CBG MEB

# Public Assessment Report

# Scientific discussion

# Panadol S 500 mg, film-coated tablets

# NL License RVG: 112182

# Date: 23 May 2019

**This module reflects the scientific discussion for the approval of Panadol S 500 mg, film-coated tablets. The marketing authorisation was granted on 24 February 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

## List of abbreviations

| | |
|---|---|
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| EDQM | European Directorate for the Quality of Medicines |
| ERA | Environmental Risk Assessment |
| FD | Fast Dissolving |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| PDA | Percent of Drug Absorbed |
| Ph.Eur. | European Pharmacopoeia |
| PK | Pharmacokinetics |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Panadol S 500 mg, film-coated tablets from GlaxoSmithKline Consumer Healthcare B.V.

The product is indicated for the symptomatic treatment of mild to moderate pain and/or fever in adults and children aged 6 years and over.

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

This national application concerns a line extension to Panadol Gladde Tablet 500 mg (NL License RVG 18550), which has been registered in the Netherlands since 24 July 1995.
The rationale for product development was obtaining a formulation with more rapid absorption of paracetamol. Changes were made to the excipients in the new formulation to improve the dissolution and absorption characteristics. According to the MAH, the rate and degree of early absorption of paracetamol from the standard tablet has been reported to be slow and variable and this may be attributed to slow tablet disintegration/dissolution in the gastrointestinal tract (Kelly et al, 2003[1]).

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

No new non-clinical studies were submitted with this application, which is acceptable given that the product is a line extension of an approved product license containing a well-known active substance.

To support the application, four pharmacokinetic studies were submitted: a single dose (2*500 mg tablets) bioequivalence study (A1900260) in healthy subjects under fasting conditions, a replicate design study (A1900265) in healthy subjects under fasting conditions, a pharmacokinetic study (A1900385) with a single dose treatment in subjects with type II diabetes in a semi-fed state and a gamma scintigraphy study with a single dose treatment in healthy volunteers (A1900279). These are discussed in section IV.1 of this report.

# II. QUALITY ASPECTS

## II.1 Introduction

Panadol S is a white to off-white film-coated capsule-shaped tablet, with “P” in a beacon on one side and a score line on the other side. The tablet can be divided into equal halves. Each tablet contains 500 mg paracetamol.

The film-coated tablets are packed in white opaque PVC/Al blisters.

The excipients are:
*tablet core* - pregelatinised starch, calcium carbonate (E170), alginic acid (E400), crospovidone (E1202), povidone K25 (E1201), magnesium stearate (E470B), colloidal anhydrous silica
*Film coating* - carnauba wax and Opadry white (film-coating agent containing hypromellose 2910 (E464), titanium dioxide (E171), macrogol 400 and polysorbate 80 (E433)).

## II.2 Drug Substance

The active substance is paracetamol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder, which is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride. There are only two significant polymorphs of paracetamol. These are the monoclinic form and

[1] Kelly K, O'Mahony B, Lindsay B, Jones T, Grattan TJ, Rostami-Hodjegan A, Stevens HN, Wilson CG. Comparision of the rates of disintegration, gastric emptying, and drug absorption following administration of a new and a conventional paracetamol formulation, using γ scintigraphy. Pharm Res. 2003;20:1668-73.

orthorhombic form. The stable monoclinic form is commercially available. The orthorhombic form is considered metastable.

The CEP procedure is used for all three suppliers of 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 European Pharmacopoeia.

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

Quality control of drug substance
The drug substance specification of the MAH is in line with the Ph.Eur. requirements and the CEPs. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches of each CEP-holder.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

## II.3 Medicinal Product

Pharmaceutical development
The main development studies were performed to obtain a product with faster dissolution than the existing paracetamol product, Panadol Gladde Tablet. Initial formulation development studies screened a number of pharmaceutically suitable adjuvants for their ability to speed up the dissolution rate of paracetamol when included in tablets at a low level. The development of the product has been described, the choice of excipients is justified and their functions explained. The choices of packaging and manufacturing process have been justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of four steps: wet granulation, milling/blending, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot scaled batches. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur. requirements or in-house requirements (Opadry colouring agent). These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, uniformity of dosage units, identification, assay, related substances, microbial quality and dissolution. The release specification limits are identical to the shelf life limits with the exception of assay. The specification is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on two full scaled batches, demonstrating compliance with the release specification. Data of three pilot scaled batches from another production location have also been provided, also demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided on three pilot scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (12 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in white opaque PVC/Alu blisters and HDPE

bottles with PP screw cap (100 count and 1000 count). No changes were seen in the stability results. Based on the stability data provided a shelf life of 18 months, without special storage conditions can be granted.

Specific measures for 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 MEB considers that Panadol S 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 Pharmacology, pharmacokinetics and toxicology

The pharmacological, pharmacokinetic and toxicological properties of paracetamol are well-known. This product is a line extension of an approved product license. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical data. Therefore, the MEB agreed that no further non-clinical studies are required.

### III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Panadol S is a line extension which is expected to substitute an available product, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

## IV. CLINICAL ASPECTS

### IV.1 Pharmacokinetics

The MAH submitted 4 pharmacokinetic studies in support of this application:

- study A1900260, an open label, randomized 2-way cross-over pharmacokinetic study
- study A1900265, an open label, randomized 4-way cross-over pharmacokinetic study
- study A1900279, an open label, randomized 2-way cross-over scintigraphy study
- study A1900385, an open label, randomized 2-way cross-over study in type II diabetes patients

Formulations used in PK studies
The test formulation used in the pharmacokinetic studies is referred to as ‘Panadol FD’ (fast dissolving). The reference formulation is the registered Panadol 500 mg tablet.

The commercial batch is different from the test batch used in the pharmacokinetic studies. The test product in these studies contained a preservative, potassium sorbate, at less than 0.2% of the content of the tablets. The commercial batch is preservative-free. The PK profile is not expected to be different from the commercial batch, as potassium sorbate is not expected to have an influence on bioequivalence.

Dissolution tests among batches with and without preservative were conducted. For both products more than 85% dissolved within 15 minutes. No dissolution data at pH 4.5 and 6.8 were provided as according to the MAH, batches with preservative do not exist anymore. However, dissolution data at pH 4.5 and 6.8 were provided for the preservative-free batch: at pH 4.5 dissolution was more than 85% within 15 minutes while at pH 6.8 it was poorly dissolved (at 30 minutes, only 64% is dissolved).

Considering that the only difference between the test product used in the bioequivalence study and the proposed product is the presence of 0.60 mg potassium sorbate as preservative and there are no expected safety concerns, the proposed preservative-free product is considered acceptable based on similarity in dissolution only at pH 1.3 with the formulation containing preservative, as no differences are expected at the other pHs.

- **Study A1900260 – single dose, fasting conditions in healthy subjects**

Design

This study was a randomised, single centre, open label, single dose, 2-way crossover human pharmacology study in healthy subjects. The test product was 2 x Panadol FD 500 mg tablet and the reference product was 2 x Panadol 500 mg tablet.
The number of subjects in this study was 40 (male 14, female 26) with an age range from 18 to 49. The study subjects received single doses of both study medications with at least a 3-day wash out period in between dosing. The blood sampling period was 10 hours.

Pharmacokinetic variables measured were $AUC_{0-t}$, $AUC_{0-inf}$, $C_{max}$ (primary), $T_{max}$ (secondary) and $AUC_{0-30mins}$ (other). The primary objective of this study was to compare the $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{max}$ for test and reference in the fasted state. The secondary objective was to compare the $T_{max}$ for Panadol FD tablets and standard paracetamol tablets in the fasted state. Comparisons between treatments for $AUC_{0-30mins}$ were added after analysis had been performed on other variables.

Results

**Table 1. Point estimate and 90% CI for AUC and $C_{max}$ (n=40)**

| | Panadol Tablets (new formula) versus Standard paracetamol tablets |
|---|---|
| $AUC_{0-t}$ | |
| Point estimate | 1.02 |
| 90% CI | 0.98, 1.05 |
| $AUC_{0-\infty}$ | |
| Point estimate | 1.02 |
| 90% CI | 0.98, 1.05 |
| $C_{max}$ | |
| Point estimate | 1.12 |
| 90% CI | 0.99, 1.28 |

**Table 2. Median difference and 95% CI for $AUC_{0-30mins}$ and $T_{max}$ (n=40)**

| | Panadol Tablets(new formula) versus Standard paracetamol tablets |
|---|---|
| $AUC_{0-30\ mins}$ | |
| Median difference | 1.52 |
| 95% CI | 0.18, 2.91 (p=0.0318) |
| $AUC_{0-60\ mins}$ | |
| Median difference | 1.73 |
| 95% CI | 0.09, 3.88 (p=0.0466) |
| $T_{max}$ (hr) | |
| Median difference | -0.25 |
| 95% CI | -0.46, -0.08 (p=0.0061) |

$AUC_{0-t}$ and $AUC_{0-inf}$ were comparable between the study medications and both 90% CI were within the range 0.80-1.25. $C_{max}$ was higher for Panadol FD (new formulation) with upper 90% CI above 1.25.

Other values for Panadol FD vs Panadol $C_{max}$ were: min 7.35 vs 7.91; max 39.92 vs 31.70: median 18.97 vs 16.86. $AUC_{0\text{-}30mins}$ was greater for Panadol FD and $T_{max}$ was faster.

- **Study A1900265 – replicate design, fasting conditions in healthy subjects**

Design

This study was a randomised, single centre, open label study in healthy subjects to compare the rate of and variability in absorption of paracetamol following administration of Panadol FD and Panadol tablets in fed state. The study had 2 parts: Part A consisted of a single dose, 2-way cross-over design on days 1-2, and Part B consisted of a replicate cross-over design on days 3-8 and included the 0-4 hour data from Part A (days 1-2). The test product was 2 x Panadol FD tablet and the reference product was 2 x Panadol tablet, each containing 500 mg of paracetamol.

The number of subjects in this study was 76 (42 male, 34 female) and 75 completed the study. Age range was from 18 to 54. The subjects received during each study session one of the two study treatments in a random order, 2 hours after a standard meal. Blood samples were taken pre-dose and up to 10 hours post-dose on days 1-2 and up to 4 hours post-dose on days 3-8 with a 24 hour washout between each dosing.

Since the study treatments were administered 2 hours after meal, it is not considered a fed study.

This study was designed to compare:

- in part A: $AUC_{0\text{-}30mins}$ (primary), $AUC_{0\text{-}60mins}$, $C_{plasma}$ at 30 mins, $T_{max}$, $T_{lag}$, individual percent of drug absorbed (PDA) (secondary), $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and $C_{max}$ (other).
- in part B: $AUC_{0\text{-}30mins}$ (primary), $AUC_{0\text{-}60mins}$, $C_{plasma}$ at 30 minutes, $T_{max}$, $T_{lag}$ (secondary) and $AUC_{0\text{-}4hrs}$ (other) and between-subject variability (coefficient of variation (CV)).

Results

**Table 3. Median difference and 95% CI for early exposure pharmacokinetic variables after initial dosing. Part A (n=76)**

| | Panadol Tablets(new formula) versus Standard paracetamol tablets |
|---|---|
| **$AUC_{0\text{-}30\ mins}$** | |
| Median difference | 0.77 |
| 95% CI | 0.53, 1.01 (p<0.0001) |
| **$AUC_{0\text{-}60\ mins}$** | |
| Median difference | 2.57 |
| 95% CI | 1.79, 3.42 (p<0.0001) |
| **$C_{plasma}$ at 30 mins (mcg/ml)** | |
| Median difference | 4.15 |
| 95% CI | 2.76, 5.39 (p<0.0001) |
| **$PDA_{30\ mins}$ (%)** | |
| Median difference | 25.28 |
| 95% CI | 18.28, 33.69 (p<0.0001) |
| **$PDA_{60\ mins}$ (%)** | |
| Median difference | 18.63 |
| 95% CI | 11.16, 26.67 (p<0.0001) |
| **$T_{max}$ (hr)** | |
| Median difference | -0.38 |
| 95% CI | -0.59, -0.17 (p=0.0004) |

**Table 4. Median difference and 95% CI for early exposure pharmacokinetic variables after initial dosing, study after replicate dosing, part B (n=75)**

| | Panadol Tablets versus Standard paracetamol tablets |
|---|---|
| $AUC_{0\text{-}30\ mins}$ | |
| Median difference | 0.99 |
| 95% CI | 0.81, 1.19 (p<0.0001) |
| $AUC_{0\text{-}60\ mins}$ | |
| Median difference | 2.66 |
| 95% CI | 2.18, 3.20 (p<0.0001) |
| $C_{plasma}$ at 30 mins (mcg/ml) | |
| Median difference | 3.88 |
| 95% CI | 3.09, 4.69 (p<0.0001) |
| $T_{max}$ (hr) | |
| Median difference | -0.31 |
| 95% CI | -0.43, -0.19 (p<0.0001) |

**Table 5. Summary results from analysis of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and $C_{max}$, part A**

| PK Variable | LS Mean | | Point estimate | 90% CI for point estimate |
|---|---|---|---|---|
| | Panadol FD | Panadol | | |
| $AUC_{0\text{-}t}$ (mcg·h/mL) | 41.10 | 39.76 | 1.03 | 1.02, 1.05 |
| $AUC_{0\text{-}inf}$ (mcg·h/mL) | 44.30 | 43.08 | 1.03 | 1.01, 1.04 |
| $C_{max}$ (mcg/mL) | 11.97 | 12.12 | 0.99 | 0.94, 1.04 |

*Study part A*
$AUC_{0\text{-}30mins}$, $AUC_{0\text{-}60mins}$, $C_{plasma}$ at 30 mins and PDAs at all levels were significantly higher with Panadol FD compared to Panadol. $T_{max}$ was significantly faster with Panadol FD. $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and $C_{max}$ were comparable between the study medications and 90% CI within range 0.80-1.25. Between-subject relative variability in PK parameters was lower after Panadol FD compared to Panadol in all parameters except for $T_{max}$ and $T_{lag}$.

*Study part B*
$AUC_{0\text{-}30mins}$, $AUC_{0\text{-}60mins}$, $C_{plasma}$ at 30 mins and PDAs at all levels were significantly higher with Panadol FD compared to Panadol. $T_{max}$ was significantly faster with Panadol FD. Within-subject relative variability in PK parameters was lower after Panadol FD compared to Panadol in all other parameters except for $T_{max}$ and $T_{lag}$ where there was no significant difference.

- **Study A1900279 – single-dose gamma scintigraphy study in healthy volunteers**

Design
This study was an open, randomised 2-way cross-over study in healthy subjects to investigate whether the greater early exposure from Panadol FD tablets compared to the reference Panadol tablets is due to faster dissolution/disintegration of the new formulation. The number of subjects in this study was 24 (all male), age range from 21 to 64. Single doses (2 x 500 mg tablets) of radio-labelled treatments were administered to study subjects 2 hours after a standard, radio-labelled breakfast. There was at least a 7 day wash-out period between dosing. Scintigraphy images were taken from 2 hours post-dose to 5 hours post-dose.
The primary objective of the study was to assess the time of complete dissolution/disintegration of the tablets. Gastric emptying times for both formulations were also evaluated.

Results

**Table 6. Mean (± SD) values and statistical comparisons for disintegration/dissolution of tablets and gastric emptying**

| Study A1900279 (n=24) | | | |
|---|---|---|---|
| | Panadol tablets (new formula) Mean (SD) | Standard paracetamol tablets Mean (SD) | p-value |
| **Onset of tablet disintegration/dissolution (mins)** | 6.4 (± 4.3) | 46.7 (± 20.5) | p<0.0001 |
| **Complete tablet disintegration/dissolution (mins)** | 12.9 (± 6.4) | 69.6 (± 30.2) | p<0.0001 |
| **Onset of gastric emptying (mins)** | 41.9 (± 28.8) | 85.0 (± 28.2) | p<0.0001 |
| **$t_{50}$ gastric emptying (mins)** | 72.4 (± 36.4) | 100.7 (± 30.6) | p=0.0013 |
| **$t_{90}$ gastric emptying (mins)** | 128.4 (± 41.2) | 142.0 (± 33.8) | p=0.10 |

The mean (± SD) time to complete tablet disintegration was significantly faster (P < 0.0001) for Panadol FD (12.9 ± 6.41 minutes) compared to standard paracetamol tablets (69.6 ± 30.21 minutes). For Panadol FD complete disintegration occurred in the stomach for 23 subjects and in the stomach/ small intestine for one subject. For standard paracetamol tablets complete disintegration occurred in the stomach for 16 subjects, and in the stomach/small intestine for 8 subjects.

Panadol FD tablets demonstrated a significantly faster dissolution/disintegration and gastric emptying compared to Panadol. No gastric emptying occurred until the tablets had disintegrated/dissolved.
Gastric emptying of the meal was similar for both formulations.

- **Study A1900385, PK study in subjects with type II diabetes**

The MAH performed this pharmacokinetic study in patients with diabetes mellitus (type II) to investigate paracetamol PK parameters in a gastric dysmotility model. Involvement of the autonomic nervous system in diabetes mellitus includes gastric enteropathy characterised by gastrointestinal dysmotility (Bassotti 1991[2]). Long-standing diabetes mellitus may reduce gastric emptying in up to 50% of patients (O'Mahony 2002[3]).
Results of this study are in line with the results from other PK studies performed by the MAH.

## IV.2 Risk Management Plan

The MAH did not submit a risk management plan for this line extension, as it was not required at the time the application was made. The active ingredient, paracetamol, is present in the same quantity (500 mg) as in the original formulation and there are no changes to dosage form, the route of administration or indication. The MAH has a pharmacovigilance system in place, in compliance with the applicable guidelines.

## IV.3 Discussion on the clinical aspects

The PK studies showed that the rate of absorption was faster after the new formulation compared to conventional Panadol tablet (median $T_{max}$ 30 minutes versus 40 minutes, p < 0.01, $C_{max}$ ratio new/old product: 1.12; 90% CI 0.99-1.28). However, the overall amount of absorption from the new and old tablets was similar (AUC was bioequivalent).
The results in the PK studies were obtained with a formulation containing a preservative, potassium sorbate. The commercial batch is preservative-free. The PK profile is however not expected to be

[2] Bassotti G, Antonelli E, Villanacci V, Salemme M, Coppola M, Annese V. Gastrointestinal motility disorders in inflammatory bowel diseases. World Journal of Gastroenterology : WJG. 2014;20(1):37-44.
[3] O'Mahony D, O'Leary P, Quigley EM. Aging and intestinal motility: a review of factors that affect intestinal motility in the aged. Drugs & aging. 2002;19(7):515-27

different from the commercial batch, as potassium sorbate is not expected to have an influence on bioequivalence.

The clinical relevance of the line extension cannot be established based on the PK data alone. A difference of 10 minutes of median $T_{max}$ seems marginal. Clinical studies of head-to-head comparisons between the new and conventional Panadol 500 mg tablets are however lacking.
Study reports of two randomised trials were included in the dossier, both performed in a model of moderate-severe post-operative acute pain (3rd molar extraction). One study was placebo-controlled, and the other was placebo- and active-controlled with paracetamol 325 mg caplets (immediate-release formulation). The studies confirmed that paracetamol was superior to placebo, and reduced pain in a dose dependent way. These studies are however not relevant to support a claim of a more rapid onset of effect, because of the choice of the comparators (placebo or lower dose).

In section 5.2 of the SmPC, it is stated that plasma levels required for efficacy are more instantly achieved with the new formulation, with less variability, thereby suggesting an improved and earlier onset of effect. A statement has been added that the clinical relevance of the changes in the formulation are unclear, as no comparative clinical studies were performed where Panadol S was compared to conventional Panadol tablets.

$C_{max}$ is slightly higher (about 12%). However, it is not expected that this small increment if the $C_{max}$ would lead to serious adverse events. Paracetamol is not considered a narrow-therapeutic drug, within the proposed dosing regimen of maximally 3000 mg, spread over the day.

## V. USER CONSULTATION

The text of the package leaflet (PL) is in accordance with the harmonised wording for paracetamol containing products (UK/H/1253/DC) and the recommendations of the PhVWP (CMDh/PhVWP/032/2011). A bridging report has been provided, referring to the successful readability tests on other paracetamol formulations of the MAH. The bridging report has been found acceptable.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Panadol S 500 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is an approvable line extension to Panadol Gladde Tablet 500 mg. Panadol Gladde Tablet is a well-known medicinal product with an established favourable efficacy and safety profile.

Comparison of PK data of the Panadol S formulation to conventional Panadol tablets has shown that absorption is more rapid, although clinical relevance remains unclear since no comparative clinical studies were conducted.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that the benefit/risk balance is positive, and has therefore granted a marketing authorisation. Panadol S 500 mg, film-coated tablets was authorised in the Netherlands on 24 February 2015.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Type of modification | Date of start of the procedure | Date of end of the procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|
| Introduction of the Summary of the Pharmacovigilance System. | IA | 24-6-2015 | 10-7-2015 | Approval | N |
| Changes to SmPC and PL due to update of the company Global Data Sheet. | II | 7-10-2015 | 13-10-2016 | Approval | N |
| Change in the address of the active substance manufacturer. | IA | 22-7-2016 | 26-7-2016 | Approval | N |
| Changes to the SmPC. | II | 10-11-2016 | 23-1-2017 | Approval | N |
| Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking;<br>Change in immediate packaging of the finished product;<br>Change in the specification parameters and/or limits of the immediate packaging of the finished product;<br>Change in the shelf-life or storage conditions of the finished product | IA, IB Grouped | 20-12-2018 | 03-04-2019 | Approval | N |