

IPAR



**Public Assessment Report for a
Medicinal Product for Human Use**

Scientific Discussion

Celecoxib 100 mg hard capsules
Celecoxib
PA23176/002/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6239/001-002/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 12th September 2019 under procedure number IE/H/1050/001-002/DC.

Please note the following detail for the product in IE:

Marketing Authorisation Number: PA0343/002/001-002

Marketing Authorisation Holder: Key Pharmaceuticals Ltd.

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

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 hard capsules (PL 34424/0003-4; UK/H/6239/001-2/DC), are approvable. The 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 Ireland as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The applicant has cross-referred to Celebrex 100 mg and 200 mg Capsules originally authorised to Monsanto PLC (PL00790/0024& PL 08821/0058) on 02 May 2000. These licenses underwent change of ownership procedures to Pharmacia limited (PL 00032/0399-0400) on 01 September 2002 and then to the current Marketing Authorisation holder, Pfizer Limited (PL 00057/1275-1256), on 03 May 2011.

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.

Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane.

Celecoxib is a diaryl-substituted pyrazole, chemically similar to other non-arylamine sulfonamides (e.g. thiazides, furosemide) but differs from arylamine sulfonamides (e.g. sulfamethoxazole and other sulfonamide antibiotics).

A bioequivalence study was submitted to support these applications comparing the applicant's test product Celecoxib 200 mg hard capsules with the reference product Celebrex 200 mg hard Capsules, hard (Pfizer Limited, UK) under fasting conditions. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

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

The finished product is presented as a capsule and each capsule contains 100 mg or 200 mg of celecoxib, as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

Capsules content:

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

Capsules shells:

Titanium dioxide E171 and gelatin.

Printing ink:

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

All excipients comply with their respective European Pharmacopoeia monographs with the exception of printing ink, which is controlled by an in-house 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.

The finished products are packaged in clear or opaque Alu- polyvinylchloride (PVC) blisters with pack sizes of 30 and 60 capsules.

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

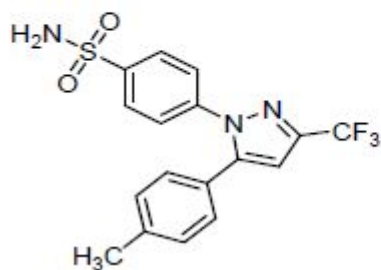
II.2 Drug Substance

INN: Celecoxib

Chemical name:

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

Structure:



Molecular formula: C₁₇H₁₄F₃N₃O₂S

Molecular weight: 381.4 g/mol

Description: White to off-white powder.

Solubility Practically insoluble in water, soluble in anhydrous ethanol and soluble in methylene chloride.

Celecoxib is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential impurities have been identified and monitored appropriately.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been provided supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a 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 (Pfizer Limited, UK). A satisfactory account of the pharmaceutical development has been provided.

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

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing processes have been validated using the minimum commercial scale batch sizes and has shown satisfactory results. The applicant has committed to perform further process validation on three full scale commercial batches of each capsule strength post approval.

Finished Product Specification

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 Product

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 27 months with a storage condition 'Do not store above 30°C'.

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

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

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 100 mg and 200 mg hard capsules are intended for generic substitution, their use 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 generic medicinal products of originator products that have 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 application. 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 hard capsules (Pfizer Limited, UK).

IV.2 Pharmacokinetics

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

STUDY

An open-label, balanced, randomised, two treatment, two-period, two-sequence, single oral dose, crossover, comparative bioequivalence study of the applicant's test product Celecoxib 200 mg hard capsules versus the reference product, Celebrex 200 mg hard capsules (Pfizer Limited, UK), 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 10 hours. Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 14 days.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} median,range)

Treatment	AUC _{0-t} ng/ml/h	AUC _{0-∞} ng/ml/h	C _{max} ng/ml	t _{max} h
Test	8653.430 ± 4659.2270	9099.066 ± 5320.4628	917.960 ± 548.0126	2.667 (1.000 – 6.000)
Reference	8891.976 ± 5565.6533	9537.958 ± 7677.5915	992.022 ± 570.4658	2.667 (1.333 – 6.017)
*Ratio (90% CI)	98.5% (93.78 – 103.36%)	98.6% (93.93 – 103.54)	91.6% (84.29 – 99.48%)	
<p>AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products</p> <p>AUC_{0-∞} Area under the plasma concentration curve extrapolated to infinite time. AUC_{0-∞} does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}</p> <p>C_{max} Maximum plasma concentration</p> <p>t_{max} Time until C_{max} is reached</p>				

*In-transformed values

Conclusion

The 90% confidence intervals of the test/reference ratio for AUC_{0-t} and C_{max} 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 hard Capsules (Pfizer Limited, UK).

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 Pharmacodynamics

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

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application 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 hard capsules.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk: Allergic and bronchopulmonary reactions in patients sensitive to sulphonamides, aspirin or other NSAIDs	<p>The risk of allergic and bronchopulmonary reactions in patients sensitive to sulphonamides, aspirin or other NSAIDs including celecoxib is described in SPC sections 4.3 and 4.4 and PIL section 2.</p> <p>Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise this risk.</p> <ul style="list-style-type: none"> • Prescription only medicine 	None
Important Identified Risk: Gastro-intestinal effects (including perforation, ulcer and bleeding)	<p>The risk of gastrointestinal effects including perforation, ulcer and bleeding associated with use of medicinal product is described in SPC sections 4.3 and 4.4 and PIL sections 2.</p> <p>Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise this risk.</p> <ul style="list-style-type: none"> • Prescription only medicine 	None
Important Identified Risk: Arterial thrombotic events (myocardial infarction; stroke)	<p>The risk of arterial thrombotic events such as myocardial infarction and stroke associated with use of medicinal product is described in SPC sections 4.3, 4.4, 4.8 and 5.1 and PIL sections 2 and 4.</p> <p>Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks.</p> <ul style="list-style-type: none"> • Prescription only medicine 	None
Important Identified Risk: Fluid retention and oedema	<p>The risk of fluid retention and oedema associated with use of medicinal product is described in SPC sections 4.4 and 4.8 and PIL sections 2 and 4.</p> <p>Appropriate advice is provided to the prescriber and other healthcare professionals through SPC</p>	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p>and to the patients through PIL to minimise these risks.</p> <ul style="list-style-type: none"> • Prescription only medicine 	
<p>Important Identified Risk:</p> <p>Hypertension</p>	<p>The risk of onset of new hypertension or worsening of pre-existing hypertension associated with use of medicinal product is described in SPC sections 4.4 and 4.8 and PIL sections 2 and 4.</p> <p>Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks.</p> <ul style="list-style-type: none"> • Prescription only medicine 	None
<p>Important Identified Risk:</p> <p>Renal toxicity</p>	<p>The risk of renal toxicity associated with use of medicinal product is described in SPC sections 4.2, 4.3, 4.4 and 5.2 and PIL sections 2 and 3.</p> <p>Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks.</p> <ul style="list-style-type: none"> • Prescription only medicine 	None
<p>Important Identified Risk:</p> <p>Severe hepatic reactions including hepatitis and hepatic failure</p>	<p>The risk of severe hepatic reactions including hepatitis, liver necrosis and hepatic failure associated with use of medicinal product is described in the SPC sections 4.2, 4.3, 4.4 and 5.2 and PIL sections 2 and 3.</p> <p>Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks.</p> <ul style="list-style-type: none"> • Prescription only medicine 	None
<p>Important Identified Risk:</p> <p>Serious skin and systemic hypersensitivity reactions</p>	<p>The risk of serious skin and systemic hypersensitivity reactions associated with use of medicinal product is described in SPC sections 4.3 and 4.4 and PIL sections 2 and 4.</p> <p>Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks.</p>	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<ul style="list-style-type: none"> • Prescription only medicine 	
Important Identified Risk: Concurrent use with warfarin and other anticoagulants (increased risk of serious bleeding events)	The risk of bleeding events associated with use of medicinal product is described in SPC sections 4.4 and 4.5 and PIL section 2. Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks. <ul style="list-style-type: none"> • Prescription only medicine 	None
Important Identified Risk: Dose dependent increased risk of adverse effects in CYP2C9 poor metabolisers	Dose dependent increased risk of adverse effects in CYP2C9 poor metabolisers associated with use of medicinal product is described in SPC sections 4.2, 4.4, 4.5 and 5.2 and PIL section 2. Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks. <ul style="list-style-type: none"> • Prescription only medicine 	None
Important Identified Risk: Concurrent use with CYP2D6 substrates	The risk of side effects due to overdose when celecoxib is concurrently administered with CYP2D6 substrates is described in SPC sections 4.4 and 4.5 and PIL section 2. Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks. <ul style="list-style-type: none"> • Prescription only medicine 	None
Important Identified Risk: Use during pregnancy (embryo/foetal effects; premature closure of the ductus arteriosus; increased bleeding risk)	The risks of use of celecoxib during pregnancy such as embryo/foetal effects; premature closure of the ductus arteriosus; increased bleeding risk are described in SPC sections 4.3, 4.6 and 5.3 and PIL section 2. Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks. <ul style="list-style-type: none"> • Prescription only medicine 	None
Important Potential	The risk of infertility in women trying to become pregnant associated with use of medicinal	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Risk: Impairment of female fertility	product is described in SPC sections 4.6 and 4.8 and PIL sections 2 and 4. Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks. <ul style="list-style-type: none">• Prescription only medicine	
Important Potential Risk: Safety during breast-feeding	The risk of adverse effects to new born receiving celecoxib through breast milk of lactating woman is described in SPC sections 4.3, 4.6 and 5.3 and PIL section 2. Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks. <ul style="list-style-type: none">• Prescription only medicine	None
Missing information: Use in children	Celecoxib is not indicated for use in children. A warning statement concerning not using celecoxib in children is included in SPC section 4.2 and PIL section 3. Appropriate advice is provided to the prescriber and other healthcare professionals through SPC and to the patients through PIL to minimise these risks. <ul style="list-style-type: none">• Prescription only medicine	None

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 hard capsules versus the reference product, Celebrex 200 mg hard capsules (Pfizer Limited, UK).

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. OVERALL CONCLUSIONS

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

The package leaflet meets the criteria for readability, as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Bioequivalence has been demonstrated between the applicant's products and the reference products. Extensive clinical experience with celecoxib is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

VI. REVISION DATE

April 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/6239/001-002/ DC to IE/H/1050/001-002/D C	N/A	N/A	N/A	Approved 12/09/2019
MA Transfer	CRN00C5D7	SmPC Section 7, 8, 10 Leaflet New MA Holder: Lexon Pharmaceuticals (Ireland) Limited New PA number: PA23176/002/001	16/04/2021	16/04/2021	Approved