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Public Assessment Report

Name of the Product:

Roticox

30 mg, 60 mg, 90 mg, 120 mg film-coated tablets

(etoricoxib)

Procedure number: HU/H/0435/001-003/DC

Marketing authorisation holder: Krka d.d.

Date: 22 December 2016

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Roticox (Etoricoxib Krka in Belgium and Iceland, Etoxib in Bulgaria, Croatia and Estonia, Etoriax in Germany, Bericox in Latvia and Lithuania) 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets. The holder of the marketing authorisation is Krka d.d.

The active substance is etoricoxib. Each film-coated tablet contains 30 mg, 60 mg, 90 mg or 120 mg etoricoxib, respectively.

The other ingredients are:
tablet core: microcrystalline cellulose, calcium hydrogen phosphate, anhydrous, croscarmellose sodium, sodium stearyl fumarate and colloidal anhydrous silica;
film coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3000, talc, also ferric oxide yellow E172 in the 60 mg tablets while ferric oxide red E172 in the 90 mg and 120 mg tablets.

The 30 mg film-coated tablets are white or almost white, round (diameter: 6 mm), slightly biconvex, film coated tablets with bevelled edges.

The 60 mg film-coated tablets are slightly brownish yellow, round (diameter: 8 mm), biconvex, film coated tablets with bevelled edges, engraved with mark “60” on one side of the tablet.

The 90 mg film-coated tablets are pink, round (diameter: 9 mm), biconvex, film coated tablets with bevelled edges, engraved with mark “90” on one side of the tablet.

The 120 mg film-coated tablets are brownish red, round (diameter: 10 mm), slightly biconvex, film coated tablets with bevelled edges, scored on one side of the tablet. The score line is not intended for breaking the tablet.

The tablets are available in boxes in blisters.

The active substance etoricoxib what 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).

Roticox helps 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.

Roticox is also used for the short term treatment of moderate pain after dental surgery in people 16 years of age and older.

What is osteoarthritis?

Osteoarthritis is a disease of the joints. It results from the gradual breakdown of cartilage that cushions the ends of the bones. This causes swelling (inflammation), pain, tenderness, stiffness and disability.

What is rheumatoid arthritis?
Rheumatoid arthritis is a long term inflammatory disease of the joints. It causes pain, stiffness, swelling, and increasing loss of movement in the joints it affects. It may also cause inflammation in other areas of the body.

What is gout?
Gout is a disease of sudden, recurring attacks of very painful inflammation and redness in the joints. It is caused by deposits of mineral crystals in the joint.

What is ankylosing spondylitis?
Ankylosing spondylitis is an inflammatory disease of the spine and large joints.

What patients need to know before taking Roticox?

Those who
- are allergic to etoricoxib or any of the other ingredients of this medicine,
- are allergic to non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid and COX-2 inhibitors (see 'Possible Side Effects'),
- have a current stomach ulcer or bleeding in the stomach or intestines,
- have serious liver disease,
- have serious kidney disease,
- are or could be pregnant or are breast-feeding (see 'Pregnancy, breast feeding, and fertility'),
- are under 16 years of age,
- have inflammatory bowel disease, such as Crohn's Disease, Ulcerative Colitis, or Colitis,
- have high blood pressure that has not been controlled by treatment (patients should check with their doctor or nurse if not sure whether their blood pressure is adequately controlled),
- have been diagnosed heart problems including heart failure (moderate or severe types), angina (chest pain),
- have had a heart attack, bypass surgery, peripheral arterial disease (poor circulation in legs or feet due to narrow or blocked arteries),
- have had any kind of stroke (including mini-stroke, transient ischaemic attack or TIA, for etoricoxib may slightly increase the risk of heart attack and stroke and this is why it should not be used in those who have already had heart problems or stroke)

must not take Roticox without consulting a doctor.

Warnings and precautions

Patients should discuss their doctor before taking Roticox if they
- have a history of stomach bleeding or ulcers,

- are dehydrated, for example by a prolonged bout of vomiting or diarrhoea,
- have swelling due to fluid retention,
- have a history of heart failure, or any other form of heart disease,
- have a history of high blood pressure (Roticox can increase blood pressure in some people, especially in high doses, and the doctor will want to check the blood pressure from time to time),
- have any history of liver or kidney disease,
- are being treated for an infection (Roticox can mask or hide a fever, which is a sign of infection),
- have diabetes, high cholesterol, or are smoker. These can increase the risk of heart disease,
- are woman trying to become pregnant,
- are over 65 years of age.

Roticox works equally well in older and younger adult patients. If the patient is over 65 years of age, the doctor will want to appropriately keep a check on him/her, however, no dosage adjustment is necessary for patients over 65 years of age.

Children and adolescents

This medicine is not for children and adolescents under 16 years of age.

Other medicines and Roticox

Patients who are taking, have recently taken or might take any other medicines should inform their doctor. This is particularly important if the following medicines are taken for the doctor may want to monitor the patient to check that the medicines are working properly, once taking Roticox has been started:

- medicines that thin their blood (anticoagulants), such as warfarin,
- rifampicin (an antibiotic),
- methotrexate (a drug used for suppressing the immune system, and often used in rheumatoid arthritis),
- ciclosporin or tacrolimus (drugs used for suppressing the immune system),
- lithium (a medicine used to treat some types of depression),
- medicines used to help control high blood pressure and heart failure called ACE inhibitors and angiotensin receptor blockers, examples include enalapril and ramipril, and losartan and valsartan,
- diuretics (water tablets),
- digoxin (a medicine for heart failure and irregular heart rhythm),
- minoxidil (a drug used to treat high blood pressure),
- salbutamol tablets or oral solution (a medicine for asthma),
- birth-control pills (the combination may increase your risk of side effects),
- hormone replacement therapy (the combination may increase the risk of side effects),
- acetylsalicylic acid, the risk of stomach ulcers is greater if taking Roticox with acetylsalicylic acid. However,
  - acetylsalicylic acid for prevention of heart attacks or stroke: Roticox can be taken with low-dose acetylsalicylic acid. If the patient is currently taking low dose acetylsalicylic

acid to prevent heart attacks or stroke, it should not be stopped taking acetylsalicylic acid until discussing the doctor;
- acetylsalicylic acid (like other non-steroidal anti-inflammatory drugs, NSAIDs) in high doses should not be taken while taking Roticox.

Roticox with food and drink

The onset of the effect of Roticox may be faster when taken without food.

Pregnancy, breast-feeding and fertility

Roticox tablets must not be taken during pregnancy. Those who are pregnant or think they could be pregnant, or are planning to become pregnant, do not take the tablets. Those who become pregnant, stop taking the tablets and consult their doctor. Also those who are unsure or need more advice should consult their doctor.

It is not known if Roticox is excreted in human milk. Those who are breast-feeding, or planning to breast-feed, consult their doctor before taking Roticox. Those who are using Roticox must not breast-feed.

As for *fertility*, Roticox is not recommended in women attempting to become pregnant.

Driving and using machines

Dizziness and sleepiness have been reported in some patients taking Roticox. Those who experience dizziness or sleepiness should not drive or use any tools or machines.

How to take Roticox

Patients must not take more than the recommended dose for their condition. The doctor will want to discuss the treatment from time to time. It is important that the patients use the lowest dose that controls their pain and they should not take Roticox 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 the doctor will prescribe the tablet strength that is appropriate for the given patient.

The recommended doses are:

Osteoarthritis: 30 mg etoricoxib once a day that may be increased to a maximum of 60 mg once a day if needed.

Rheumatoid arthritis: 60 mg etoricoxib once a day. The dose can be increased to a maximum of 90 mg.

Ankylosing spondylitis: 60 mg etoricoxib once a day. The dose can be increased to a maximum of 90 mg once a day if needed.

Treatment of acute pain: etoricoxib should be used only for the acute painful period.

Gout: 120 mg once a day which should only be used for the acute painful period, limited to a maximum of 8 days treatment.

Postoperative dental surgery pain: 90 mg once daily, limited to a maximum of 3 days treatment.

People with liver problems

Those who have mild liver disease, you should not take more than 60 mg a day. Those who have *moderate* liver disease should not take more than 30 mg a day.

Use in children and adolescents

Roticox tablets should not be taken by children or adolescents under 16 years of age.

Elderly

No dose adjustment is necessary for elderly patients. As with other medicines, caution should be exercised in elderly patients.

Method of administration: Roticox is for oral use. The tablets should be taken once a day. Roticox can be taken with or without food.

What to do if more Roticox has been taken than it should have been?

Patients should never take more tablets than the doctor recommends. If taking too many Roticox tablets, they should seek medical attention immediately.

What to do if taking Roticox has been forgotten?

It is important to take Roticox as the doctor has prescribed. If missing a dose, patients are advised just to resume their usual schedule the following day. They should not take a double dose to make up for the forgotten tablet.

Possible side effects

Like all medicines, Roticox tablets can cause side effects, although not everybody experiences them.

If developing any of the following signs the patient should stop taking Roticox and see the doctor immediately:
- shortness of breath, chest pains, or ankle swelling appear or if they get worse,
- yellowing of the skin and eyes (jaundice) – these are signs of liver problems,
- severe or continual stomach pain or the stools become black,
- an allergic reaction, which can include skin problems such as ulcers or blistering, or swelling of the face, lips, tongue, or throat which may cause difficulty in breathing

Other side effects that may occur during treatment with Roticox are as follows.

Very common (may affect more than 1 in 10 people): stomach pain.

Common (may affect up to 1 in 10 people):
- dry socket (inflammation and pain after a tooth extraction),
- swelling of the legs and/or feet due to fluid retention (oedema),
- dizziness, headache,
- palpitations (fast or irregular heartbeat), irregular heart rhythm (arrhythmia),
- increased blood pressure,
- wheezing or shortness of breath (bronchospasms),
- constipation, wind (excessive gas), gastritis (inflammation of the lining of the stomach), heartburn, diarrhoea, indigestion (dyspepsia)/stomach discomfort, nausea, being sick (vomiting), inflammation of the oesophagus, mouth ulcers,
- changes in blood tests related to the liver,
- bruising,
- weakness and fatigue, flu-like illness.

Uncommon (may affect up to 1 in 100 people)
- gastroenteritis (inflammation of the gastrointestinal tract that involves both the stomach and small intestine/stomach flu), upper respiratory infection, urinary tract infection,
- changes in laboratory values (decreased number of red blood cells, decreased number of white blood cells, platelets decreased),
- hypersensitivity (an allergic reaction including hives which may be serious enough to require immediate medical attention),
- appetite increases or decreases, weight gain,
- anxiety, depression, decreases in mental sharpness; seeing, feeling or hearing things that are not there (hallucinations),
- taste alteration, inability to sleep, numbness or tingling, sleepiness,
- blurred vision, eye irritation and redness,
- ringing in the ears, vertigo (sensation of spinning while remaining still),
- abnormal heart rhythm (atrial fibrillation), fast heart rate, heart failure, feeling of tightness, pressure or heaviness in the chest (angina pectoris), heart attack,
- flushing, stroke, mini-stroke (transient ischaemic attack), severe increase in blood pressure. inflammation of the blood vessels,
- cough, breathlessness, nose bleed,

- stomach or bowel bloating, changes in your bowel habits, dry mouth, stomach ulcer, inflammation of the stomach lining that can become serious and may lead to bleeding, irritable bowel syndrome, inflammation of the pancreas,
- swelling of the face, skin rash or itchy skin, redness of the skin,
- muscle cramp/spasm, muscle pain/stiffness,
- high levels of potassium in the blood, changes in blood or urine tests relating to the kidney, serious kidney problems,
- chest pain.

Rare (may affect up to 1 in 1,000 people)
- angioedema (an allergic reaction with swelling of the face, lips, tongue and/or throat which may cause difficulty in breathing or swallowing, which may be serious enough to require immediate medical attention)/anaphylactic/anaphylactoid reactions including shock (a serious allergic reaction that requires immediate medical attention),
- confusion, restlessness,
- liver problems (hepatitis),
- low blood levels of sodium,
- liver failure, yellowing of the skin and/or eyes (jaundice),
- severe skin reactions.

How to store Roticox

This medicinal product does not require any special storage conditions but it must be kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Roticox (Etoricoxib Krka, Etoxib, Etoriax, Bericox) 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets. The procedure was finalised at 13 September 2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Belgium, Bulgaria, the Czech Republic, Denmark, Finland, Germany, Ireland, Latvia, Lithuania, Norway, Poland, Portugal, the Slovak Republic, Slovenia, Spain, Sweden and the United Kingdom) concerned the generic version of etoricoxib 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets (Roticox tablets, named Etoricoxib Krka in Belgium and Iceland, Etoxib in Bulgaria, Croatia and Estonia, Etoriax in Germany, Bericox in Latvia and Lithuania).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary.

The originator (reference) product was Arcoxia® 120 mg film-coated tablets (Merck Sharp & Dohme B.V., The Netherlands), authorised for marketing since 2002 in the European Economic Area.

The applicant has adequately demonstrated bioequivalence between the product and reference products.

The product is indicated is 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 and indicated in adults and adolescents 16 years of age and older for the short-term treatment of moderate pain associated with dental surgery.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Roticox film-coated tablets from Krka d.d. Novo mesto, Slovenia.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Roticox 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. generic application).The products have been developed by Krka dd., Novo mesto.

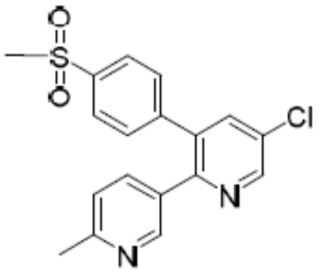
The reference product is Arcoxia® 120 mg film-coated tablet manufactured by Merck Sharp & Dohme B.V., authorised in 2002 in the United Kingdom.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorisation dossier. The Quality Overall Summary is adequate.

International non-proprietary name (INN): etoricoxib
Chemical name: 5-Chloro-6'-methyl-3-[*p*-(methylsulfonyl)phenyl]-2,3'-bi-pyridine

Structure:



The active substance is a white or slight yellowish, crystalline powder. It is freely soluble in methanol, tetrahydrofuran, dimethyl sulfoxide, methyl ethyl ketone, dimethyl formamide, and chloroform, soluble in isopropyl acetate, ethanol and toluene, sparingly soluble in 2-propanol, and practically insoluble in water. Etoricoxib has no asymmetric carbon atom in the molecule. It shows polymorphism, the manufacturer consistently produces the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by elementary analysis, mass spectra, NMR spectra, FT-IR spectra and by XRDP. The impurity profile of the drug substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Etoricoxib is not official in the European Pharmacopoeia (Ph. Eur.). Therefore, an in-house specification has been set for the drug substance, which includes the following tests: appearance, solubility, identification by IR, related substances, assay, residual solvent, genotoxic impurities water content, sulphated ash and microbiological quality.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Council on Harmonisation (ICH) Q6A guideline. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period of is acceptable with no special storage condition.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim of the development was to design a finished product of specified quality, essentially similar to the originator (i.e. reference product) and to establish its manufacturing process to consistently deliver the aimed drug, e.g. easily manufactured, stable formulation in the proposed packaging.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained.

The description of Roticox film-coated tablets per strength are as follows:
- 30 mg: White or almost white, round, slightly biconvex, film-coated tablets with bevelled edges. Diameter: 6 mm, thickness: 2.0 – 3.5 mm;

- 60 mg: slightly brownish yellow, round, biconvex, film-coated tablets with bevelled edges, engraved with mark "60" on one side of the tablet. Diameter: 8 mm, thickness: 2.8 – 3.8 mm;
- 90 mg: pink, round, biconvex, film-coated tablets with bevelled edges, engraved with mark "90" on one side of the tablet. Diameter: 9 mm, thickness: 3.6-4.6 mm;
- 120 mg: Brownish red, round, slightly biconvex, film-coated tablets with bevelled edges, scored on one side of the tablet. The score is not intended for breaking the tablet. Diameter: 10 mm, thickness: 3.6 – 4.6 mm.

The excipients used in the finished products are
- tablet core: microcrystalline cellulose, anhydrous calcium hydrogen phosphate, croscarmellose sodium, sodium stearyl fumarate and anhydrous collidal silica;
- film-coating: poly(vinyl alcohol), titanium dioxide, macrogol, as well as certain strengths yellow or red iron oxide.

The excipients used comply with their respective Ph. Eur. monographs. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is cold form OPA/Al/PVC/Aluminium blisters. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 24 months without any storage restriction is acceptable.

The Summary of Product Characteristics, patient Information Leaflet (package leaflet) and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of etoricoxib are well known. As etoricoxib is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required for a generic application.

III.2 Pharmacology

Etoricoxib is a nonsteroidal anti-inflammatory agent (NSAIA) that is a selective inhibitor of cyclooxygenase-2 (COX-2). It is used in the management of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and the pain and signs of inflammation associated with acute gouty arthritis.

III.3 Pharmacokinetics

The pharmacokinetics of etoricoxib has been well established. There was no need for submission of new non-clinical data.

III.4 Toxicology

Toxicological studies indicated low toxicity of etoricoxib after single administration. Results of repeated dose toxicity revealed that major target organs were gastrointestinal tract where gastritis and gastrointestinal ulceration occurred and kidney with renal papillar necrosis. No mutagenic activity was found in several genotoxicity studies. No carcinogenic potential of etoricoxib was found in mice carcinogenicity studies, while hepatocellular and thyroid follicular cell adenomas occurred in rats. Tumours of these types are a species-specific consequence of hepatic CYP enzyme induction in the rat, while etoricoxib has not been shown to cause hepatic CYP enzyme induction in humans.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Roticox 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets 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

Abridged applications avoid the need for repetitive tests on animals.

The pharmaco-toxicological properties of etoricoxib are well-known. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to etoricoxib.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application for a marketing authorisation, submitted by Krka d. d. Novo mesto, Slovenia via decentralised procedure with Hungary as RMS, concerns an abridged application according to the article 10(1) of the Directive 2001/83/EC (i.e. a generic application). The reference product is Arcoxia® 120 mg film-coated tablet from Merck Sharp & Dohme B.V., The Netherlands (authorised since 2002 in the EU).

IV.2 Pharmacokinetics

This application is a generic one, therefore, demonstration of therapeutic equivalence is shown by means of pharmacokinetic studies.

IV.2.1 Literature data

Orally administered etoricoxib is well absorbed. The absolute bioavailability is approximately 100%. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} = 3.6 μg/ml) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean area under the curve ($AUC_{0\text{-}24hr}$) was 37.8 μg•hr/ml.

The pharmacokinetics of etoricoxib are linear across the clinical dose range.

Dosing with food (a high-fat meal) had no effect on the extent of absorption of etoricoxib after administration of a 120 mg dose. The rate of absorption was affected, resulting in a 36% decrease in C_{max} and an increase in T_{max} by 2 hours. These data are not considered clinically significant. In clinical trials, etoricoxib was administered without regard to food intake.

Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 μg/ml. The volume of distribution at steady state (V_{dss}) was approximately 120 l in humans.

Etoricoxib is extensively metabolised with <1% of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalyzed by CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo*. *In vitro* studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles *in vivo* have not been studied.

Five metabolites have been identified in man. The principal metabolite is the 6'-carboxylic acid derivative of etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.

Following administration of a single 25-mg radiolabelled intravenous dose of etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in faeces, mostly as metabolites. Less than 2% was recovered as unchanged drug.

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to a half-life of approximately 22 hours. The plasma clearance after a 25-mg intravenous dose is estimated to be approximately 50 ml/min.

IV.2.2 Bioequivalence study

One bioequivalence study has been reported in the submitted dossier in order to support essential similarity between etoricoxib 120 mg film-coated tablets (Krka, d.d.) and Arcoxia® 120 mg film-coated tablets (120 mg etoricoxib, Merck Sharp & Dohme B.V., The Netherlands) in healthy adult volunteers under fasting conditions according to the bioequivalence guideline in force (CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010).

The design of this investigation was a pivotal, single-centrum, single-dose, randomized, open-label, laboratory blind, crossover, two-period, two-treatment, two-sequence, bioequivalence study of etoricoxib with a suitable washout period between the two periods, in healthy adult subjects under fasting condition.

Descriptive statistics of pharmacokinetic parameters were arithmetic mean, standard deviation, minimum and maximum, median, CV%, geometric LS (least squares) means for test (T) and reference (R) pharmacokinetic data, log-transformation of $AUC_{0-\infty}$, AUC 0-72 h and C_{max} data, evaluation of data using a linear mixed-effects model, with the main effects of treatment, period, sequence and subjects nested within sequence in ANOVA, calculation of 90% confidence intervals for the difference between the least square means (LSM) for primary parameters, application of non-parametric analysis of T_{max} on untransformed data (Wilcoxon test), descriptive statistics of safety data collected during the whole study period.

Both treatments were well tolerated, with no major side effects and no relevant differences in safety profiles.

The 90% confidence intervals were within the normal acceptance range of 0.80 – 1.25 for AUC_t, AUC_{inf} and C_{max}.

The results are indicated in the next Table.

Pharmacokinetic parameter	*Geometric mean ratio Test/Reference*	*Confidence intervals*	*CV%*
AUC_{0-t}	105.35%	102.71% – 108.07%	6.8
C_{max}	104.14%	98.51% – 110.10%	14.8

The above results prove that the single dose of Test product is bioequivalent with the single dose of Reference product in healthy adult subjects under fasting condition as the point estimates and also their 90% confidence intervals of the primary parameters are entirely in the 80-125% acceptance range.

Biowaiver

The applicant claimed for biowaiver for the dose strengths of 30 mg, 60 mg and 90 mg on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**):

a) All the strengths i.e. 30, 60, 90 and 120mg of proposed pharmaceutical products are manufactured by the same manufacturer and using the same manufacturing process.
b) The qualitative composition of the different strengths is the same.
c) The compositions of the claimed four strengths (30, 60, 90 and 120mg) are proportionally similar.
d) In-vitro dissolution data confirm the in vivo similarity between the claimed strengths.
e) Etoricoxib exhibits linear pharmacokinetics in the claimed therapeutic range (30 mg – 120 mg).

Since all the above requirements have been met, the results of the bioequivalence study with the 120 mg formulation can be extrapolated to the lower strengths, according to conditions in *Guideline on the Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98 Rev. 1/corr*, section 4.1.6.

IV.3 Pharmacodynamics

Etoricoxib is a COX-2 selective inhibitor with anti-inflammatory and anti-rheumatic properties belonging to the group of NSAIDS that selectively inhibits isoform 2 of the enzyme cyclooxygenase (COX-2).

No new pharmacodynamic studies have been submitted what is acceptable for a generic application.

IV.4 Clinical efficacy

The efficacy of etoricoxib has already been demonstrated during the clinical development of the reference product to which Roticox is bioequivalent. No new data have been submitted.

IV.5 Clinical safety

The clinical safety of etoricoxib has been well established. There was no need for submission of new data.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	• Serious gastrointestinal events • Thrombotic cardiovascular events • Renovascular events: Oedema, hypertension and Congestive Heart Failure • Hypersensitivity-related events and serious skin reactions
Important potential risks	• None
Missing information	• Use in pregnancy and lactating women • Use in patients less than 16 years of age • Use in patients with renal insufficiency • Use in patients with hepatic impairment

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to the products Roticox 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets of Krka. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in Summary of Product Characteristics, package leaflet and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to the products of Roticox 30 mg,

60 mg, 90 mg and 120 mg film-coated tablets of Krka. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

Abridged applications avoid the need for repetitive tests on humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

The product has been shown to be essentially similar and refer to a product approved on the basis of a full application with regard to clinical efficacy/safety data. No further such studies have been submitted or are considered necessary. There is no concern about granting of the marketing authorisation from clinical points of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Roticox 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets, generic versions of etoricoxib. The applicant and the future holder of authorisation is Krka d.d., Novo mesto, Slovenia.

The products are indicated for the short term treatment of mild to moderate pain of different origin, as well as for the relief of fever and symptomatic treatment of pain associated with common cold or influenza.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The originator product was Arcoxia® 120 mg film-coated tablets from Merck Sharp & Dohme B.V., The Netherlands.

To support the application the applicant has adequately demonstrated bioequivalence between the test and reference products. The results may be extrapolated to the other strengths on the basis of bioequivalence guideline (*Appendix III, CPMP/EWP/QWP/1401/98/rev 1/Corr***).

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Roticox film-coated tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

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 was English.

The results show that 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. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached