COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Etoricoxib Strides 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets (etoricoxib)

NL/H/4720/001-004/DC

Date: 6 March 2023

This module reflects the scientific discussion for the approval of Etoricoxib Strides 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/6365/001-004/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

ETORICOXIB 30 MG FILM-COATED TABLETS
ETORICOXIB 60 MG FILM-COATED TABLETS
ETORICOXIB 90 MG FILM-COATED TABLETS
ETORICOXIB 120 MG FILM-COATED TABLETS
(etoricoxib)

Procedure No: UK/H/6365/001-004/DC

UK Licence No: PL 42852/0003-0006

Generic Partners UK Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

Etoricoxib 30 mg film-coated tablets
Etoricoxib 60 mg film-coated tablets
Etoricoxib 90 mg film-coated tablets
Etoricoxib 120 mg film-coated tablets
(etoricoxib)

This is a summary of the Public Assessment Report (PAR) for Etoricoxib 30 mg film-coated tablets (PL 42852/0003; UK/H/6365/001/DC), Etoricoxib 60 mg film-coated tablets (PL 42852/0004; UK/H/6365/002/DC), Etoricoxib 90 mg film-coated tablets (PL 42852/0005; UK/H/6365/003/DC) and Etoricoxib 120 mg film-coated tablets (PL 42852/0006; UK/H/6365/004/DC). It explains how the applications for Etoricoxib 30, 60, 90 & 120 mg film-coated tablets 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 Etoricoxib 30, 60, 90 & 120mg film-coated tablets.

For practical information about using Etoricoxib 30, 60, 90 & 120 mg film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

These medicinal products will be referred to as Etoricoxib tablets for the remainder of this summary, for ease of reading.

What are Etoricoxib tablets and what are they used for?
Etoricoxib tablets are 'generic medicines'. This means that Etoricoxib tablets are similar to 'reference medicines' already authorised in the European Union (EU) called ARCOXIA 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets.

Etoricoxib tablets are used to reduce the pain and swelling (inflammation) in the joints and muscles of people 16 years of age and older with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and gout. Etoricoxib tablets are also used for the short-term treatment of moderate pain after dental surgery in people 16 years of age and older.

How do Etoricoxib tablets work?
These products contain the active substance etoricoxib. Etoricoxib is one of a group of medicines called selective COX-2 inhibitors. These belong to a family of medicines called non-steroidal anti-inflammatory drugs (NSAIDs), which work by reducing inflammation.

How are Etoricoxib tablets used?
These medicines can only be obtained with a prescription.

Patients should not take more than the recommended dose for their condition. A doctor will want to discuss the treatment from time to time. It is important that patients use the lowest dose that controls their pain and they should not take Etoricoxib tablets for longer than necessary. This is because the risk of heart attacks and strokes might increase after prolonged treatment, especially with high doses.

There are different strengths available for this medicinal product and depending on the disease a doctor will prescribe the tablet strength that is appropriate.

The recommended dose for osteoarthritis is 30 mg once a day, increasing to a maximum of 60 mg once a day if needed.

The recommended dose for rheumatoid arthritis is 60 mg once a day, increasing to a maximum of 90 mg once a day if needed.

The recommended dose for ankylosing spondylitisis is 60 mg once a day, increasing to a maximum of 90 mg once a day if needed.

When used for the treatment of acute pain conditions, Etoricoxib tablets should be used only for the acute painful period.

The recommended dose for gout is 120 mg once a day which should only be used for the acute painful period, limited to a maximum of 8 days treatment.

The recommended dose for postoperative dental surgery pain is 90 mg once daily, limited to a maximum of 3 days treatment.

This medicine should not be taken by children or adolescents under 16 years of age.

What benefits of Etoricoxib tablets have been shown in studies?
As Etoricoxib tablets are generic medicines, studies in people have been limited to tests to determine that they are bioequivalent to the reference medicines, ARCOXIA 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Etoricoxib tablets?
As Etoricoxib tablets are generic medicines, their possible side effects are taken as being the same as those of the reference medicines, ARCOXIA 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets.

For the full list of all side effects reported with Etoricoxib tablets, see section 4 of the package leaflet.

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

Why were Etoricoxib tablets approved?
It was concluded that, in accordance with EU requirements, Etoricoxib tablets have been shown to have comparable quality and to be bioequivalent to ARCOXIA 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets. Therefore, the MHRA decided that, as for ARCOXIA 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets, the benefits outweigh the identified risks and recommended that Etoricoxib tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Etoricoxib tablets?
A risk management plan (RMP) has been developed to ensure that Etoricoxib tablets 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 leaflets for Etoricoxib tablets 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 and reviewed continuously.

Other information about Etoricoxib tablets
Italy, Spain, the Netherlands and the UK agreed to grant Marketing Authorisations for Etoricoxib tablets on 04 October 2017.
Following a National phase, Marketing Authorisations were granted in the UK on 31 October 2017.

The full PAR for Etoricoxib tablets follows this summary. For more information about treatment with Etoricoxib tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2017.

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Etoricoxib 30, 60, 90 & 120 mg film-coated tablets (PL 42852/0003-6; UK/H/6365/001-004/DC) could be approved. The applications were submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS) and Italy, the Netherlands and Spain as Concerned Member States (CMS).

These products are prescription only medicines (legal classification POM).

These applications were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of ARCOXIA 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets (PL 04900/0001-4) which were granted Marketing Authorisations to Merck Sharp and Dohme BV on 31 October 2015, following a Change of Ownership from Merck, Sharp & Dohme Limited. The 30 mg film-coated tablets were originally granted a Marketing Authorisation (PL 00025/0478) on 22 October 2007. The 60 mg, 90 mg and 120 mg tablets were originally granted Marketing Authorisations (PL 00025/0422-24) on 13 February 2002.

Etoricoxib 30, 60, 90 & 120mg film-coated tablets are indicated in adults and adolescents 16 years of age and older for the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis, and the pain and signs of inflammation associated with acute gouty arthritis. They are also indicated in adults and adolescents 16 years of age and older for the short-term treatment of moderate pain associated with dental surgery. The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.

These products contain the active substance etoricoxib, which is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor. Across clinical pharmacology studies, etoricoxib produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily. Etoricoxib did not inhibit gastric prostaglandin synthesis and had no effect on platelet function.

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.

With the exception of the bioequivalence study, no new clinical or 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.

A bioequivalence study was performed, which compared the pharmacokinetics of the test product, Etoricoxib 120 mg film-coated tablets, to those of the reference product, ARCOXIA 120 mg film-coated tablets (Merck Sharp and Dohme BV), under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved at the end of procedure on 04 October 2017. After a subsequent national phase, licences were granted in the UK on 31 October 2017.

II QUALITY ASPECTS

II.1 Introduction

Etoricoxib 30 mg film-coated tablets are blue-green, apple-shaped, biconvex film-coated tablets debossed with 'ET' on one side and '30' on the other side. Each film-coated tablet contains 30 mg of etoricoxib.

Etoricoxib 60 mg film-coated tablets are dark-green, apple-shaped, biconvex film-coated tablets debossed with 'ET' on one side and '60' on the other side. Each film-coated tablet contains 60 mg of etoricoxib.

Etoricoxib 90 mg film-coated tablets are white, apple-shaped, biconvex film-coated tablets debossed with 'ET' on one side and '90' on the other side. Each film-coated tablet contains 90 mg of etoricoxib.

Etoricoxib 120 mg film-coated tablets are pale-green, apple-shaped, biconvex film coated tablets debossed with 'ET' on one side and '120' on the other side. Each film-coated tablet contains 120 mg of etoricoxib.

Other ingredients consist of the pharmaceutical excipients, as follows:
Tablet core:

Microcrystalline cellulose
Calcium hydrogen phosphate (anhydrous)
Croscarmellose sodium
Magnesium stearate

Tablet coating:

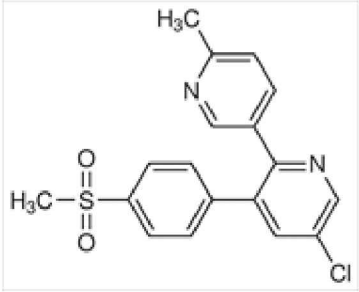
Hypromellose 2910
Lactose monohydrate
Titanium dioxide
Triacetin
Carnuba wax
Iron oxide yellow
Indigo carmine aluminium lake (FD&C Blue#2) (30 mg, 60 mg and 120 mg)

The finished products are packaged in aluminium blisters, in cartons, in a pack sizes of 7 (120 mg only), 28 (all strengths) and 98 (30, 60 and 90 mg only) film-coated tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance

INN: Etoricoxib
Chemical name: 5-Chloro-6'methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine
Structure:



Molecular formula:	$C_{18}H_{15}ClN_2O_2S$
Molecular weight:	358.8
Appearance:	White to yellow powder
Solubility:	Freely soluble in dimethyl sulfoxide and methanol; soluble in ethanol; practically insoluble in water

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture, control, packaging and stability of the active substance.

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 known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

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 generated to support 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 globally acceptable and stable products that could be considered generic medicinal products of the currently licensed products, ARCOXIA 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets (Merck Sharp and Dohme NV).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the highest strength of the applicant's product versus the highest strength of reference product. In addition comparative dissolution profiles of Etoricoxib 120mg Tablets and the lower strengths of Etoricoxib (90mg, 60mg and 30 mg) tablets are also provided.

With the exception of the tablet coating, which is controlled to an in-house specification, all excipients comply with their respective European Pharmacopoeia (Ph. Eur.) monographs.

With the exception of lactose monohydrate, none of the excipients are sourced from animal or human origin. The milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as for human consumption. The magnesium stearate is of vegetable origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products. The manufacturing process has been validated using two production-scale batches of each strength of product. The Applicant commits to performing process validation on a third batch of each strength. The results are satisfactory.

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

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished products in the packaging proposed for marketing.

The results from these studies support a shelf-life of 3 years with the special storage conditions of "Store in the original package in order to protect from moisture".

II.4 Discussion on chemical, pharmaceutical and biological aspects

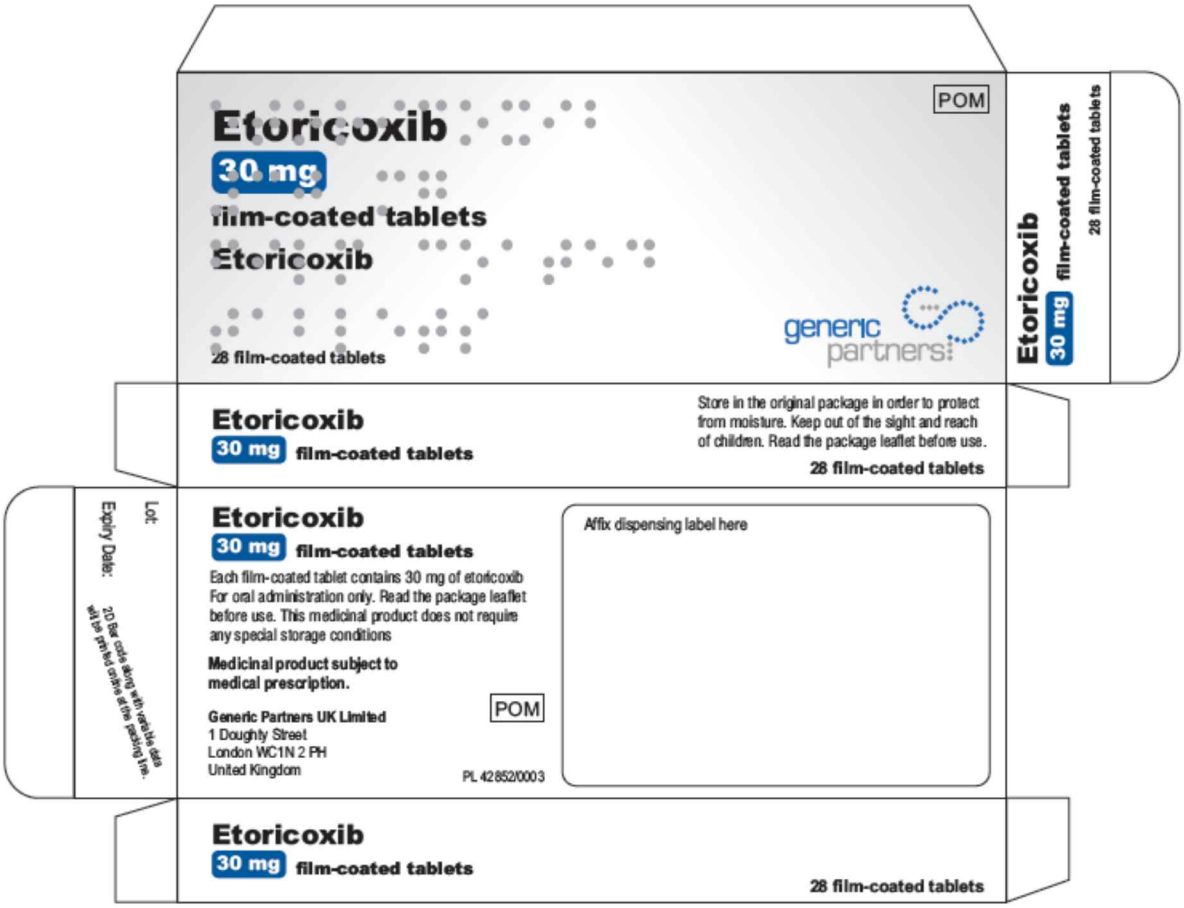
It is recommended that Marketing Authorisations are granted for Etoricoxib 30, 60, 90 & 120 mg film-coated tablets.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPCs, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PIL are available on the MHRA website.

The approved labels are shown below:


Etoricoxib
30 mg
film-coated tablets
Etoricoxib
28 film-coated tablets
POM
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Etoricoxib
30 mg film-coated tablets
28 film-coated tablets
Etoricoxib
30 mg film-coated tablets
Store in the original package in order to protect from moisture. Keep out of the sight and reach of children. Read the package leaflet before use.
28 film-coated tablets
Lot:
Expiry Date:
2D Bar code along with variable data will be printed online at the packing line.
Etoricoxib
30 mg film-coated tablets
Each film-coated tablet contains 30 mg of etoricoxib
For oral administration only. Read the package leaflet before use. This medicinal product does not require any special storage conditions
Medicinal product subject to medical prescription.
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London WC1N 2 PH
United Kingdom
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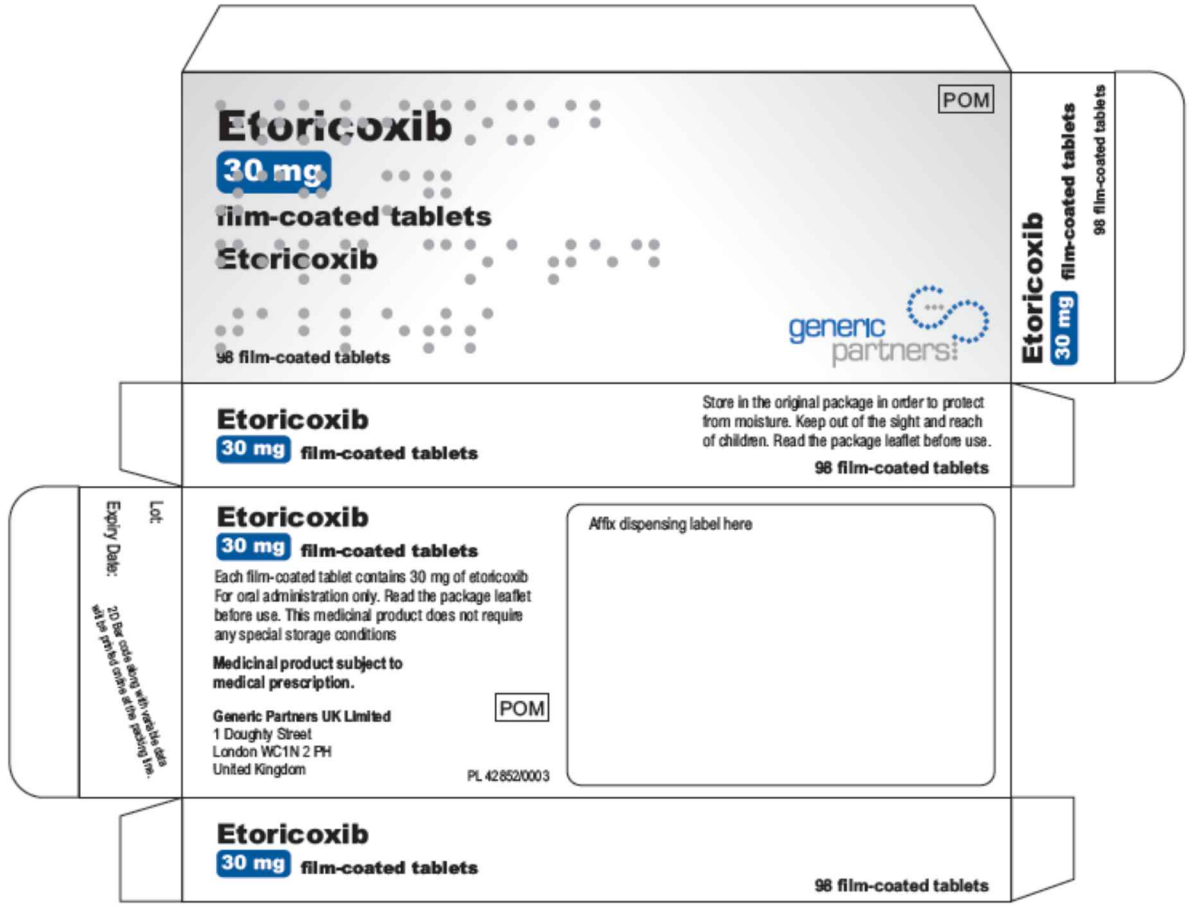
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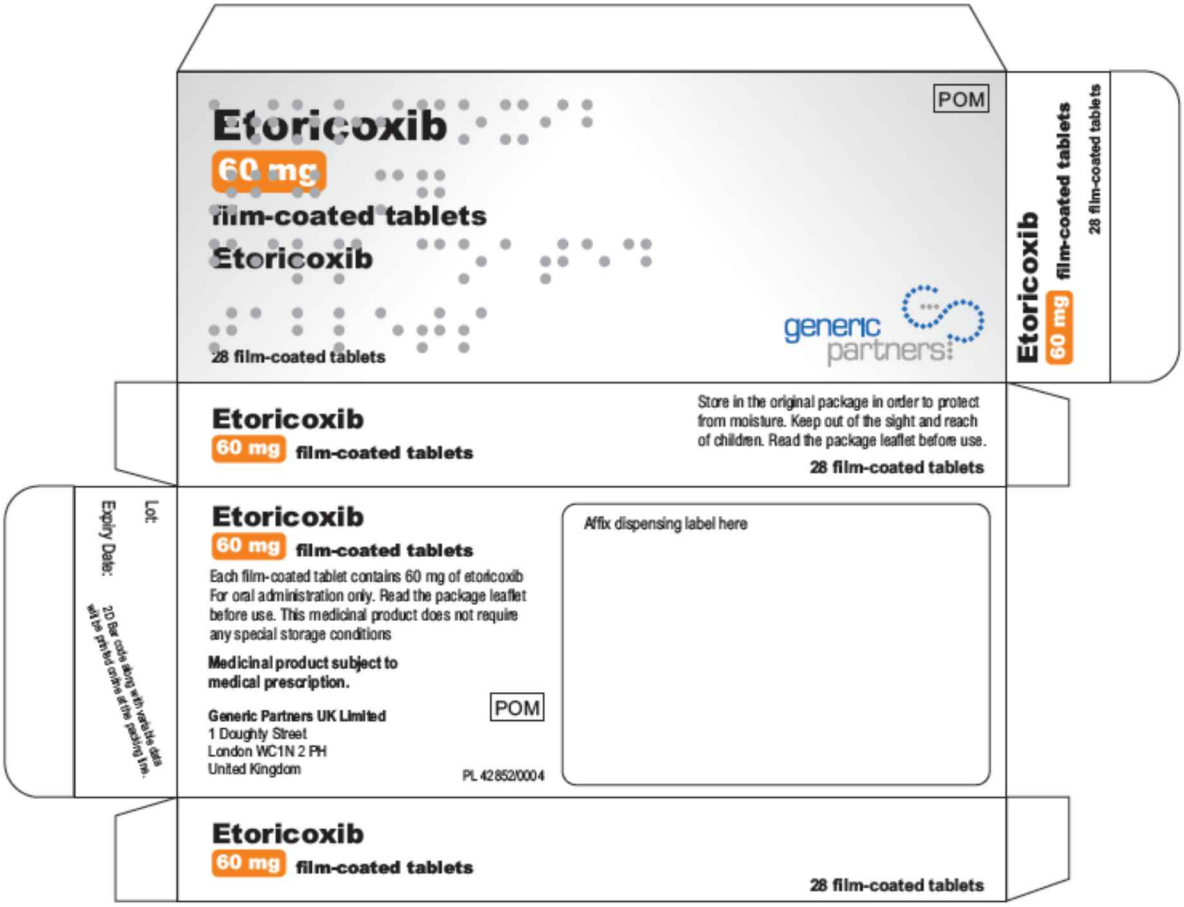
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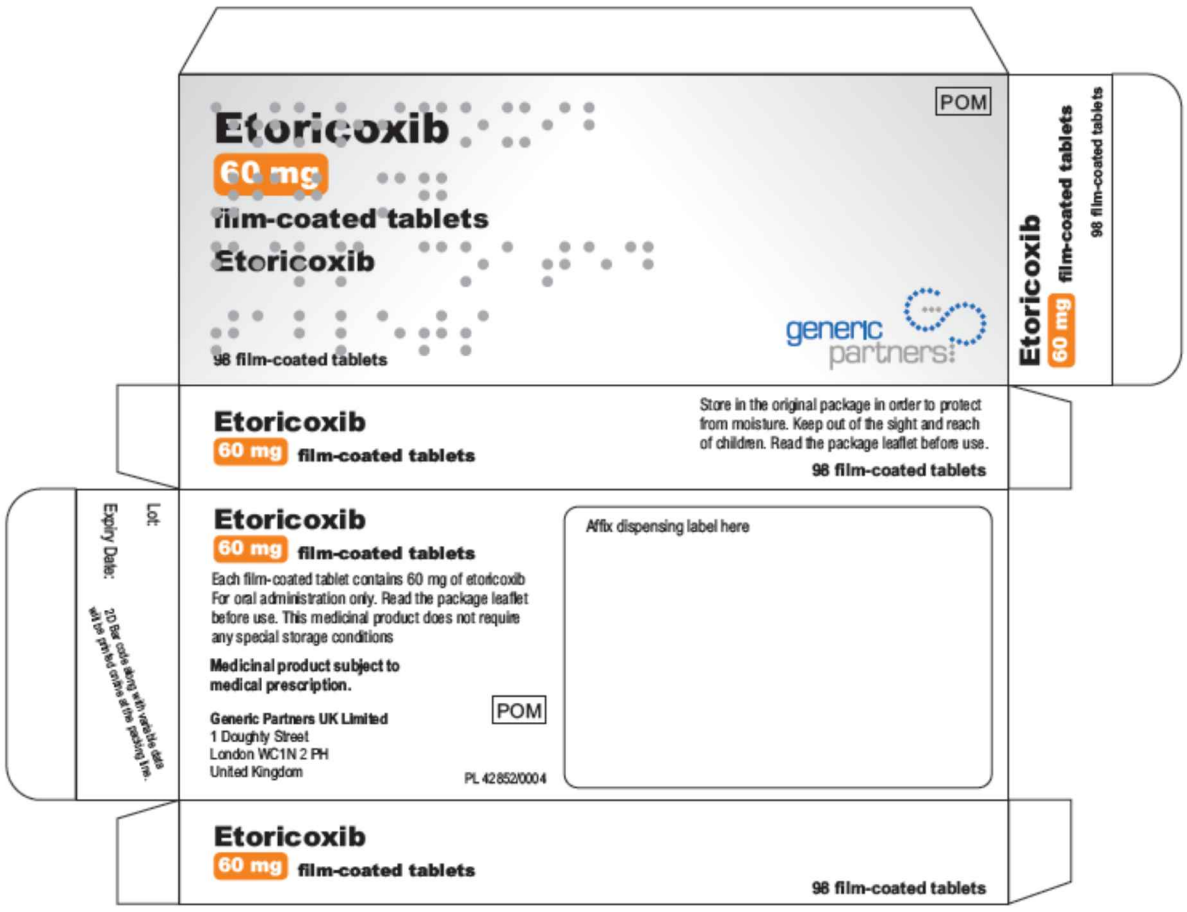
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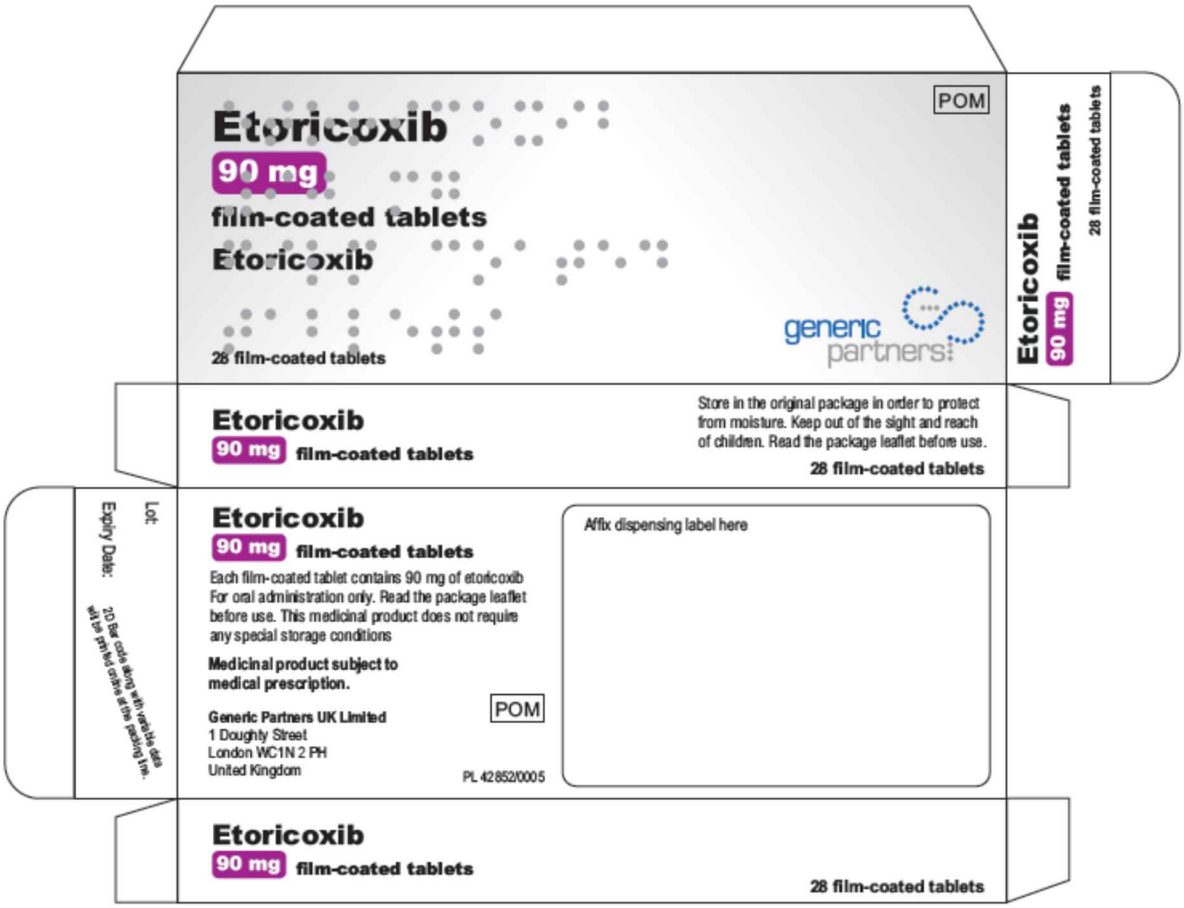
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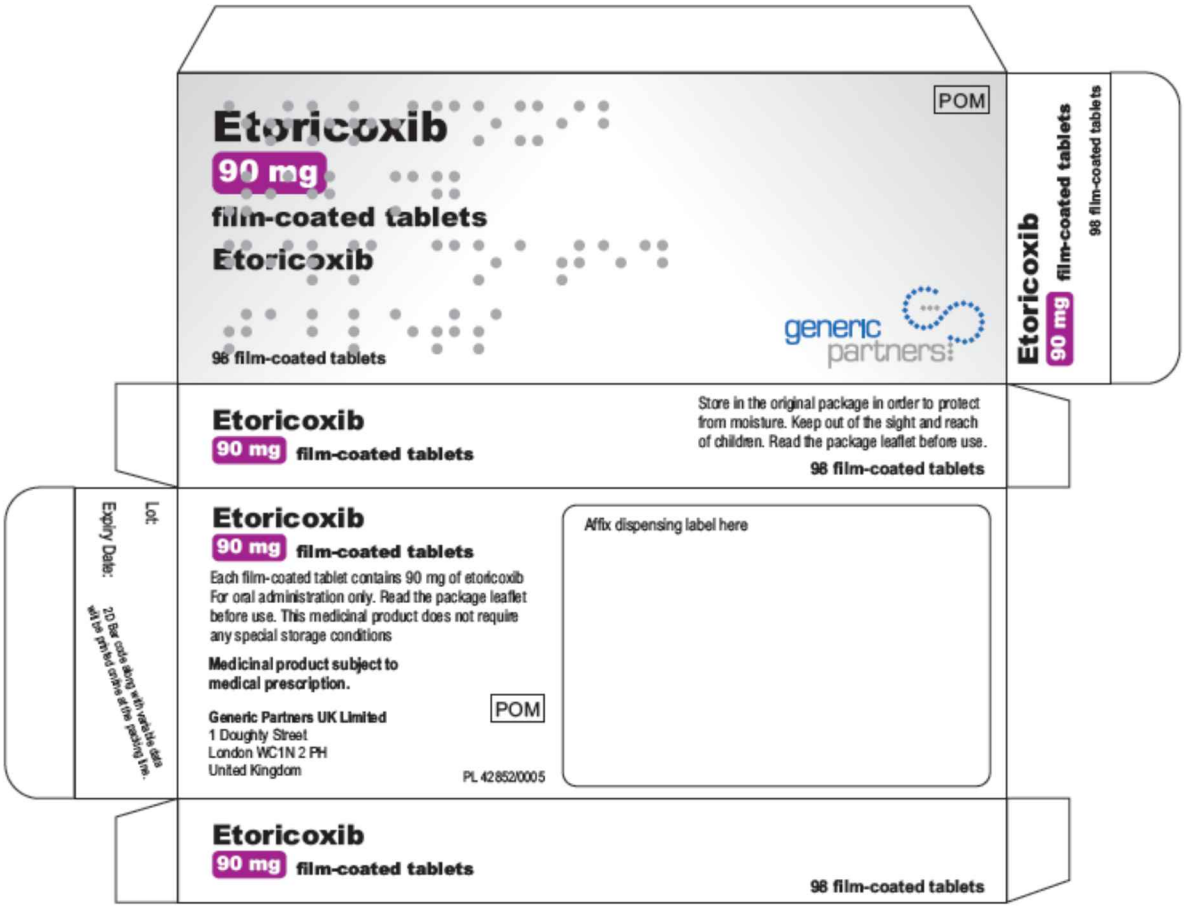
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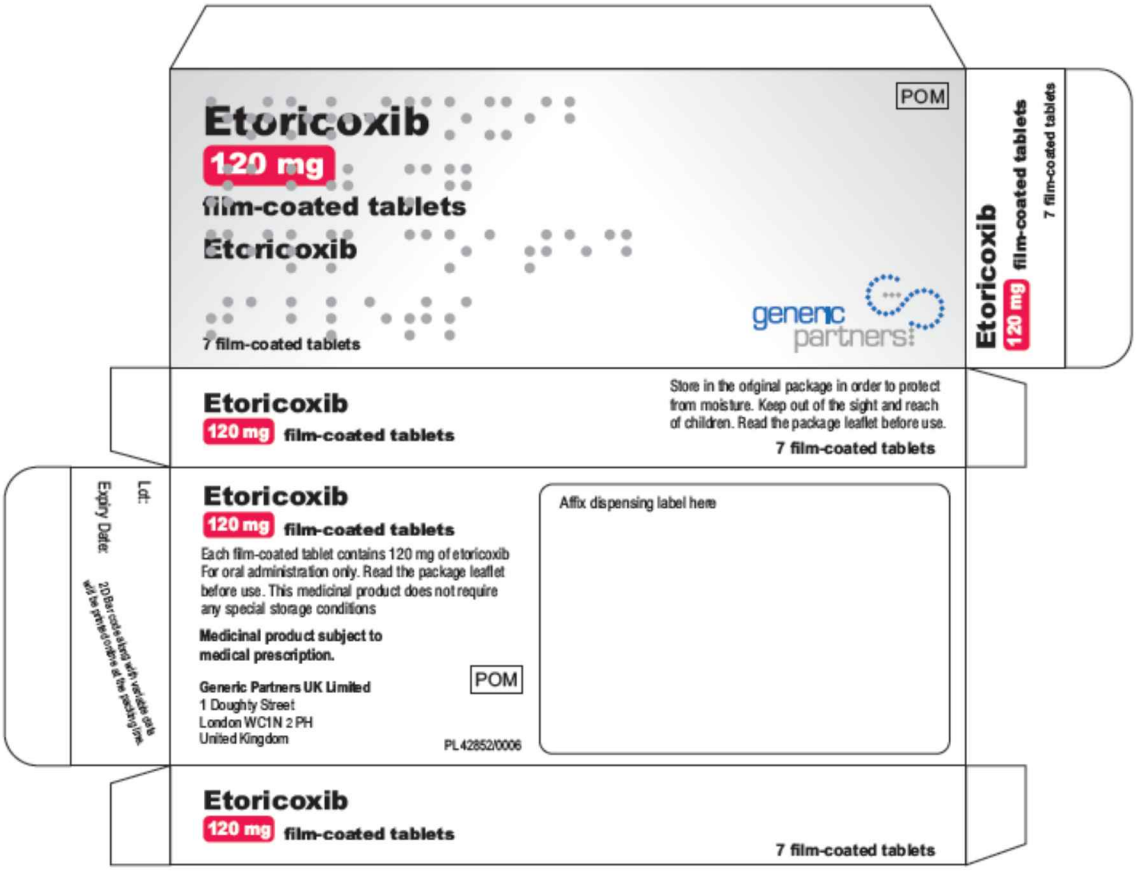
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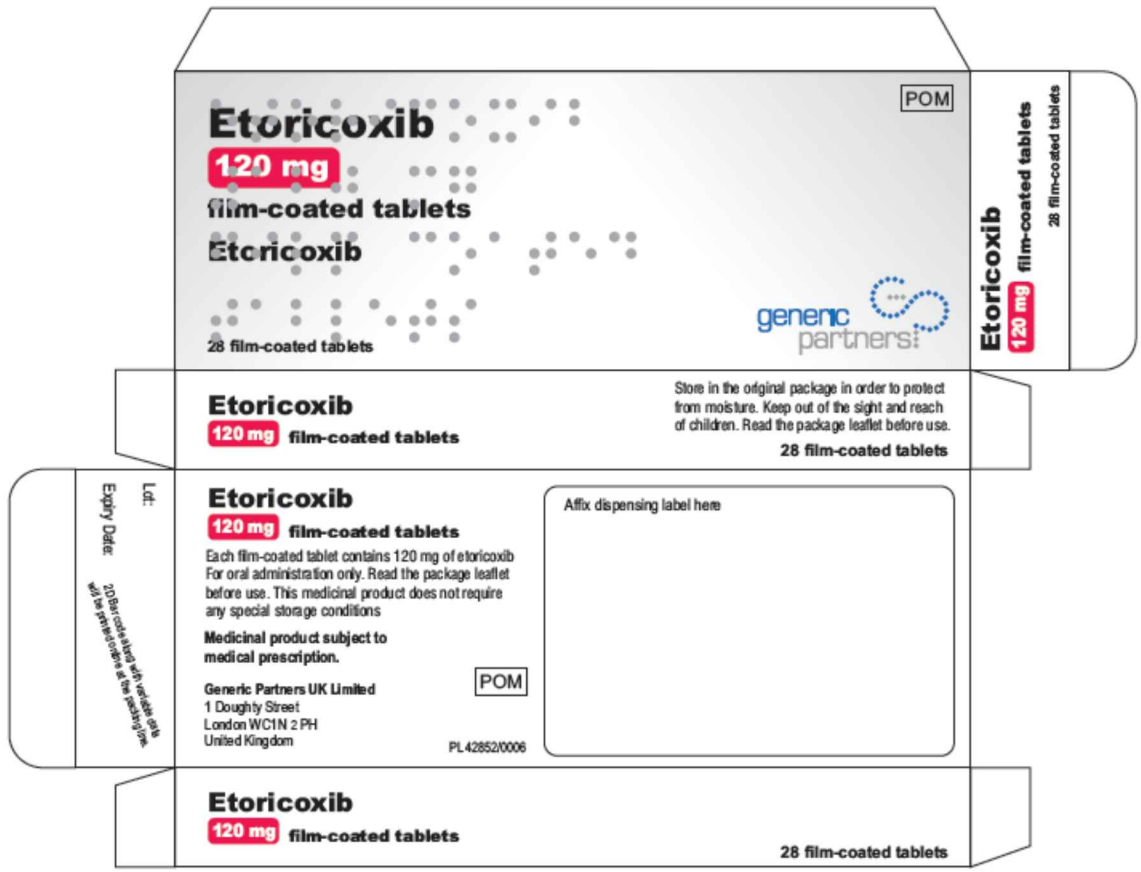
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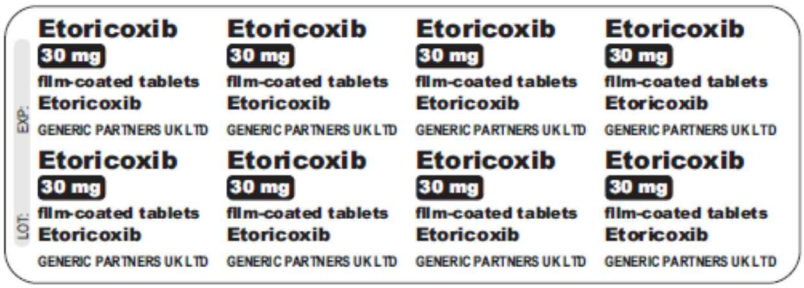
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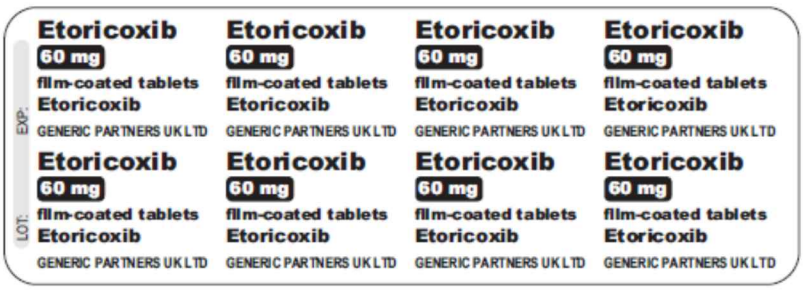
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III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of etoricoxib are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology

No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

As these products are intended for generic substitution of products that are already marketed, no increase in environmental exposure to etoricoxib is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that Marketing Authorisations are granted for Etoricoxib 30, 60, 90 & 120mg film-coated tablets.

IV. CLINICAL ASPECTS

IV.1 Introduction

With the exception of the bioequivalence study detailed below, no new clinical studies have been performed and none are required for this type of application. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

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

A randomised, open-label, single dose, two-treatment, two-period, crossover bioequivalence study, comparing the pharmacokinetics of the test product, Etoricoxib 120mg film-coated tablets, to those of the reference product, ARCOXIA 120 mg film-coated tablets (Merck Sharp and Dohme Ltd) in healthy human volunteers, under fasting conditions.

Following a supervised fast of at least 10 hours, volunteers were given a single oral dose with 240 ml of water. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. Each treatment was separated by a washout period of 10 days.

A summary of the main pharmacokinetic results is presented below:

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

Treatment	AUC_{0-72} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	52332.280 ± 14598.901	N/A	3187.312 ± 973.448	1.00 (0.33-12.00)
Reference	54009.302 ± 13362.859	N/A	2876.929 ± 850.967	1.00 (0.33-8.00)
***Ratio (90% CI)**	96.33% (91.94 - 100.93%)	N/A	111.03% (102.92 - 119.77%)	

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
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

The 90 % confidence intervals for etoricoxib for the ratio of test/reference are within 80.00-125.00% for C_{max} and AUC. Etoricoxib 120 mg film-coated tablets are, therefore, considered bioequivalent to Arcoxia 120 mg Film-coated Tablets (Merck Sharp & Dohme Limited).

As these products meet the bio-waiver criteria specified in the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence studies on the 120mg strength can be extrapolated to the 30, 60 and 90 mg strength tablets.

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety

No new data on safety have been submitted and none are required for applications of this type.

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

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has submitted a 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 Etoricoxib 30, 60, 90 & 120 mg film-coated tablets.

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

Safety concern Etoricoxib 30mg/60mg/ 90mg/120mg Film-Coated Tablets	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Serious gastrointestinal events	Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome , have occurred in patients treated with Etoricoxib. Therefore, Etoricoxib should not be used in patients with active peptic ulceration, active gastro-intestinal (GI) bleeding or inflammatory bowel disease. This information is included with appropriate wording in 4.3 Contraindications of SPC. Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding. There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when Etoricoxib is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see section 5.1). This information is included with appropriate wording in 4.4 Special warnings and precautions for use / 4.5 Interaction with other medicinal products and other forms of interaction of SPC. Undesirable effects regarding gastrointestinal disorders are listed in SPC section 4.8. In the PIL this information is included with appropriate wording in 2. What you need to know before you take ETORICOXIB – Do not take ETORICOXIB, -Warnings and precautions, - Other medicines and ETORICOXIB and 4. Possible side effects.	None proposed

Safety concern Etoricoxib 30mg/60mg/ 90mg/120mg Film-Coated Tablets	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Thrombotic cardiovascular events	The cardiovascular risks of Etoricoxib may increase with dose and duration of exposure. Therefore, the shortest duration possible and the lowest effective daily dose should be used. This information is included with appropriate wording in 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use of the SPC. Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs. Therefore, Etoricoxib should not be used in patients with established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease. This information is included with appropriate wording in 4.3 Contraindications of the SPC. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (see sections 4.2, 4.3, 4.8 and 5.1). Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with Etoricoxib after careful consideration (see section 5.1). COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued (see SPC sections above, 4.5 and 5.1). Medically appropriate supervision should be maintained when using Etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction. This information is included in 4.4 Special warnings and precautions for use of the SPC. Undesirable effects regarding gastrointestinal disorders are listed in SPC section 4.8. Besides, pharmacodynamic properties have been discussed and the results of the studies of the MEDAL Programme are summarized in section 5.1. Etoricoxib should be used at the lowest effective dose and for the shortest duration possible. Since ulcers, bleedings and perforations of the stomach and small intestine can occur without any warning patients should understand the importance of periodic follow-ups. In the PIL this information is included with appropriate wording in 2. What you need to know before you take ETORICOXIB –Do not take ETORICOXIB and –Warnings and precautions; and 4. Possible side effects.	None proposed

Safety concern Etoricoxib 30mg/60mg/ 90mg/120mg Film-Coated Tablets	**Routine risk minimisation measures**	**None proposed**
Important Identified Risks		
Renovascular events: oedema, hypertension and congestive heart failure	As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking Etoricoxib. Therefore, Etoricoxib should not be used in patients with congestive heart failure (NYHA II-IV) and patients with hypertension whose blood pressure is persistently elevated. This information is included in 4.3 Contraindications of the SPC. Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of Etoricoxib should be taken. Hypertension should be controlled before treatment with Etoricoxib (see section 4.3). This information is included with appropriate wording in 4.4 Special warnings and precautions for use. Undesirable effects regarding renovascular events are listed in SPC section 4.8. Besides, pharmacodynamic properties have been discussed and the results of the studies of the MEDAL Programme are summarized in section 5.1. In PIL this information is included with appropriate wording in 2. What you need to know before you take ETORICOXIB –Do not take ETORICOXIB and –Warnings and precautions; and 4. Possible side effects.	None proposed
Hypersensitivity-related events and serious skin reactions	Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance (see section 4.8 of SPC). Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving etoricoxib (see section 4.8 of SPC). Therefore, Etoricoxib should not be used in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Etoricoxib is also contraindicated in patients who, after taking acetylsalicylic or NSAIDs including COX-2	None proposed

	(cyclooxygenase-2) inhibitors, experience bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions. This information is included in 4.3 Contraindications of the SPC. Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. This information is included in 4.4 Special warnings and precautions for use. Undesirable effects regarding hypersensitivity-related events and serious skin reactions are listed in SPC section 4.8 of the SPC. In the PIL this information is included with appropriate wording in 2. What you need to know before you take ETORICOXIB –Do not take ETORICOXIB and 4. Possible side effects.	
Important Potential Risks		
None	Not applicable	Not applicable
Missing Information		
Use in pregnancy and lactating women	The following information is included in 4.3 Contraindications of SPC: Etoricoxib is contraindicated for pregnancy and lactation (see sections 4.6 and 5.3). The following text is included in SPC section 4.6 Fertility, pregnancy and lactation: No clinical data on exposed pregnancies are available for Etoricoxib. Studies in animals have shown reproductive toxicity (see section 5.3). The potential for human risk in pregnancy is unknown. Etoricoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Etoricoxib is contraindicated in pregnancy (see section 4.3). If a woman becomes pregnant during treatment, Etoricoxib must be discontinued. It is not known whether Etoricoxib is excreted in human milk. Etoricoxib is excreted in the milk of lactating rats. Women who use Etoricoxib must not breast feed (see sections 4.3 and 5.3). The use of Etoricoxib, as with any drug substance known to inhibit COX-2, is not recommended in women attempting to conceive. Preclinical safety data have been summarised in section 5.3 of the SPC. In the PIL this information is included with appropriate wording in–Do not take ETORICOXIB; -Warnings and precautions and –Pregnancy, breast-feeding and fertility.	None proposed

Use in patients less than 16 years of age	There is not much experience with Etoricoxib in patients less than 16 years of age. Therefore, Etoricoxib is indicated in adults and adolescents 16 years of age and older. This information is included with appropriate wording in SPC section 4.1 Therapeutic indications. Etoricoxib is contra-indicated in children and adolescents under 16 years of age (sections 4.2 Posology and method of administration and 4.3 Contraindications). Pharmacokinetics have been discussed in section 5.2. In the PIL this information is included with appropriate wording in 1. What ETORICOXIB is and what it is used for; -Do not take ETORICOXIB; -Warnings and precautions; 3. How to take ETORICOXIB and 5. How to store ETORICOXIB.	None proposed
Use in patients with renal insufficiency	Etoricoxib is contraindicated in patients with estimated renal creatinine clearance <30 ml/min. (SPC section 4.3 Contraindications). The following information is included in SPC section 4.4 Special warnings and precautions for use: Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of Etoricoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Monitoring of renal function in such patients should be considered. Undesirable effects are listed section 4.8. Pharmacodynamics have been discussed in section 5.1. Pharmacokinetics have been discussed in section 5.2. In the PIL this information is included with appropriate wording in 2. What you need to know before you take ETORICOXIB –Do not take ETORICOXIB and –Warnings and precautions; and 4. Possible side effects.	None proposed
Use in patients with hepatic impairment	The following information is included in SPC section 4.2 Posology and method of administration. Regardless of indication, in patients with mild hepatic dysfunction (Child-Pugh score 5-6) a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic dysfunction (Child-Pugh score 7-9), regardless of indication, the dose of 30 mg once daily should not be exceeded. Clinical	None proposed

	experience is limited particularly in patients with moderate hepatic dysfunction and caution is advised. There is no clinical experience in patients with severe hepatic dysfunction (Child-Pugh score ≥10); therefore, its use is contra-indicated in these patients (see sections 4.3, 4.4 and 5.2). The following information is included in SPC section 4.4 Special warnings and precautions for use: Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials treated for up to one year with Etoricoxib 30, 60 and 90 mg daily. Any patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored. If signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected, Etoricoxib should be discontinued. Undesirable effects are listed in section 4.8. Pharmacodynamics have been discussed in section 5.1. Pharmacokinetics have been discussed in section 5.2. In the PIL this information is included with appropriate wording in 2. What you need to know before you take ETORICOXIB –Do not take ETORICOXIB and –Warnings and precautions, 3. How to take ETORICOXIB and 4. Possible side effects.	

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Etoricoxib 30, 60, 90 & 120 mg film-coated tablets.

V. USER CONSULTATION

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant's products and the reference products are interchangeable. Extensive clinical experience with etoricoxib is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

Annex 1 Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)