



# **Public Assessment Report**

## **Decentralised Procedures**

**Celecoxib 100 mg capsules, hard**  
**Celecoxib 200 mg capsules, hard**

**(Celecoxib)**

**Procedure Numbers: UK/H/5979/001-02/DC**

**UK Licence Numbers: PL 17907/0526-0527**

**Bristol Laboratories Ltd**

**LAY SUMMARY**  
**Celecoxib 100 mg capsules, hard**  
**Celecoxib 200 mg capsules, hard**  
**(celecoxib)**

This is a summary of the Public Assessment Report (PAR) for Celecoxib 100 mg capsules, hard (PL 17907/0526; UK/H/5979/001/DC) and Celecoxib 200 mg capsules, hard (PL 17907/0527; UK/H/5979/002/DC). It explains how Celecoxib 100 mg and 200 mg capsules, hard were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be collectively referred to as Celecoxib capsules throughout the remainder of this public assessment report (PAR).

For practical information about using Celecoxib capsules, patients should read the package leaflet or contact their doctor or pharmacist.

**What are Celecoxib capsules and what are they used for?**

Celecoxib capsules are ‘generic medicines’. This means that Celecoxib capsules are similar to ‘reference medicines’ already authorised in the European Union (EU) called Celebra 100 mg and 200 mg Capsules, hard (Pfizer AB, Sweden).

Celecoxib capsules are used for the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

**How do Celecoxib capsules work?**

Celecoxib capsules contain the active ingredient celecoxib, which belong to a group of medicinal products called nonsteroidal anti-inflammatory drugs (NSAID), and specifically a sub-group known as (COX-2) inhibitors. The human body makes prostaglandins that may cause pain and inflammation. In conditions such as rheumatoid arthritis and osteoarthritis the patient’s body makes more of these. This medicine acts by reducing the production of prostaglandins, thereby reducing the pain and inflammation.

**How are Celecoxib capsules used?**

The pharmaceutical form of Celecoxib capsules is a capsule and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them too. The patient should check with their doctor or pharmacist if they are not sure. If the patient thinks or feels that the effect of Celecoxib capsules is too strong or too weak, they should talk to their doctor or pharmacist.

The patient’s doctor will tell them what dose they should take depending on the condition being treated. Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

As the risk of side effects associated with heart problems may increase with dose and duration of use, it is important that the patient uses the lowest dose that controls their pain and they should not take Celecoxib capsules for longer than necessary to control symptoms.

Celecoxib capsules should be swallowed whole with a drink of water. The capsules can be taken at any time of the day, with or without food. However, the patient should try to take each dose of Celecoxib capsules at the same time each day.

Patients with difficulty swallowing the capsules can sprinkle the entire capsule content onto a spoonful of semi-solid food, such as cool or room temperature apple sauce, rice gruel, yogurt or mashed banana, and swallow with a drink of water.

The patient should contact their doctor within two weeks of starting treatment if they do not experience any benefit.

This medicine can only be obtained with a prescription.

### **What benefits of Celecoxib capsules have been shown in studies?**

Because Celecoxib capsules are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference products, Celebrex 100 mg and 200 mg Capsules, hard (Pharmacia GmbH/Pfizer Pharma GmbH, Germany), which are equivalent to Celebra 100 mg and 200 mg Capsules, hard (Pfizer AB, Sweden). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

### **What are the possible side effects of Celecoxib capsules?**

Because Celecoxib capsules are generic medicines and are bioequivalent to the reference medicines, Celebrex 100 mg and 200 mg Capsules, hard, their benefits and possible side effects are taken as being the same as those for the reference products.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Celecoxib capsules, see section 4 of the package leaflet available on the MHRA website.

### **Why was Celecoxib capsules approved?**

It was concluded that, in accordance with EU requirements, Celecoxib capsules have been shown to have comparable quality and to be bioequivalent to Celebrex 100 mg and 200 mg Capsules, hard. Therefore, the MHRA decided that, as for Celebrex 100 mg and 200 mg Capsules, hard; the benefits are greater than the risks and recommended that they can be approved for use.

### **What measures are being taken to ensure the safe and effective use of Celecoxib capsules?**

A risk management plan (RMP) has been developed to ensure that Celecoxib capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Celecoxib capsules including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

### **Other information about Celecoxib capsules**

Germany, Spain and the UK agreed to grant Marketing Authorisations for Celecoxib capsules on 11 January 2016. Marketing Authorisations were granted in the UK on 22 January 2016. The full PAR for Celecoxib capsules follows this summary.

This summary was last updated in June 2021.

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## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Celecoxib 100 mg and 200 mg capsules, hard (PL 17907/0526-0527; UK/H/5979/001-02/DC) could be approved. These products are Prescription-Only Medicines (POM), indicated in adults for the symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

The decision to prescribe a selective cyclooxygenase-2 (COX-2) inhibitor should be based on an assessment of the individual patient's overall risks.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany and Spain as Concerned Member States (CMSs). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The originator products for these applications are Celebra 100 mg and 200 mg capsule, hard (Pfizer AB, Sweden). The UK reference products are Celebrex 100 mg and 200 mg Capsules, hard (PL 00057/1275-1276; Pfizer Limited). The reference product used in the bioequivalence study was Celebrex 200 mg Capsules, hard (Pharmacia GmbH/Pfizer Pharma GmbH, Germany). This reference product is accepted as belonging to the same global marketing authorisation as Celebrex 200 mg Capsules, hard (Pfizer AB, Sweden) and is considered to be acceptable for the purposes of demonstration of bioequivalence.

Celecoxib is an oral, selective, cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range (200-400 mg daily). No statistically significant inhibition of COX-1 (assessed as *ex vivo* inhibition of thromboxane B2 [TxB2] formation) was observed in this dose range in healthy volunteers.

One bioequivalence study was submitted to support these applications comparing the applicant's test product, Celecoxib 200 mg capsules, hard with the reference product, Celebrex 200 mg Capsules, hard (Pharmacia GmbH/Pfizer Pharma GmbH, Germany) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki; ICH GCP; Schedule-Y and other regulatory provisions under the Drug Cosmetics Rules; GCP Guidelines issued by Central Drugs Standard Control Organisation (CDSCO); "Ethical Guidelines for Biomedical Research on Human Subjects" published by Indian Council of Medical Research (ICMR) and in accordance with European guidelines (EMA) requirement.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on products being generic medicinal products of originator products that have been in clinical use for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products.

## II QUALITY ASPECTS

### II.1 Introduction

These products are hard capsules. Each capsule contains 100 mg or 200 mg of celecoxib, as an active ingredient. Other ingredients consist of the pharmaceutical excipients:

Capsules content:

Lactose monohydrate, sodium laurilsulfate, povidone, croscarmellose sodium and magnesium stearate.

Capsules shells:

Titanium dioxide E171, gelatin and sodium laurilsulfate.

Printing ink:

Shellac, propylene glycol, yellow iron oxide E172, indigotine E132 (100 mg strength only) and shellac, propylene glycol and yellow iron oxide E172 (200 mg strength only).

The finished products are packaged in aluminium/polyvinylchloride (PVC) or aluminium/aluminium blister packs containing 2, 5, 6, 10, 20, 30, 40, 50, 60 or 100 capsules.

Alternatively the products can be supplied in high density polyethylene (HDPE) containers with child resistant polypropylene caps containing 60, 100 or 500 capsules.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

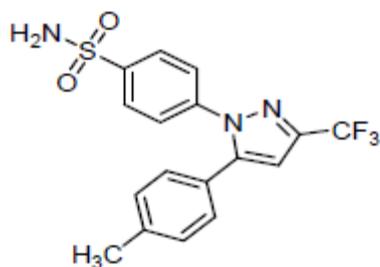
### II.2 ACTIVE SUBSTANCE

INN: Celecoxib

Chemical name:

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-  
1H-pyrazole-1-yl] benzene sulfonamide.

Structure:



Molecular formula: C<sub>17</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S

Molecular weight: 381.38 g/mol

Description: White to off-white powder

Solubility Practically insoluble in water, soluble in anhydrous ethanol and soluble in dichloromethane.

Celecoxib is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, celecoxib, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

## **II.3 DRUG PRODUCTS**

### **Pharmaceutical development**

The objective of the development programme was to formulate safe, efficacious, capsules containing 100 mg or 200 mg celecoxib that are generic versions of the reference products Celebrex 100 mg and 200 mg Capsules, hard (Pfizer AB, Sweden). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* dissolution profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of yellow iron oxide, which is controlled to a suitable National Formulary (NF) specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable specifications and certificates of analysis data have been provided for each excipient.

With the exception of lactose monohydrate and gelatin, none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE). Confirmation has also been given that the magnesium stearate used in the capsules is of vegetable origin.

### **Manufacture of the products**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial scale batches have been provided.

### **Finished Product Specifications**

The finished product specifications proposed are acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

### **Stability of the Products**

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for blister packs. Once the bottle is opened the product should be used within 60 days. This medicine does not require any special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

## **II.4 Discussion on chemical, pharmaceutical and biological aspects**

The grant of marketing authorisations is recommended.

## **III NON-CLINICAL ASPECTS**

### **III.1 Introduction**

As the pharmacodynamic, pharmacokinetic and toxicological properties of celecoxib are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

### **III.2 Pharmacology**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### **III.3 Pharmacokinetics**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### **III.4 Toxicology**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### **III.5 Ecotoxicity/environmental risk assessment (ERA)**

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

### **III.6 Discussion on the non-clinical aspects**

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

## **IV CLINICAL ASPECTS**

### **IV.1 Introduction**

The clinical pharmacology of celecoxib is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of applications. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of celecoxib.

Based on the data provided, Celecoxib capsules can be considered bioequivalent to Celebrex 100 mg and 200 mg Capsules, hard (Pharmacia GmbH/Pfizer Pharma GmbH, Germany).

### **IV.2 Pharmacokinetics**

In support of these applications, the applicant submitted the following bioequivalence study:

**This is an open label, randomised, two-treatment, two-period, two-sequence single dose, crossover study to compare the pharmacokinetics of the applicant's test product, Celecoxib 200 mg capsules, hard versus the reference product, Celebrex 200 mg Capsules, hard (Pharmacia GmbH/Pfizer Pharma GmbH, Germany), in healthy adult subjects under fasting conditions.**

The subjects were administered a single dose (200 mg) of either the test or the reference product following an overnight fast of at least 8 hours. Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 16 days.

## Results

**Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  median, range)**

| Treatment          | AUC <sub>0-t</sub><br>ng/ml/h   | AUC <sub>0-∞</sub><br>ng/ml/h | C <sub>max</sub><br>ng/ml    | t <sub>max</sub><br>h |
|--------------------|---|-------------------------------|------------------------------|-----------------------|
| Test               | 6057.18 (2478.76)   | 6287.54 (2462.20)             | 643.89 (392.84)              | 2.25 (1.00 – 6.00)    |
| Reference          | 5696.18 (2255.84)   | 5921.80 (2249.24)             | 611.54 (320.00)              | 2.13 (1.00 – 6.00)    |
| *Ratio (90% CI)    | 105.45%<br>(98.33 – 113.09%)  |                               | 103.70%<br>(93.45 – 115.07%) |                       |
| AUC <sub>0-t</sub> | Area under the plasma concentration curve from administration to last observed concentration at time t.<br>AUC <sub>0-72h</sub> can be reported instead of AUC <sub>0-t</sub> , in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products |                               |                              |                       |
| AUC <sub>0-∞</sub> | Area under the plasma concentration curve extrapolated to infinite time.<br>AUC <sub>0-∞</sub> does not need to be reported when AUC <sub>0-72h</sub> is reported instead of AUC <sub>0-t</sub>   |                               |                              |                       |
| C <sub>max</sub>   | Maximum plasma concentration  |                               |                              |                       |
| t <sub>max</sub>   | Time until C <sub>max</sub> is reached  |                               |                              |                       |

*\*ln-transformed values*

## Conclusion

The 90% confidence intervals of the test/reference ratio for AUC<sub>0-t</sub> and C<sub>max</sub> values for celecoxib for the 200 mg strength lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr\*\*). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Celebrex 200 mg Capsules, hard (Pharmacia GmbH/Pfizer Pharma GmbH, Germany).

As the 100 mg and 200 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 200 mg capsule strength can be extrapolated to the 100 mg strength capsule.

### IV.3 Pharmacodynamic

No new pharmacodynamic data were submitted and none were required for applications of this type.

### IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

### IV.5 Clinical safety

No new safety data were submitted and none were required for these applications.

#### **IV.6 Risk Management Plan (RMP) and Pharmacovigilance System**

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Celecoxib 100 mg and 200 mg capsules, hard.

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

#### **IV.7 Discussion on the clinical aspects**

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant's test product Celecoxib 200 mg capsules, hard versus the reference product, Celebrex 200 mg Capsules, hard (Pharmacia GmbH/Pfizer Pharma GmbH, Germany).

As the 100 mg and 200 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 200 mg capsule strength can be extrapolated to the 100 mg strength capsule.

The grant of Marketing Authorisations is recommended for these applications.

### **V USER CONSULTATION**

A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to (UK/H/5680/001-02/DC) for scientific content and (SE/H/1275/01-03/DC). The bridging report submitted by the applicant is acceptable.

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

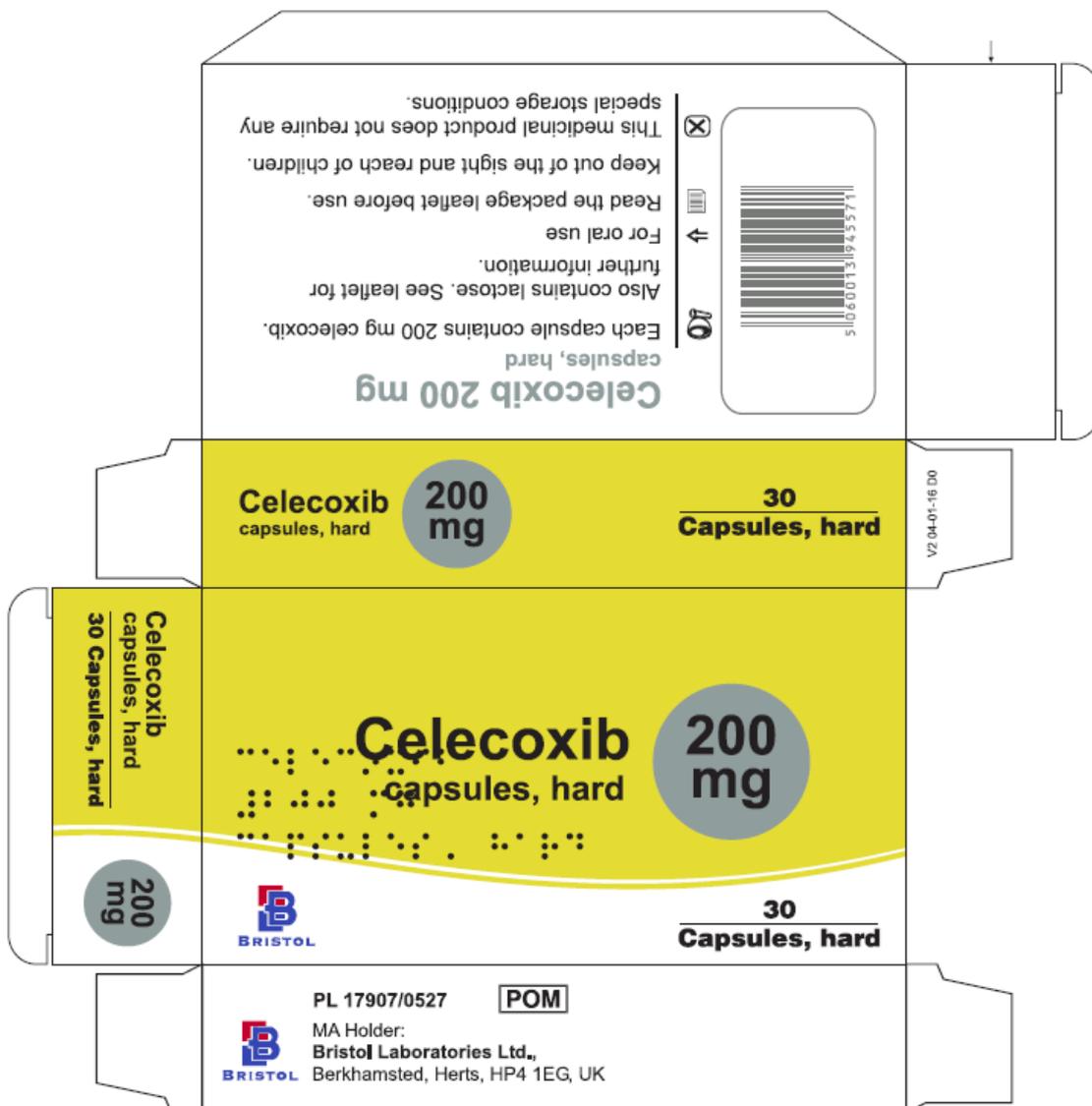
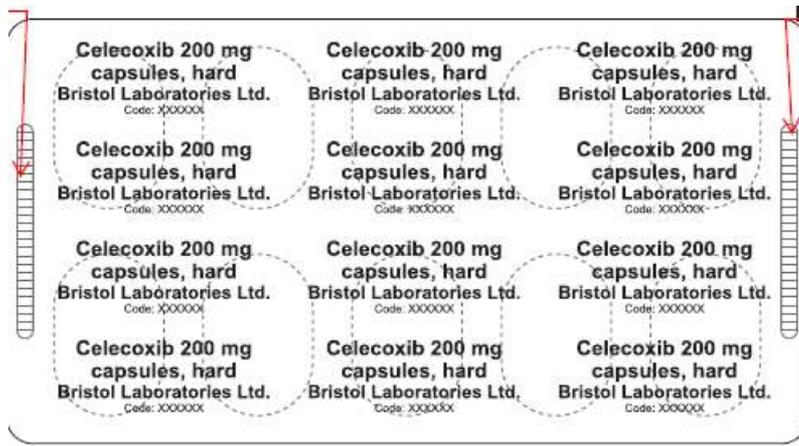
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with celecoxib is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.





**TABLE OF CONTENT OF THE PAR UPDATE**

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

| <b>Applicat<br/>ion type</b> | <b>Scope</b>  | <b>Product<br/>information<br/>affected</b> | <b>Date of<br/>grant</b> | <b>Outcome</b> | <b>Assessment<br/>report<br/>attached<br/>Y/N</b> |
|------------------------------|---|---|--------------------------|----------------|---|
| Type IB                      | To update Sections 4.4 and 5.1 of the SmPCs and PIL in line with the reference products Celebrex capsules, hard | SmPC and PIL                                | 05/05/2021               | Approved       | Yes   |

## Annex 1

**Reference:** PL 17907/0526-7 – 0013  
**Product:** Celecoxib 100 mg and 200 mg capsules, hard  
**Type of Procedure:** National  
**Submission category:** Type IB Variation

### Reason

To update Sections 4.4 and 5.1 of the SmPC and PIL in line with the reference products Celebrex capsules, hard.

### Supporting evidence

The Company has submitted updated sections of the SmPCs and PIL.

### Evaluation

The updated documents are satisfactory.

### Conclusion

The proposed changes are acceptable.

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

**Decision:** Grant

**Date:** 05 May 2021