the interaction of the tableting excipients with the available water in the digestive tract.

The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia, Czechia, Denmark, Finland, Greece, Hungary, Iceland, Ireland, Italy, Norway, Poland, Portugal, Romania, Slovakia, Slovenia and Sweden.

For this application, formal scientific advice was given by the CMS Ireland (Health Products Regulatory Authority (HPRA) in 2017 and by the RMS the Netherlands (Medicines Evaluation Board (MEB)) in 2018.

For this medicine product an over-the-counter (Pharmacies Only ‘UA’) status has been granted.

II. QUALITY ASPECTS

II.1 Introduction

Nurofen Retard 300 mg is a white to off-white capsule-shaped, prolonged-release tablet, debossed with 'N12' on one side and plain on the other side. Each tablet contains as active substance 300 mg ibuprofen.

The excipients are:
Core - hypromellose (E464), microcrystalline cellulose (E460), silica, colloidal hydrated (E551), croscarmellose sodium (E468), glycine (E640) and stearic acid (E570).
Coating - hypromellose (E464), titanium dioxide (E171), macrogol and polysorbate 80 (E433).
Polishing - carnauba wax (E903).

The prolonged-release tablets are packed in blister-packs comprised of polyvinyl chloride/aluminium /polyamide (PVC/Alu/PA) with aluminium foil lidding. The blisters are packed in an outer carton.

II.2 Drug Substance

The active substance is ibuprofen, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder or colourless crystals and is practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates. The molecule is optically active and is supplied as a racemic mixture. However, there are no stereochemical or polymorphic concerns. As it is well known that ibuprofen does not display multiple stable polymorphic forms, it is acceptable that no test for the polymorphic form is performed.

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.

<u>Manufacturing process</u>
A CEP has been submitted; therefore no details on the manufacturing process have been included.

<u>Quality control of drug substance</u>
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements tests for residual solvents and particle size distribution as stated in de CEP. The specification is

acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

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

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 choice of excipients is justified and their functions explained. The drug substance particle size limit is justified based on dissolution data. A suitable QC dissolution method has been developed. However, no comparative dissolution data was required because it concerns a hybrid application for a prolonged release tablet with an immediate release tablet as reference. Nonetheless, comparative dissolution data of the 600 mg and 300 mg strength at pH 1.2, 4.5, 6.8 and 7.2 of media have been submitted. The dissolution profiles of the two strengths in multimedia are comparable. The pharmaceutical development of the product has been adequately performed.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1, section 6.9), for generic oral formulations, *in vitro* studies of the release in alcohol solutions should be performed. Alcohol induced dose dumping has been investigated for this product. For this, dissolution tests in 0.1N HCl with 0, 5, 10, 20 and 40% (v/v) alcohol were performed, the drug release in the different media was measured every 15 minutes between 0 and 120 minutes. The data presented is according to the guidelines (the QC release method is employed). EMA/CPMP/EWP/280/96 Corr1. The *in vitro* data show that 40% alcohol increases the release of ibuprofen by about 24% after 2 hours. For *in vivo*, this possible 24% increase in release at a 40% alcohol concentration is considered not clinically relevant. Furthermore, because the reference product is an immediate release dosage form, no comparison with the reference product is required.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scaled and three full scaled batches.

Control of excipients
The excipients comply with compendial Ph.Eur. or in-house specifications. The 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 description, uniformity of dosage units (mass

variation), water content, dissolution, primary and secondary identification, assay, related substances (identified, unidentified and total impurities) and microbiological quality. The release and shelf-life limits are identical and acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified. Furthermore, an elemental impurities assessment has been performed according to ICH Q3D option 2b, whereby the concentrations of each Class 1 and 2A element is based on vendor declarations. The sums of all these elements are below the control threshold of 30% of their Permitted Daily Exposure (PDE) and therefore no specific controls are required.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three pilot scaled and three full scaled batches, from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three pilot scaled and three full scaled batches stored at 25°C/ 60% RH (24 months), 30°C/65%RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. The results under accelerated conditions (6 months at 40°C/75%RH) show that the dissolution limits were not met. Therefore, stability was also tested under intermediate conditions. The stability results under intermediate and long term conditions show no changes for any of the tested stability indicating parameters. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. Based on the data submitted (including variation data NL/H/5350/001/IB/006), a shelf life was granted of 3 years. The labelled storage conditions are: 'Store below 30°C. Store in the original pack in order to protect from moisture'.

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 Nurofen Retard 300 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made by the MAH:

- to submit the mock-ups, the braille declaration and the declaration regarding the technical aspects of the readability by notification to the MEB according to art. 61.3 notification. At the time this PAR was written, the requested data have been submitted fulfilling so this commitment.

- to submit a complete ERA that includes the results of a chronic fish toxicity study, together with all study reports and publications referenced to in the updated ERA. This data must be submitted through the applicable variation (type II) procedure once the studies have been finalised.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are well known. As ibuprofen is a widely used, well-known active substance, no further studies are required and the MAH provides none. Overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

The MAH is requested to submit a complete ERA that includes the results of a chronic fish toxicity study, together with all study reports and publications referenced in the updated ERA. As committed, the data must be submitted through the applicable variation procedure once the studies have been finalised.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Nurofen 200 mg coated tablets which is available on the European market. Reference was made to the preclinical data obtained with the reference 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

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

According to the SmPC of Nurofen Retard 300 mg, the initial dose is two tablets (2 x 300 mg ibuprofen). Then, if necessary, another dose of two tablets (2 x 300 mg ibuprofen) can be taken after 12 hours. The interval between doses should be at least 12 hours. Maximum daily dose is 1200 mg ibuprofen (4 tablets) which must not be exceeded in any 24-hour period.

To support the efficacy of the ibuprofen 300 mg prolonged release (PR) tablets, the MAH submitted data of one pivotal clinical study (5003601) and one supportive study (SCO-0001). The pivotal clinical study was randomised, double-blind, placebo and active controlled study in patients with dental pain following extraction of impacted third molar teeth. This study is

considered as the pivotal one for demonstrating efficacy and safety. The study duration was 24 hrs after the dental procedure. Ibuprofen 300 mg PR tablets (2 x) were given at baseline and at 12 hrs, while Ibuprofen 200 mg IR tablets (2x) were given at 0, 8 and 16 hours. Paracetamol, or oxycodone as second choice, were allowed as rescue drugs.

The supportive study (SCO-0001) was a randomised placebo-controlled study, with the ibuprofen 600 mg PR tablet, dosed as 1 x 600 mg, 12-hourly in dental extraction of the third molar (data not shown).

In addition, the MAH performed two pivotal relative bioavailability studies (single doses BE/17/279 and multiple doses BE/17/281) with ibuprofen 300 mg and 600 mg prolonged release (PR) tablets versus the reference Nurofen 200 mg immediate release (IR) tablet. The *in vivo* studies with the 600 mg PR formulation included a comparison between fasted and fed conditions. These data complement the food interaction data obtained for the 300 mg PR dose in the single-dose study versus Nurofen 200 mg tablets. In addition to the *in vivo* studies, *in vitro* dissolution data and *in vitro* alcohol interaction data were submitted as described in section II.3 Pharmaceutical development of this PAR.

The MAH also submitted three supportive studies (data not shown) under fasted conditions which include a single dose study (139-15) with the 300 mg PR tablets (administered as 2 x 300 mg tablets) compared with 200 mg IR tablets (administered every 4 hours , 3 doses), a single dose study (AAI-US-577) comparing the 600 mg PR tablets and 200 mg IR tablets and a multiple-doses study (AAI-US-576) comparing the 600 mg PR tablets (administered every 12 hours , 7 doses) with 200 mg IR tablets (administered every 4 hours, 21 days).

The MEB has been assured that the bioavailability studies have 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.2 Pharmacokinetics

The MAH submitted two pivotal studies to investigate the relative bioavailability of Nurofen Retard 300 mg prolonged-release tablets. The choice of the reference product in these studies has been justified by comparison of dissolution study results and composition. The 300 and 600 mg PR tablets are dose proportional. The pivotal studies are described below.

Relative bioavailability studies

Study BE/17/279, single-dose

Single-dose study with the 300 mg and 600 mg ibuprofen prolonged release (PR) tablets versus the reference Nurofen 200 mg immediate release (IR) tablet.

Design
This was a randomised, open label, four-treatment, four-period, four-sequence, single oral dose, four-way crossover relative bioavailability study under fasted and fed conditions.

The primary objective of this study was to compare the oral bioavailability of two different formulations of ibuprofen following administration of a single dose (2 tablets of 300 mg) of the prolonged release (PR) Ibuprofen 300 mg tablets (Reckitt Benckiser Healthcare B.V, India) and the immediate release (IR) reference product Nurofen 200 mg tablets (Reckitt Benckiser Healthcare (UK) Ltd.) administered as three doses (200 mg each) at 4-hour intervals. In addition, this study also compared the relative bioavailability of the test product under both fasting and fed conditions, as well as the test product compared with the Ibuprofen 600 mg prolonged release tablets formulation (Reckitt Benckiser Healthcare B.V., India) under fasted conditions. For the study under fasted conditions, the tablet was orally administered with 240 mL water after a fasting period of at least 10 hours prior to dosing and 5 hours post dose. For the study under fed conditions, the tablet was orally administered with 240 mL water after a fasting period of at least 10 hours prior to starting to consume a high-fat, high-calorie breakfast and 5 hours post dose. Standardised meals were consumed by the subjects at 5, 9 and 13 hours post-dose. A wash-out period of 7 days was maintained between each study period. An overview of the four treatment arms included in the study is shown in table 1.

Table 1. Treatment arms study BE/17/279, single-dose

Arm	Product	Dose	Conditions
A1 Test	Ibuprofen 300 mg PR tablet	Single dose administered at a dose of 600 mg (2 x 300 mg tablets)	Fasted
A2 Test	Ibuprofen 300 mg PR tablet	Single dose administered at a dose of 600 mg (2 x 300 mg tablets)	Fed
B Test	Ibuprofen 600 mg PR tablet	Single dose administered at a dose of 600 mg (1 x 600 mg tablet)	Fasted
C Reference	Nurofen (ibuprofen) 200 mg IR tablet	Three dose administered as doses of 200 mg every 4 hours (0, 4 and 8 h.)	Fasted

Blood samples were taken pre-dose (within 2 hours prior to dosing) and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 8.5, 9, 9.5, 10, 11, 12, 14, 17 and 20 hours post (first) dose administration.

Analytical/statistical methods
The analytical methods for S-ibuprofen and R-ibuprofen in plasma have 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
A total of 58 (including two standby subjects to replace any withdrawal prior dosing in period I) healthy, adult, human subjects were enrolled in the study. Two subjects withdrew due to personal reasons prior to dosing in period I. There were three dropouts (subjects did not report to the clinical facility for check-in) in period II, four dropouts in period III and five dropouts in period IV. There were two subjects withdrawn due to positive urine drug of abuse test during period II and one subject during period III. Plasma samples were analysed for 51 subjects who completed at least two study periods. 49 subjects completed arm A1 and A2, 50 subjects arm B and 51 subjects arm C. As the drug substance is a racemic mixture, the pharmacokinetic variables of the two enantiomers (the active S-ibuprofen and the R-ibuprofen) and the total ibuprofen were calculated. The data for the for R-ibuprofen and total ibuprofen are supportive and therefore not shown. The results of the S-ibuprofen (pivotal) are shown in table 2.

Table 2. Pharmacokinetic parameters of S-ibuprofen of the ibuprofen formulations single doses BE/17/279. A1 (Test): Single dose of 300 mg PR tablet administered at a dose of 600 mg (2 x 300 mg tablets) under fasted conditions. A2 (Test): Single dose of 300 mg PR tablet administered at a dose of 600 mg (2 x 300 mg tablets) under fed conditions. B (Test): Single dose 600 mg PR tablet administered at a dose of 600 mg (1 x 600 mg tablet) under fasted conditions. C (Reference): Nurofen (ibuprofen) 200 mg IR tablet administered as three doses of 200 mg every 4 hours (0, 4 and 8 h) under fasted conditions.

Pharmacokinetic parameters (units)	Mean ± SD (CV %)			
	Test product (A1); (N=49)	Test product (A2); (N=49)	Test product (B); (N=50)	Reference product (C); (N=51)
C_{max} (ng/mL)	13033.83 ± 4204.68 (32.26)	19724.70 ± 5870.25 (29.76)	11498.23 ± 4363.16 (37.95)	14201.41 ± 3530.96 (24.86)
AUC_{0-t} (ng.hr/mL)	108978.14 ± 34197.93 (31.38)	120043.18 ± 41997.70 (34.99)	106961.09 ± 46337.56 (43.32)	122707.96 ± 43282.53 (35.27)
AUC_{0-inf} (ng.hr/mL)	113313.27 ± 36341.86 (32.07)	122043.35 ± 44653.06 (36.59)	118547.85 ± 68663.85 (57.92)#	126282.23 ± 47817.96 (37.87)
AUC_{0-4} (ng.hr/mL)	30764.79 ± 9577.84 (31.13)	25990.06 ± 15390.36 (59.22)	25487.56 ± 12801.98 (50.23)	24997.60 ± 6426.70 (25.71)
AUC_{4-8} (ng.hr/mL)	34583.47 ± 14923.84 (43.15)	53403.26 ± 17435.96 (32.65)	28432.75 ± 15010.61 (52.79)	37266.54 ± 11897.38 (31.93)
AUC_{8-12} (ng.hr/mL)	24189.58 ± 9708.65 (40.14)	27110.15 ± 17689.56 (65.25)	25749.08 ± 13231.11 (51.38)	30242.53 ± 13841.12 (45.77)
T_{max} (hr)*	3.00 (1.33 - 12.00)	5.50 (2.00 - 11.00)	5.25 (1.33 - 17.00)	5.50 (0.50 - 11.00)
T_{lag} (hr)	0.11 ± 0.13 (112.04)	0.78 ± 0.47 (60.32)	0.06 ± 0.11 (179.82)	0.14 ± 0.17 (117.56)
K_{el} (hr^{-1})	0.29 ± 0.08 (27.13)	0.32 ± 0.05 (15.35)	0.28 ± 0.09 (31.75)#	0.33 ± 0.06 (19.16)
$t_{1/2}$ (hr)	2.66 ± 1.11 (41.83)	2.20 ± 0.38 (17.42)	3.54 ± 4.62 (130.42)#	2.20 ± 0.51 (23.19)
Residual area (%)	3.46 ± 5.47 (158.02)	1.38 ± 1.18 (85.56)	5.83 ± 10.55 (180.91)#	2.36 ± 1.94 (82.13)

C_{max} Maximum measured concentration of drug in plasma
AUC_{0-t} Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
AUC_{0-inf} Area under the plasma concentration-time curve from time zero to infinity
t_{max} Time to observe maximum drug concentration
t_{lag} Lag times (the finite time taken for a drug to appear in systemic circulation following extravascular administration
$t_{1/2}$ Apparent terminal elimination half-life (ln^2/K_{el})
K_{el} (=λz) Terminal elimination rate constant

*N-Number of evaluated subjects; *Median (range), #N=46*

No value of Kel, t½, AUC_{0-inf} and residual area were reported for: two subjects (treat B) in period II and two subjects (treat B) in period III, as these subjects did not exhibit a terminal log linear phase in the concentrations versus time profile.

Study BE/17/281, multiple-dose

Multiple-dose study with the 300 mg and 600 mg ibuprofen prolonged release (PR) tablet versus the reference Nurofen 200 mg immediate release (IR) tablet.

Design
This was a randomised, open label, balanced, three-treatment, three-period, six-sequence, three-way crossover, multiple doses, relative bioavailability study under fasted conditions.

The primary objective of this study was to compare the oral bioavailability of the prolonged release (PR) ibuprofen tablet following multiple dose administration of 600 mg (2 tablets of 300 mg) every 12 hours for four days and the immediate release (IR) reference product Nurofen 200 mg tablets (Reckitt Benckiser Healthcare (UK) Ltd., following multiple dose administration of 400 mg (2 tablets of 200 mg) every 8 hours for four days. In addition, this study also compared the relative bioavailability of the 300 mg prolonged release test product (Reckitt Benckiser Healthcare, India) versus the 600 mg test prolonged release formulation (Reckitt Benckiser Healthcare, India) at steady state, and the test 600 mg prolonged release formulation with the Nurofen 200 mg formulation at steady state. All treatment arms were under fasted conditions. The tablet was orally administered with 240 mL water after an overnight fasting period of at least 10 hours prior to first dosing and 5 hours post dose. Standardised meals were provided to subjects at 2, 5, 9, 13, 26, 29, 33, 37, 50, 53, 57, 61, 77, 81 and 85 hours post-dose. A wash-out period of 7 days was maintained between each study period. An overview of the three treatment arms included in the study is shown in table 3.

Table 3. Treatment arms study BE/17/281, multiple-dose

Arm	Product	Dose	Conditions
A Test	Ibuprofen 300 mg PR tablet	Multiple doses administered at a dose of 600 mg (2 x 300 mg tablets) every 12 hours, for 4 days. 8 doses total.	Fasted
B Test	Ibuprofen 600 mg PR tablet	Multiple doses administered at a dose of 600 mg (1 x 600 mg tablet) every 12 hours, for 4 days. 8 doses total.	Fasted
C Reference	Nurofen (ibuprofen) 200 mg IR tablet	Multiple doses administered at a dose of 400 mg (2 x 200 mg tablet) every 8 hours, for 4 days. 12 doses total.	Fasted

Blood samples were taken at pre-dose (within 5 minutes prior to morning dose) and 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20 and 24 hours post dose administration.

Analytical/statistical methods

The analytical methods for S-ibuprofen and R-ibuprofen in plasma have 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

A total of 54 healthy, adult, human subjects were enrolled in the study. There was one dropout (subject did not report to the clinical facility for check-in) in period II and III. One subject did not swallow the tablet in period III and was therefore withdrawn from the study. Plasma samples were analysed for the 53 subjects who completed at least two study periods. 53 subjects completed arm A, B and C. Based upon the pre-dose concentrations, steady state was achieved in most of the subjects. In a few subjects the steady state could not be concluded, these subjects were not included in the analysis. As the drug substance is a racemic mixture, the pharmacokinetic variables of the two enantiomers (the active S-ibuprofen and the R ibuprofen) and the total ibuprofen were calculated. The data for the for R-ibuprofen and total ibuprofen are supportive and therefore not shown. The results of the S-ibuprofen (pivotal) are shown in table 4. This study also provide 12-hours efficacy results. For this, the decrease in pain with ibuprofen PR compared to placebo (at 12, 24, 36 and 48 hours after dose 1) were measured by PID. The results are shown in table 5.

Table 4. Pharmacokinetic parameters of S-ibuprofen of the ibuprofen formulations multiple doses BE/17/281. A (Test): multiple doses (8 doses total) of 300 mg PR tablet administered at a dose of 600 mg (2 x 300 mg tablets) every 12 hours for 4 days and under fasted conditions. B (Test): multiple doses (8 doses total) of 600 mg PR tablet administered at a dose of 600 mg (1 x 600 mg tablets) every 12 hours for 4 days and under fasted conditions. C (Reference): multiple doses (12 doses total) Nurofen IR tablet administered at a dose of 400 mg (2 x 200 mg IR tablet) every 8 hours for 4 days and under fasted conditions.

Pharmacokinetic parameters (units)	Mean ± SD (CV %)		
	Test product (A); (N=53)	Test product (B); (N=51)	Reference product (C); (N=52)
$C_{max,ss}$ (ng/mL)	14509.55 ± 3172.01 (21.86)	12738.49 ± 2819.45 (22.13)	21957.65 ± 3869.90 (17.62)
$AUC_{tau,ss}$ (ng.hr/mL)	93668.58 ± 22408.89 (23.92)	86007.99 ± 20145.93 (23.42)	117870.56 ± 33424.45 (28.36)
$C_{tau,ss}$ (ng/mL)	4838.70 ± 2445.42 (50.54)	5450.72 ± 3493.17 (64.09)	12626.08 ± 5076.17 (40.20)
$C_{min,ss}$ (ng/mL)	3030.24 ± 1375.18 (45.38)	3155.46 ± 1621.57 (51.39)	2409.01 ± 1537.98 (63.84)
$C_{avg,ss}$ (ng/mL)	7805.71 ± 1867.41 (23.92)	7167.33 ± 1678.83 (23.42)	9822.55 ± 2785.37 (28.36)
$T_{max,ss}$ (hr)*	2.00 (0.75 - 12.00)	2.00 (0.00 - 11.00)	9.00 (0.75 - 12.00)
Fluctuation (PTF%)	151.97 ± 41.48 (27.29)	141.06 ± 52.07 (36.91)	210.33 ± 55.94 (26.60)
$AUC_{0-4,ss}$ (ng.hr/mL)	39120.00 ± 11087.35 (28.34)	37714.46 ± 9586.82 (25.42)	51013.89 ± 11733.49 (23.00)
$AUC_{4-8,ss}$ (ng.hr/mL)	32435.43 ± 12709.07 (39.18)	27210.06 ± 7600.60 (27.93)	25147.62 ± 12595.25 (50.09)
$AUC_{0-8,ss}$ (ng.hr/mL)	71555.43 ± 18068.37 (25.25)	64924.52 ± 14724.78 (22.68)	76161.50 ± 18848.97 (24.75)
$AUC_{8-12,ss}$ (ng.hr/mL)	22113.15 ± 8778.93 (39.70)	21083.47 ± 10165.51 (48.22)	41709.06 ± 18006.26 (43.17)
$AUC_{0-24,ss}$ (ng.hr/mL)	205254.31 ± 44755.64 (21.80)	197407.92 ± 45821.32 (23.21)	224805.12 ± 53764.31 (23.92)

$C_{max,ss}$ Maximal plasma concentration achieved in systemic circulation following multiple dosing at steady state.

C_{min} Minimal plasma concentration achieved in systemic circulation following multiple dosing at steady state.

$AUC_{tau,ss}$ (tau=12 hours) Area Under Curve during a dosage interval of 12 hours at steady state, calculated using the linear trapezoidal rule.

$C_{tau,ss}$ (tau=12 hours) Concentration at the end of the dosing interval of 12 hours.

t_{max} Time to reach maximum (peak) plasma concentration following drug administration at steady state

$C_{avg,ss}$ Average steady-state plasma drug concentration during multiple-dose Administration

$AUC_{0-t,ss}$ Area Under Curve during a dosage interval (t) at steady state, calculated using the linear trapezoidal rule.

Fluctuation (PTF%) $100 \times [(C_{max,ss} - C_{min,ss}) / C_{avg,ss}]$

*N-Number of evaluated subjects; *Median (range)*

One subject (Test: B) in period I and one subject (Ref: C) in period II did not achieve steady state, hence these subjects period data were excluded from the pharmacokinetic and statistical analysis.

Discussion on the bioavailability studies

Comparing the immediate release (IR) tablets with the Nurofen 200 mg prolonged release (PR) tablet, single dose C_{max} was observed later (3 hours versus about 1 hour) and plasma concentrations declined in a prolonged manner. For the active S-ibuprofen, comparing the 2x 300 mg PR tablets given as a single dose (BE/17/279, A1) versus 200 mg Nurofen IR tablets administered every 4 hours, 3 administrations (BE/17/279, C), comparable C_{max} values are observed. C_{max} was observed at a later time point for the Nurofen tablet (t_{max} 5.25 hours, after the second administration) compared to the PR tablet (t_{max} 3 hours). However, a comparable t_{lag} was observed (0.11 hours versus 0.14 hours). AUC was within bioequivalence criteria. $AUC_{0\text{-}4\ hours}$ was comparable for the test and reference formulations, which may indicate that the time of onset of analgesic effect is comparable for the PR and Nurofen IR formulations.

Administration of the 300 mg PR tablet with food (BE/17/279, A2), resulted in 52% higher C_{max} and a 9% higher AUC. For the 600 mg PR tablet (B) a comparable food effect was observed (C_{max} +33%, AUC-8%). The higher peak concentration is considered not clinically relevant, as the concentration is lower than that expected following a standard single 400 mg dose of IR ibuprofen dose. Accordingly, the Ibuprofen 300 mg and 600 mg PR tablets, can be dosed without reference to food.

At steady state, for the active S-ibuprofen, comparing the 2 x 300 mg PR tablets administered every 12 hours (BE/17/281, A) versus 2 x 200 mg Nurofen IR tablets administered every 8 hours (BE/17/281, C) $C_{max,\ ss}$ values were 35% lower, $AUC_{0\text{-}12hours}$ values were about 20% lower and $C_{min,ss}$ values were about 31% higher.

Overall, the prolonged release characteristics are shown for the PR tablets. Furthermore, the PR tablets 300 mg (administered as 2 x 300 mg tablets) and 600 mg are bioequivalent for AUC and C_{max} after a single dose and at steady state.

For the active S-ibuprofen, comparing the 1 x 600 mg PR tablets administered every 12 hours (BE/17/281, B) versus 2 x 200 mg IR tablets administered every 8 hours (BE/17/281, C), $C_{max,ss}$ values were 42% lower, $AUC_{0\text{-}12hours}$ values were about 26% lower and $C_{min,ss}$ values were about 35% higher. A lower peak trough fluctuation (PTF) was observed for the PR formulations (152% and 141% for the 300 and 600 mg formulation, respectively) versus the Nurofen 200 mg tablet (210 %). It was observed that the plasma profiles for the test and reference formulations of the final dose (at 12 hours on the final dosing/sampling day) was associated with higher peak concentrations during the second 12-hours dosing interval, compared to the first 12-hours dosing interval. This is most likely a result of the evening meal, administered 1 hour after dosing, which increased the absorption of ibuprofen.

The overall exposure over 24 hours at steady state was comparable between the 300 mg PR tablet (administered as 2x 300 mg tablet), the 600 mg PR formulation and the IR formulation. The 90% confidence (interval limits) for the geometric least squares means for $AUC_{0\text{-}24,ss}$ were 91.4 (87.9 – 95.0) and 87.9 (84.6 - 91.4), respectively, for comparisons between the 300 mg PR tablet (BE/17/281, A) and Nurofen IR tablet (BE/17/281, C), and between the 600 mg PR tablet (BE/17/281, B) and Nurofen IR tablet (BE/17/281, C).

Comparable patterns were observed after a single dose and at steady state for the R-isomer and total ibuprofen.

For ibuprofen it is indicated that there is a positive relationship between plasma concentration and analgesic activity and that attainment and maintenance of a concentration above the minimum effective concentration (MEC) of 6.4 µg/mL is necessary to achieve an effective analgesia. After single dose, both the PR and Nurofen IR formulations maintain plasma concentrations above the MEC for total ibuprofen for a comparable time, supported by the results for occupancy time (OT0-12) showing a comparable mean (median) results of 9.7 (10.2) and 9.8 (10.1) hours for the PR and the Nurofen IR formulation, respectively. Also at steady state a comparable occupancy time was observed, i.e. median results of 9.4, 9.3 and 8.5 hours for the 300 and 600 mg PR and 200 mg IR formulation, respectively. However, a MEC of 6.4 µg/mL is considered not well supported, as for instance a clear concentration-efficacy response relationship (curve) of onset of pain relief for the proposed indications is missing. Nevertheless, the efficacy has been supported by clinical data.

The supportive studies did not indicate different findings.

The *in vitro* data show that 40% alcohol increases the release of ibuprofen by about 24% after 2 hours. For *in vivo*, this possible 24% increase in release at a 40% alcohol concentration is considered not clinically relevant. In conclusion, no major objections or concerns are identified.

IV.3 Pharmacodynamics

Ibuprofen is a well-known NSAID analgesic, which is widely used (in the over the counter (OTC) setting) for treatment of pain, fever and (joint) inflammation. The MAH has sufficiently described the mechanism of action.

IV.4 Clinical efficacy

To support the efficacy of the ibuprofen 300 mg prolonged release (PR) tablets, the MAH submitted data of one pivotal clinical study (5003601) and one supportive study (SCO-0001). The pivotal study is described below.

Efficacy studies

Study 5003601
Controlled efficacy study of ibuprofen prolonged-release tablets for the treatment of pain after surgical removal of impacted third molars.

Design
This was a randomised, double-blind, double-dummy, parallel-group, multiple-dose, active and placebo controlled study in patients with dental pain following extraction of impacted third molar teeth.
The study included a total of 280 male or female subjects aged between 18 and 50 years who required extraction of two or more third molars with at least one fully or partially bone–impacted mandibular molar and who experienced moderate to severe pain intensity within

six hours after surgery, as measured by a numeric scale score of ≥5 on a 0-10 scale were eligible. Prior to surgery, all subjects received local anaesthesia (2% lidocaine with 1:100,000 epinephrine); during surgery, all but one subject received nitrous oxide at the discretion of the investigator. The study duration was 24 hours after the dental procedure. Ibuprofen 300 mg PR tablets (2 x tablets) were given at baseline and at 12 hours, while Ibuprofen 200 mg IR tablets (2x tablets) were given at 0, 8 and 16 hours. Paracetamol or oxycodone as second choice, were allowed as rescue drugs. In total, 120 patients were assigned to ibuprofen 300 mg PR tablets, 120 to the control ibuprofen 200 mg IR tablets and 39 to placebo + double dummies intention-to-treat population (ITT). The primary endpoint was the summed pain intensity difference (SPID) over 0 to 12 hours (SPID12). The key secondary endpoint was SPID over 24 hours (SPID24). The primary objective of the study was to evaluate the superiority of 2 x 300 mg ibuprofen PR tablets compared with placebo. The key secondary objectives included evaluation of the analgesic performance of a total daily dose of 1200 mg of the ibuprofen PR formulation compared to ibuprofen IR tablets over 24 hour post initial dose and evaluation of the safety and tolerability of 2 x 300 mg ibuprofen PR tablets.

Analytical/statistical methods

The chosen model is representative for acute moderate-severe pain, according to the EMA guideline on pain (EMA/CHMP/970057/2011, version 2017). The statistical methods of the primary analysis, including the correction for the use of rescue medication and missing data, are justified and are accepted.

Results

A total of 258 subjects completed the study and were included in the statistics. 9 of 120 patients assigned to the 300 mg PR arm dropped out of the study prematurely, versus 8 of 120 patients in the 200 mg IR arm, and 4 of 39 patients in the placebo arm.

Table 5. Analysis of summed pain intensity difference-12 scores, ibuprofen PR and IR tablets and placebo in ITT population (SPID12)

Statistic	Ibuprofen PR (N=120)	Ibuprofen IR (N=120)	Placebo (N=39)
n	120	120	39
Mean	51.84	56.33	19.11
SD	21.457	18.769	24.630
Median	55.13	57.44	14.72
Min, Max	-11.8, 102.2	0.0, 98.0	-34.2, 78.8
ANCOVA Statistics[a]			
LS Mean (SE)	52.11 (1.839)	56.40 (1.838)	18.06 (3.233)
LS Mean Difference from Placebo (95% CI)	34.05 (26.72, 41.38)	38.34 (31.02, 45.67)	
P-value	<0.0001	<0.0001	

Table 6. Comparison of summed pain intensity difference-24 scores, ibuprofen PR and IR tablets in ITT population (SPID24)

Statistic	Ibuprofen PR (N=120)	Ibuprofen IR (N=120)
ANCOVA Statistics[a]		
LS Mean (SE)	116.42 (3.821)	122.09 (3.820)
LS Mean Difference (95% CI)	-5.67 (-16.30, 4.97)	
P-value	0.2952	

Discussion on the efficacy studies

The primary objective was met, the 300 mg tablets were clearly superior over placebo in achieving analgesia. The LS mean SPID24 scores were similar for the ibuprofen PR and IR groups (table 5) and the difference in LS means (P-value = 0.2952, table 6) was not statistically significant when analysed in the ITT population, as well as when analysed using sensitivity analyses with no rescue medication adjustment and multiple imputation.

The number of responders in the ibuprofen PR group (81 [67.5%] subjects) and the ibuprofen IR group (76 [63.3%] subjects) was statistically significantly higher than in the placebo group (5 [12.8%] subjects), or (95% CI) 13.93 (5.00, 38.86) for the ibuprofen PR group compared to placebo and 11.65 (4.20, 32.36) for the ibuprofen IR group compared to placebo, P-value <0.0001). Several other secondary endpoints on pain, such as the TOTPAR (Sum of total pain relief) scores and the SPRID (Summed pain relief and intensity difference) scores were all statistically significantly greater for both the ibuprofen PR group and the ibuprofen IR group compared to the placebo group (P-value < 0.0001 for all), as several time points (4, 8, 12 hrs). But no comparisons were made between the two active study drugs. As might be expected given the difference in drug release profile between the IR and PR tablet, the onset of effect tended to be faster for the IR tablets. E.g. the median (95% CI) time to meaningful pain relief was faster for the ibuprofen IR group (0.99 [0.84, 1.21] hours), followed by the ibuprofen PR group (1.25 [0.94, 1.54] hours) as compared to the placebo group (2.88 [1.98, not estimable] hours, P-value = 0.0075 and <0.0001 and for the ibuprofen PR and IR group, respectively). The percentage of patients using rescue mediation is higher for PR, as compared to IR (25% versus 15.8%). Also opioids were required in 2 patients assigned to PR and 2 in the Placebo group, versus none in the IR group. PRO (patients' reported outcome) was also more favourable for IR. Approximately twice as many of patients had a negative appraisal of the PR treatment, as compared IR. While 90% of the patient receiving IR evaluated the treatment as good-excellent, this was 77.4% for PR. Furthermore, the supportive study (SCO-0001) was a randomised placebo-controlled study, with the ibuprofen 600 mg PR tablet, dosed as 1 x 600 mg, 12-hourly in dental extraction of the third molar. As expected, ibuprofen 600 mg PR tablets was superior in achieving analgesia compared to placebo. These results provide support for the maintenance of efficacy after multiple doses of ibuprofen PR 600 mg.

IV.5 Clinical safety

The clinical studies were nor designed and neither powered to demonstrate any difference between PR and IR tablets regarding safety. It is considered that the safety profile of the IR

reference product applies to the safety profile of the PR product. There are no clinically meaningful differences in the PK profile of the 2x 300 mg PR tablets, compared to the 2x 400 mg IR tablets, which would give rise to safety concerns. Safety was acceptable for the PR and IR tablet in the two clinical dental surgery studies. The overall incidence of adverse events (AEs) was numerically slightly lower for the PR than for the Ibuprofen IR tablet and GI disorders were in the same range for either product, no safety events emerged that were unexpected.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan (version 2.2. with date of final sign off 31 March 2023), 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 Nurofen Retard 300 mg prolonged-release tablets.

Table 4. 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.7 Discussion on the clinical aspects

Ibuprofen 200 mg is a well-known medicinal product with an established favourable efficacy and safety profile. The lower efficacy of the PR formulation compared to the IR formulation, notably in the first 1-5 hours of the pivotal trial, is considered to be unlikely of clinical relevance. Although the first hours after first dose are clinically important, the period did not clearly extend beyond 1-5 hours, the lower efficacy is relatively small compared to the baseline pain values and is lower than what can be considered as Minimal Clinically Important Difference (MCID). It can be agreed that there is a convenience in less frequent dosing with PR as compared to IR, in conditions of which pain longer than 6-8 hours may be foreseen. The concept of prolonged release formulation in an acute pain indication is only possible in restricted pain indications of which the future course can be estimated (with period pain or dental pain after surgery as good examples), which is reflected in the proposed wording of the indication. It is considered that the safety profile of the immediate release (IR) reference product applies to the safety profile of the prolonged release (PR) product. There are no significant clinical differences in the PK profile of the 2x 300 mg PR tablets compared to 2x 400 mg IR tablets that would give rise to safety concerns. Safety was acceptable for the PR and IR tablet in the two clinical dental surgery studies. The overall incidence of AEs was numerically marginally lower for the PR than for the Ibuprofen IR tablet and GI disorders were in the same range for either product, no safety events emerged that were unexpected. The Risk management is adequately addressed. Overall, the clinical aspects of this product are approvable.

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. 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 Nurofen for Children Meltlet 200 mg Orodispersible tablets, Reckitt Benckiser Healthcare (UK) Ltd. 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

Nurofen Retard 300 mg prolonged-release tablets has a proven chemical-pharmaceutical quality and is a hybrid formulation of Nurofen 200 mg coated tablets. The reference Nurofen 200 mg coated tablets is a well-known medicinal product with an established favourable efficacy and safety profile. There are no clinically meaningful differences in the PK profile of the 2x 300 mg PR tablets, compared to the 2x 400 mg IR tablets. Therefore, it is considered that the safety profile of the immediate release reference product applies to the safety profile of the prolonged release product. Safety was acceptable for the PR and IR tablet in the two submitted clinical dental surgery studies. The studies has been shown to be in compliance with the requirements of European guidance documents.

In the Board meetings of 28 Juli 2022, 9 March 2023 and 29 June 2023 the following was discussed:

<u>Board meeting nr. 1008, 28 Juli 2022</u>
The current approved indication for the reference medicinal product and Nurofen 300 mg PR tables differs. Furthermore, the PR formulation of ibuprofen has not yet been registered in the Netherlands for the requested indication. The application is supported by two bioavailability studies (single dose and multiple doses) with the 300 mg and 600 mg PR tablets versus the reference medicine Nurofen 200 mg IR tablets. Data are also presented from a pivotal clinical study. A double-blind, randomised study comparing the efficacy and safety of the PR ibuprofen tablets versus IR tablets. The study was conducted for 24 hours in patients with pain after extraction of impacted third molars. The results show that the PR tablets are less effective than the IR tablets, especially in the period between 30 minutes and 6 hours after administration. In the PR dosed group also more rescue medication was used (25% versus 16% in the IR group). The data do not show that the effect of the PR formulation is equivalent to that of the existing IR ibuprofen used in the short-term treatment. The application for the PR formulation is therefore not acceptable for the requested indication, which outlines a short-term setting.

<u>Board meeting nr. 1023, 9 March 2023</u>
In its response to the previous discussion (nr. 1008 on 28 Juli 2022), the MAH states that the difference in effectiveness between PR and IR ibuprofen tablets, which is seen during the first

1 to 5 hours after administration, is not clinically relevant and points out that PR tablets must be taken less often than the IR tablets, which would be an advantage to treat long-lasting pain. The Board agrees with the argument that the difference in effectiveness is probably not clinically relevant. However, the Board is not certain about the benefits of using PR tablets for the short-term treatment of acute pain. There are many disadvantages considered in case this medicinal product would be given an over-the-counter release status. It is known that patients often do not follow the dosage recommendations and that, especially in acute pain, medication is taken more often than indicated, which can lead to serious health risks. The over the counter (OTC) status for this product will be further discussed. Furthermore, during the previous round a CMS raised concerns about the safety of the PR tablets, because the safety profile of the PR tablets was not sufficiently equivalent to that of the IR tablets. This concern has been resolved, as no clinically relevant differences were observed based on the pharmacokinetics results. In the clinical studies, fewer side effects were seen with the PR tablets than with the IR tablets. Overall, the major objections have been resolved and the benefit/risk balance is now considered positive.

Board meeting nr. 1031, 29 June 2023

This board discussion concerns the determination of the delivery status of the product via the national procedure. The MAH justified why the 'prescription-only' status is not necessary. This is acceptable, diagnosis by a doctor is not considered necessary. In the package leaflet, patients are instructed to contact their doctor if symptoms persist or worsen, or if the product is used for more than four days. This limits possible health risks resulting from misdiagnosis or/and incorrect use. The maximum daily dose for Nurofen Retard 300 is 1200 mg, which is equal to the maximum daily dose for the previously registered 200 mg and 400 mg tablets without a prescription. The dose schedule of these products is different, but patients could mistakenly use the dose schedule known of the previously registered products, causing this way an (unintentional) overdose (>1200 mg/day) for a few days. Therefore, for this product the Pharmacies only (UA) status is considered the most appropriate, as the intervention of a pharmacist is considered necessary to inform patients about the risks of overdose and about other suitable alternatives.

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 considered, on the basis of the data submitted, that the efficacy and safety for Nurofen Retard 300 mg prolonged-release tablets has been demonstrated and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 April 2023.

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/5350/ 001/P/001	Art.61(3): Update the outer labelling.	Yes	13-02-2024	Approved	N.A.
NL/H/5350/ 001/IA/003	Change in test procedure for the finished product: - minor changes to an approved test procedure.	No	02-05-2024	Approved	N.A.
NL/H/5350/ 001/IB/004	Change in the (invented) name of the medicinal product: - for Nationally Authorised Products.	Yes	14-08-2024	Approved	N.A.
NL/H/5350/ 001/WS/002 (DE/H/xxxx/ WS/1536)	To update section 4.4, 4.8 of the SmPC and section 2 and 4 of the PIL following the PRAC recommendation released as a result of PSUSA/00010649/202302 and adopted by CMDh on 12th October 2023.	Yes	08-10-2024	Approved	N.A.
NL/H/5350/ 001/WS/005 (DE/H/xxxx/ WS/1836)	To update section 4.9 of the SmPC and section 3 of the PIL following the PRAC recommendation adopted by CMDh on 28th May 2024.	Yes	23-04-2025	Approved	N.A.
NL/H/5350/ 001/IB/006	Change in the shelf-life or storage conditions of the finished product: - extension of the shelf life of the finished product. As packaged for sale (supported by real time data).	Yes	15-9-2025	Approved	N.A.