Public Assessment Report

Decentralised Procedure

Axorid 100mg/20mg modified-release capsules
Axorid 150mg/20mg modified-release capsules
Axorid 200mg/20mg modified-release capsules

(Ketoprofen/Omeprazole)

Procedure No: UK/H/1068/002-004/DC

UK Licence No: PL 15142/0090-0092

Meda Pharmaceuticals Limited
LAY SUMMARY

Axorid 100mg/20mg modified-release capsules
Axorid 150mg/20mg modified-release capsules
Axorid 200mg/20mg modified-release capsules

(Ketoprofen/Omeprazole)

The products may be referred to as ‘Axorid modified-release capsules’ in this report.

This is a summary of the Public Assessment Report (PAR) for Axorid 100mg/20mg, 150mg/20mg and 200mg/20mg modified release capsules (PL 15142/0090-0092, UK/H/1068/0002-004/DC, formerly Ketoprofen/Omeprazole Ethypharm 100mg/20mg, 150mg/20mg and 200mg/20mg Modified-Release Capsules). It explains how the applications for Axorid modified-release capsules 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 Axorid modified-release capsules.

For practical information about using Axorid modified-release capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Axorid modified-release capsules and what are they used for?
Axorid modified-release capsules are fixed combination products containing two known active substances, ketoprofen and omeprazole. The products are used in adults and adolescents over the age of 15 years for treating the symptoms of rheumatoid arthritis, a condition called “ankylosing spondylitis” and osteoarthritis. A patient may be given this medicine if he/she needs to be treated with an anti-inflammatory medicine and he/she:
- has a history of stomach or duodenal ulcers,
- is at risk of developing these types of ulcers.

How do Axorid modified-release capsules work?
The active substance, ketoprofen is a non-steroidal anti-inflammatory agent (NSAID) which reduces inflammation. The active substance, omeprazole is a “proton pump inhibitor” which reduces the amount of acid produced in the stomach.

How are Axorid modified-release capsules used?
Axorid modified-release capsules are available as modified-release hard capsules and the route of administration is by mouth (oral).

The patient should always take Axorid modified-release capsules exactly as his/her doctor has advised. The patient should check with his/her doctor or pharmacist if he/she is not sure.

The capsules should not be chewed or crushed; they should always be swallowed whole with a glass of water. The capsules should also be taken with food, for example, at meal times.

The patient’s doctor may prescribe:
- One 100 mg/20 mg capsule daily
- One 150 mg/20 mg capsule daily
- One 200 mg/20 mg capsule daily

The dose depends on the severity of the patient’s symptoms.
The maximum daily dose is one 200 mg/20 mg capsule.

An initial dose of one 100 mg/20 mg capsule is recommended in elderly patients, and in patients with liver, kidney or heart disorders. The dose may be increased by the patient’s doctor up to one 200 mg/20 mg capsule if necessary.

Please read section 3 of the package leaflets for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Axorid modified-release capsules can only be obtained with a prescription.

**What benefits of Axorid modified-release capsules have been shown in studies?**
As Axorid 100mg/20mg, 150mg/20mg and 200mg/20mg modified-release capsules are fixed combination products containing known active substances, studies in patients have been limited to tests to determine that these products are bioequivalent to their active constituents (ketoprofen and omeprazole) as individual products. In addition, the Marketing Authorisation Holder (MAH) has presented data from the scientific literature to support the applications. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Axorid modified-release capsules?**
Like all medicines, Axorid modified-release capsules can cause side effects, although not everybody gets them.

**Common side effects**
(probably affecting less than 1 in 10 people):
- Sleepiness/drowsiness
- Trouble sleeping
- Spinning sensation
- Headache
- Gastrointestinal effects including: blood in stools, vomiting blood, nausea, vomiting, diarrhoea, constipation, flatulence (wind), dyspepsia, abdominal pain, gastrointestinal discomfort and pain, ulcerative stomatitis (inflammation of the oral mucosa with ulcers on the cheeks, tongue, and lips), worsening of colitis and Crohn’s disease

For the full list of all side effects reported with Axorid modified-release capsules, see section 4 of the package leaflets available on the MHRA website.

For the full list of restrictions, see the package leaflet available on the MHRA website.

**Why were Axorid modified-release capsules approved?**
The view was that the benefits of Axorid modified-release capsules outweighed the identified risks and it was recommended that these products be approved for use.

**What measures are being taken to ensure the safe and effective use of Axorid modified-release capsules?**
A Risk Management Plan (RMP) has been developed to ensure that Axorid modified-release capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Axorid modified-release capsules including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Axorid modified-release capsules

Italy, Poland, Portugal, Romania, Spain and the UK agreed to grant Marketing Authorisations for Ketoprofen/Omeprazole 100mg/20mg, 150mg/20mg and 200mg/20mg Modified-Release Capsules on 08 December 2008.

Marketing Authorisations were granted in the UK to Ethypharm on 23 February 2009. Following change of ownership procedures, Marketing Authorisations were granted to Meda Pharmaceuticals Limited.

On 07 October 2009, the products underwent a variation procedure to change the product names to Axorid 100mg/20mg, 150mg/20mg and 200mg/20mg modified release capsules (PL 15142/0090-0092).

The full PAR for Axorid modified-release capsules follows this summary.

For more information about use of Axorid modified-release capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2016.
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I \ \textbf{INTRODUCTION}

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Ketoprofen/Omeprazole Ethypharm 100mg/20mg, 150mg/20mg and 200mg/20mg modified-release capsules (PL 06934/0096-0098; UK/H/1068/002-004/DC) to Ethypharm on 23 February 2009.

The products are Prescription Only Medicines for the treatment of symptomatic treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis in patients with a previous history or who are at risk of developing NSAID associated gastric ulcers, duodenal ulcers and gastro-duodenal erosions in whom continued treatment with ketoprofen is essential.

The applications were submitted as abridged applications according to Article 10b of Directive 2001/83/EC, a fixed combination application containing the active substances omeprazole and ketoprofen.

Omeprazole is a proton-pump inhibitor. It inhibits gastric acid secretion by irreversibly blocking the enzyme system of H⁺/K⁺ ATPase, the "proton pump" of gastric parietal cells. When given in a sufficient dose (e.g. 20 mg of omeprazole a day for 7 days), the daily production of acid secretion can be reduced by more than 95%. Omeprazole also selectively inhibits gastric mucosal carbonic anhydrase, which might contribute to its acid suppressive properties. Omeprazole inhibits both basal and stimulated gastric acid secretion, and protects against gastric mucosal injuries induced by a variety of ulcerogenic agents: water immersion restraint stress and haemorrhage shock.

Ketoprofen, a propionic acid derivative, is a racemic mixture, the S-enantiomer being the more active chiral moiety. The major mechanism of action of ketoprofen and of other NSAIDs is the inhibition of cyclooxygenase (COX), the first enzyme of the prostaglandin (PG) synthesis pathway, leading to a decrease in both prostaglandin and thromboxane synthesis. Ketoprofen inhibits the synthesis of PGE2, which is, with interleukin 1, interleukin 6 and tumour necrosis factor α, the most potent pro-inflammatory lymphokine. Ketoprofen is not a selective inhibitor of COX. It inhibits COX-1, the constitutive isoform found in most normal cells and tissues, including stomach and platelets, and COX-2, the isoform induced in settings of inflammation by cytokines and inflammatory mediators. This non-selectivity accounts for gastroduodenal lesions induced by NSAIDs.

The applications were submitted via the decentralised procedure (UK/H/1068/0002-0004/DC), with the UK as Reference Member State, and Italy, Poland, Portugal, Romania and Spain as Concerned Member States. The procedure was successfully concluded at Day 197 on 8th December 2008. The national licences for Ketoprofen/Omeprazole 100mg/20mg, 150mg/20mg and 200mg/20mg modified-release capsules (PL 06934/0096-0098; UK/H/1068/002-004/DC) in the UK were subsequently granted after the national phase on 23rd February 2009.

Following change of ownership procedures, Marketing Authorisations (PL 15142/0090-0092) were granted to Meda Pharmaceuticals Limited on 01 August 2009.

On 07 October 2009, the products underwent variation procedures to change the product names to Axorid 100mg/20mg, 150mg/20mg and 200mg/20mg modified release capsules (PL 15142/0090-0092).
II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Each Axorid 100 mg/20 mg modified-release capsule contains 100 mg ketoprofen and 20 mg omeprazole, as the active substances.

Each Axorid 150 mg/20 mg modified-release capsule contains 150 mg ketoprofen and 20 mg omeprazole, as the active substances.

Each Axorid 200 mg/20 mg modified-release capsule contains 200 mg ketoprofen and 20 mg omeprazole, as the active substances.

The capsules also contain pharmaceutical excipients namely sucrose, maize starch, hypromellose, dimethicone emulsion (containing propyl-p-hydroxybenzoate (E216), methyl-p-hydroxybenzoate (E218), sorbic acid, sodium benzoate, polysorbate 20, octylphenoxy polyethoxy ethanol and propylene glycol), polysorbate 80, mannitol, diacetylated monoglycerides, talc, methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30%, polyacrylate dispersion 30%, ammonio methacrylate copolymer type A, ammonio methacrylate copolymer type B, triethyl citrate, stearoyl macrogolglycerides and colloidal anhydrous silica. The capsules shell consists of titanium dioxide, gelatin, yellow iron oxide (E172 – 100mg/20mg capsules only) and black iron oxide (E172 – 150mg/20mg capsules only).

Axorid capsules are packaged in polyethylene bottles, with tamper-evident polypropylene screw caps containing silica gel desiccant, contained in cardboard boxes. Pack sizes for all strengths are 28 or 30 capsules.

Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

II.2 DRUG SUBSTANCE

Drug substance – Ketoprofen

INN: Ketoprofen
Chemical Names: (RS)-2-(3-Benzoylphenyl)propionic acid
Benzeneacetic acid, 3-benzoylethyl, (±)-m-Benzoylhydratropic acid

Molecular Formula: C_{16}H_{14}O_{3}

Structure:

![Structure of Ketoprofen]

CAS Number: 22071-15-4
Molecular Weight: 254.281
Appearance: A white or almost white crystalline powder, freely soluble in ethanol (96%), acetone, dichloromethane and practically insoluble in water.

Ketoprofen is the subject of a European Pharmacopoeia monograph.

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

Appropriate specifications are provided for the active substance ketoprofen. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and all comply with the proposed specifications.

Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

Based on stability data provided, suitable retest periods have been set.

**Drug substance – Omeprazole**

**INN:** Omeprazole  
**Chemical Names:** 5-Methoxy-2-[(RS)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-sulfinyl]-1H-benzimidazole  
**Molecular Formula:** C$_{17}$H$_{19}$N$_3$O$_3$S  
**Structure:**

![Structure of Omeprazole](image)

**CAS Number:** 73590-58-6  
**Molecular Weight:** 345.4  
**Appearance:** A white or almost white powder. It is freely soluble in ethanol, methanol acetone, isopropanol and very slightly soluble in water.

Omeprazole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of active omeprazole are supported by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

**II.3 MEDICINAL PRODUCT**  
**Pharmaceutical Development**

The objective of the pharmaceutical development programme was to produce tolerable, efficacious products containing 100mg, 150mg and 200mg ketoprofen combined with 20mg omeprazole.

A suitable product development section has been provided. The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated, and are satisfactory. The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies. Suitable data have been submitted concerning the manufacturing process development and development of the container closure system.

With the exception of the dimethicone emulsion, diacetylated monoglycerides, and yellow and black iron oxide (which all comply with suitable in-house specifications), all excipients comply with their respective European Pharmacopoeia monograph. Yellow iron oxide and black iron oxide have been shown to comply with EC Directive 95/45/EC. An EDQM Certificate of Suitability controls the
dimethicone used in the manufacture of the dimethicone emulsion. Satisfactory Certificates of Analysis have been provided for all ingredients showing compliance with their respective monograph/specification.

With the exception of gelatin, none of the excipients is of animal or human origin. EDQM Certificates of Suitability have been provided from all suppliers of gelatin, showing that it is produced in-line with current guidelines for the minimisation of transmission of BSE/TSE.

**Manufacturing Process**
A description and flow-chart of the manufacturing method has been provided. Satisfactory batch formulae have been provided for all strengths of the finished product.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results are satisfactory.

**Control of Finished Product**
The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Stability of the product**
Stability studies were performed in accordance with current guidelines, using product manufactured by the proposed finished product manufacturer and in the packaging proposed for marketing. The results support a shelf-life of 18 months, with the storage conditions “Do not store above 25 degrees” and “Store in the original container in order to protect from moisture”.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that Marketing Authorisations are granted for these applications.

**II.5 Summaries of Product Characteristics (SmPCs), 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 PILs are available on the MHRA website. The current labelling is presented below:

**Axorid 100mg/20 mg modified-release capsules:**
PAR Axorid 100mg/20mg, 150mg/20mg and 200mg/20mg modified-release capsules

One capsule contains 100 mg of Ketoprofen and 20 mg of Omeprazole. Also contains: sucrose, propyl p-hydroxybenzoate, methyl p-hydroxybenzoate. See the package leaflet for further information.

Oral route:
The capsules should be swallowed whole with a glass of water and with food e.g. at meal time. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Read the package leaflet before use.

Do not store above 25°C. Store in the original container in order to protect from moisture.

PL 1514200090 POM
Axorid 150mg/20 mg modified-release capsules:
PAR Axorid 100mg/20mg, 150mg/20mg and 200mg/20mg modified-release capsules

One capsule contains 100 mg of Ketoprofen and 20 mg of Omeprazole. Also contains: Lactose monohydrate, Corn starch, MCC, gelatin, talc, polyethylene glycol 4000, phenylalanine, magnesium stearate.

Axorid 150mg/20mg, 200mg/20mg modified-release capsules

The capsules should be swallowed whole with a glass of water and with food e.g. at meal times.

Keep out of the reach and sight of children.

The capsules should be protected from moisture.

Do not store above 25°C. Store in the original container in order to protect from moisture.

Read the package leaflet before use. Do not store above 25°C. Store in the original container in order to protect from moisture.

For further information, see the package leaflet for further information.

Aventis Pharma Limited

Axorid

Meda Pharmaceuticals Ltd.,
Skyway House, Parsonage Road,
Takeley, Bishop's Stortford, CM22 6PU

Batch n
Exp (mm/yyyy)
Axorid 200mg/20 mg modified-release capsules:
One capsule contains 200 mg of Ketoprofen and 20 mg of Omeprazole. Also contains: sucrose, propyl-p-hydroxybenzoate, methyl-p-hydroxybenzoate. See the package leaflet for further information.

Oral route.
The capsules should be swallowed whole with a glass of water and with food e.g. at meal times.

**KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.**

Read the package leaflet before use.
Do not store above 25°C. Store in the original container in order to protect from moisture.

PL 15142/0092  POM
PAR Axorid 100mg/20mg, 150mg/20mg and 200mg/20mg modified-release capsules

One capsule contains 200 mg of Ketoprofen and 20 mg of Omeprazole. Also contains: sucrose, propyl-p-hydroxybenzoate, methyl-p-hydroxybenzoate.

See the package leaflet for further information.

Oral route.

The capsules should be swallowed whole with a glass of water and with food e.g. at meal times.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Read the package leaflet before use.
Do not store above 25°C.
Store in the original container in order to protect from moisture.

MEDA
Meda Pharmaceuticals Ltd.
Seymour House, Pimlico Road,
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CM22 8BU

PL 15142/0092 PL 15142/0092

PAR Axorid 100mg/20mg, 150mg/20mg and 200mg/20mg modified-release capsules

One capsule contains 200 mg of Ketoprofen and 20 mg of Omeprazole. Also contains: sucrose, propyl-p-hydroxybenzoate, methyl-p-hydroxybenzoate. See the package leaflet for further information.

Oral route. The capsules should be swallowed whole with a glass of water and with food e.g. at meal times.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Read the package leaflet before use.

Do not store above 25°C. Store in the original container in order to protect from moisture.

PL 15142/0092  POM
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of ketoprofen and omeprazole 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 non-clinical overview (expert report) has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

The non-clinical information contained in the SmPCs is broadly similar to the information given in SmPCs for other omeprazole and ketoprofen products, and are satisfactory.

III.2 Pharmacology

Pharmacodynamics
The properties of omeprazole and ketoprofen are well-known.

Development or exacerbation of gastroduodenal or intestinal ulcers with the risk of bleeding and perforation is a well-known risk of all inhibitors of prostaglandin synthesis, especially of those like ketoprofen that inhibit both COX-1 and COX-2. Prostaglandin inhibits gastric acid secretion and has other protective effects on the gastric mucosa, such as stimulation of mucus and bicarbonate secretion, and of gastric mucosal blood flow.

Because of their mechanisms of action on their respective target cells and tissues, no pharmacodynamic interaction is anticipated between omeprazole and ketoprofen when given simultaneously.

An adequate review of the data on omeprazole and ketoprofen has been presented. The properties of both have been well-characterised and there is no need for an extensive re-assessment here. It is accepted that there is little potential for pharmacodynamic interactions.

Safety pharmacology
No safety pharmacology data have been presented, but some discussion of the secondary pharmacodynamic has been included, covering gastrointestinal damage, and effects on the kidney, platelets, gestation and labour.

Given the extensive clinical experience with omeprazole and ketoprofen, both individually and together, the absence of specific non-clinical data is acceptable.

III.3 Pharmacokinetics
Proton-pump inhibitors are unstable at a low pH. Omeprazole oral dosage forms are supplied as enteric-coated formulations. The granules dissolve only at alkaline pH, thus preventing degradation of the drug by acidity in the oesophagus and stomach.

A review of the pharmacokinetics of both drugs in humans and animals has been presented. Since these data are well-known, they will not be reproduced here.

Pertinent to the combination, omeprazole is almost completely metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP2C19 to form hydroxyl-omeprazole, and to a small extent by CYP3A to form omeprazole-sulfone. The metabolites are inactive and are excreted mostly in the urine, and to a lesser extent in bile. Ketoprofen, however, is not metabolised by the P450 system but by conjugation with glucuronic acid, nor does it induce metabolising enzymes. These differing metabolic mechanisms suggest that there will be no pharmacokinetic interactions between the two drugs.
An adequate review of the pharmacokinetic data has been presented. The data support the applicant’s view that there is little potential for pharmacokinetic interactions.

III.4 Toxicology

Omeprazole

Omeprazole is generally of a low order of toxicity; however, in both dogs and rats, a reversible gastric mucosa cell hyperplasia and rugal hypertrophy have been found after high doses of omeprazole are given for a period of 3 months or more.

In two 24-month carcinogenicity studies in rats, omeprazole at doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 5 to 420 times the human dose) caused end-life gastric carcinoid tumours and enterochromaffin-like (ECL) cell hyperplasia in a dose-related manner in both male and female animals. In a 52-week toxicity study in Sprague Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2 and 16 mg/kg/day. No astrocytomas were observed in female rats in this study. No astrocytomas were found in males and females at the high doses of 140.8 mg/kg/day for 2 years.

An 18-month mouse carcinogenicity study and a 26-week p53 (+/-) transgenic mouse carcinogenicity study of omeprazole were both negative.

The applicant notes that the mechanism for the emergence of gastric carcinoids has been investigated very carefully and various studies lead to the conclusion that this is a secondary reaction due to the hypergastrinaemia induced by the suppression of gastric acid secretion inhibition and not to a direct effect of any individual drug.

Because of these findings in rats, there have been concerns in man since hypergastrinaemia occurs following omeprazole treatment. In a review of 11 studies of 1800 patients who used PPIs (9 involved omeprazole) from 6 months to 8 years, there were no neoplastic ECL cell changes or carcinoid tumours, although ECL cell hyperplasia was reported for some patients.

Ketoprofen

Ketoprofen was generally well-tolerated except for the known ulcerogenic properties common to NSAIDs. There was no evidence of carcinogenicity.

An adequate review of the data has been presented. The finding of carcinoids with omeprazole in rats was not deemed to preclude grant of a licence for the innovator’s product. The data on human use provide some reassurance that the carcinoids seen with omeprazole in rats have not been seen in clinical use to date.

Reproductive toxicology

Omeprazole

In rabbits, omeprazole in a dose range of 6.9 to 69 mg/kg/day (about 21 to 210 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions.

In rats, dose-related embryo/fetal toxicity and post natal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138 mg/kg/day (42 to 420 times the human dose).

Ketoprofen

In teratology studies, ketoprofen administered to mice at doses up to 12 mg/kg/day and rats at doses up to 9 mg/kg/day, i.e. 3.6 and 2.7 times, respectively, the therapeutic dose for Ketoprofen/Omeprazole Ethypharm showed no teratogenic or embryotoxic effects. In separate studies in rabbits, maternally toxic doses (12 mg/kg) were associated with embryotoxicity but not with teratogenicity.
Ketoprofen administered to male rats (up to 9 mg/kg/day) had no significant effect on reproduction or fertility. In female rats administered 6 or 9 mg/kg/day, a decrease in the number of implantation sites has been noted.

Studies in rats have shown that ketoprofen at doses of 6 mg/kg/day (1.8 times the human dose) prolongs pregnancy when given before the onset of labour. Because of the known effects of prostaglandin-inhibiting drugs on the fetus and the labour when given during the second and third trimester of pregnancy, the use of Ketoprofen/Omeprazole Ethypharm is contra-indicated from the 24th week, even for a single administration, and discouraged during the second trimester.

The risks with both products are well-known and adequate warnings are provided in the SmPC.

**Genetic toxicology**

*Omeprazole*

Omeprazole was not mutagenic in a standard battery of *in vitro* and *in vivo* assays, but was positive in a DNA repair synthesis test, leading to the conclusion that it behaves as a weak genotoxic agent for the rat liver - but is presumably non-genotoxic to humans.

*Ketoprofen*

Ketoprofen was not mutagenic in *in vitro* tests, but was weakly positive *in vivo* following intraperitoneal dosing at 15 and 30 times the human dose, but was negative with oral dosing at 82 times the human oral dose. No evidence of carcinogenicity was found. It was concluded that any risk of genotoxicity to humans would be very low.

It is accepted that there is little genotoxic risk from either component or the combination.

**Excipients**

All the excipients are all commonly used in modified-release formulations and comply with the European Pharmacopoeia, except for dimethicone emulsion and deacetylated monoglycerides, the quality of which is controlled by the manufacturers’ in-house specifications.

The excipients do not raise any toxicological issues.

**Impurities/Residual solvents**

The impurity levels in the finished product are in accordance with the Note for Guidance on impurities [ICH Topic Q3B].

The finished product manufacturer has ensured that the active substance and all excipients used for the manufacture of the product comply with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary products [EMEA 410/01] and with the Note for Guidance on impurities: residual solvents [CPMP/ICH/283/95].

It is accepted that there are no safety concerns based on the impurities, residual solvents or pharmaceutical characteristics of the combination product.

**III.5 Ecotoxicity/Environmental Risk Assessment (ERA)**

The applicant has not conducted a formal Environmental Risk Assessment (ERA), but has provided a statement to the effect that the two products in the proposed combination are not known for their environmental risks. Since the combination is intended to replace individual versions of the products already in use, it is not anticipated that it will increase the amount of ketoprofen/omeprazole and their breakdown products released into the environment.
III.6 Discussion on the non-clinical aspects
The two components of the proposed new combination have different safety concerns.

The most important safety concern regarding omeprazole is its trophic effect for the ECL cells in relation to the induced hypergastrinaemia, leading to gastric carcinoid tumours in rats (but not in dogs). Long-term epidemiological studies in humans have shown that there is no risk of neoplastic changes in ECL cells nor of carcinoid tumours, although ECL cell hyperplasia has been observed in some patients.

The major safety concern of ketoprofen is the risk of gastroduodenal ulceration. It has been shown in humans by double-blind, placebo-controlled trials that omeprazole is effective in the prevention of NSAID-induced gastroduodenal lesions; this is the rationale for the development of this combination. The combination is expected to improve ketoprofen gastrointestinal safety.

Another safety concern of ketoprofen is the possibility of renal insufficiency and water/sodium retention in predisposed patients. Omeprazole has no effect on renal haemodynamics and sodium balance. Therefore, there is no risk of omeprazole increasing the potential renal deleterious effect of ketoprofen.

Omeprazole has no effect on blood coagulation or blood cells; its combination with ketoprofen is not expected to modify the potential anti-aggregation effect of ketoprofen on platelets nor to induce any possible interaction with drugs acting on blood coagulation.

Unlike ketoprofen, omeprazole has no effect on the uterus and the fetus during pregnancy. The combination with ketoprofen is not expected to worsen the deleterious effect of ketoprofen. The warnings in the SPC regarding use in pregnancy are the same as those for ketoprofen dosed alone.

The applicant has concluded that omeprazole and ketoprofen toxicities are not potentiated by either drug, and anticipates that the gastro-intestinal toxicity of ketoprofen will be reduced by the combination with omeprazole. This conclusion is accepted.

The preclinical information contained in the SmPCs is broadly similar to the information given in SmPCs for other omeprazole and ketoprofen products, and are satisfactory.

IV CLINICAL ASPECTS
IV.1 Introduction
With the exception of two bioequivalence studies, no new clinical pharmacology data were submitted for these applications. The data from bioequivalence studies comparing the marketing authorisation holder’s omeprazole and ketoprofen products versus their respective innovator products have also been provided. However, as these data have already been assessed by the MHRA for the grant of national licences for omeprazole and ketoprofen as individual products, only the two bioequivalence studies comparing the proposed omeprazole/ketoprofen capsules versus omeprazole capsules and ketoprofen capsules was assessed.

A clinical expert report (clinical overview) is provided, written by an appropriately qualified physician. It is satisfactory.
IV.2 Pharmacokinetics

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

**Bioequivalence Study 1**

*Study design*
A randomised, open-label, three-sequence, three-period, single-dose, crossover bioequivalence study comparing Ketoprofen/Omeprazole 200mg/20mg Modified Release Capsules (Test) versus 200mg Ketoprofen LP Capsules and Omeprazole 20mg Capsules (Reference) in healthy fasted volunteers.

Blood samples were taken pre- and up to 28 hours post dose for ketoprofen and pre- and up to 9 hours post dose for omeprazole. Each treatment arm was separated by a 7-day washout period.

**Results**
The results for ketoprofen and omeprazole are presented below:

<table>
<thead>
<tr>
<th>Ketoprofen</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; ng/mg/h</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; ng/mg/h</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>35.700 ± 23.5</td>
<td>37.126 ± 22.6</td>
<td>4.525 ± 30.2</td>
</tr>
<tr>
<td>Reference</td>
<td>37.019 ± 21.2</td>
<td>38.470 ± 20.7</td>
<td>4.709 ± 26.9</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>96.08</td>
<td>96.25</td>
<td>95.51</td>
</tr>
<tr>
<td></td>
<td>93.39-98.85%</td>
<td>93.92-98.63%</td>
<td>89.82-101.56%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Omeprazole</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; ng/mg/h</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; ng/mg/h</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>750.02 ± 89.5</td>
<td>785.04 ± 100.8</td>
<td>445.24 ± 51.2</td>
</tr>
<tr>
<td>Reference</td>
<td>764.08 ± 93.1</td>
<td>794.83 ± 102.5</td>
<td>465.37 ± 52.4</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>98.86</td>
<td>98.88</td>
<td>97.93</td>
</tr>
<tr>
<td></td>
<td>95.28-102.58%</td>
<td>95.32-102.56%</td>
<td>90.25-106.27%</td>
</tr>
</tbody>
</table>

**Conclusions**
The 90% confidence intervals for both ketoprofen and omeprazole lie within the acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) and the combination product can be considered bioequivalent to taking each of its constituents as individual products in fasted patients.

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200mg/20mg strength can be extrapolated to the 100mg/20mg and 150mg/20mg strength capsules also.
Bioequivalence Study 2

Study design
A randomised, laboratory-blinded, three-sequence, three-period, single-dose, crossover bioequivalence study comparing Ketoprofen/Omeprazole 200mg/20mg Modified Release Capsules (Test) versus 200mg Ketoprofen LP Capsules and Omeprazole 20mg Capsules (Reference) in healthy fed volunteers.

Results
The results for ketoprofen and omeprazole are presented below (calculated by geometric least-squares means):

<table>
<thead>
<tr>
<th></th>
<th>( \text{AUC}_{0-t} ) (( \mu \text{g/ml/h} ))</th>
<th>( \text{AUC}_{0-\infty} ) (( \mu \text{g/ml/h} ))</th>
<th>( \text{C}_{\text{max}} ) (( \mu \text{g/ml} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ketoprofen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>34.062</td>
<td>39.195</td>
<td>3.109</td>
</tr>
<tr>
<td>Reference</td>
<td>34.025</td>
<td>40.058</td>
<td>3.117</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>100.11</td>
<td>97.85</td>
<td>99.74</td>
</tr>
</tbody>
</table>

AUC\(_{0-t}\): area under the plasma concentration-time curve from time zero to t hours
AUC\(_{0-\infty}\): area under the plasma concentration-time curve from time zero to infinity
\( \text{C}_{\text{max}} \): maximum plasma concentration
\( \text{T}_{\text{max}} \): time for maximum concentration (median)

<table>
<thead>
<tr>
<th></th>
<th>( \text{AUC}_{0-t} ) (( \mu \text{g/ml/h} ))</th>
<th>( \text{AUC}_{0-\infty} ) (( \mu \text{g/ml/h} ))</th>
<th>( \text{C}_{\text{max}} ) (( \mu \text{g/ml} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Omeprazole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>314.23</td>
<td>389.33</td>
<td>127.29</td>
</tr>
<tr>
<td>Reference</td>
<td>303.77</td>
<td>353.78</td>
<td>117.94</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>103.45</td>
<td>110.05</td>
<td>107.93</td>
</tr>
</tbody>
</table>

AUC\(_{0-t}\): area under the plasma concentration-time curve from time zero to t hours
AUC\(_{0-\infty}\): area under the plasma concentration-time curve from time zero to infinity
\( \text{C}_{\text{max}} \): maximum plasma concentration
\( \text{T}_{\text{max}} \): time for maximum concentration

Conclusions
The 90% confidence intervals for both ketoprofen and omeprazole lie within the acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) and the combination product can be considered bioequivalent to taking each of its constituents as individual products in fed patients. Concomitant intake of food does not appear to have an effect on the bioavailability of ketoprofen or omeprazole.

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200mg/20mg strength can be extrapolated to the 100mg/20mg and 150mg/20mg strength capsules also.

IV.3 Pharmacodynamics
No new pharmacodynamic studies have been undertaken and none are required as the pharmacodynamic properties of ketoprofen and omeprazole are well-known and this is acceptable.

IV.4 Clinical efficacy
No new data are submitted and none are required for these types of applications.

IV.5 Clinical safety
Data obtained from a database from approximately 500 patients who received the combination of
ketoprofen and omeprazole for at least 1 year have been provided. No safety issues are identified from these data.

IV.6 Discussion on the clinical aspects
Bioequivalence has been satisfactorily demonstrated for the Ketoprofen/Omeprazole 200mg/20mg Capsules versus 200mg Ketoprofen Capsules and 20mg Omeprazole Capsules administered individually in both fasted and fed individuals. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200/20mg strength can be extrapolated to the 100mg/20mg and 150mg/20mg strengths also. In addition, it can be concluded that the bioavailability of the products is unaffected by food.

Marketing Authorisations may be granted for these products.

V USER CONSULTATION
A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. 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 the patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
Quality
The important quality characteristics of Ketoprofen/Omeprazole 100mg/20mg, 150mg/20mg and 200mg/20mg modified-release capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Non-clinical
No new preclinical data were submitted and none are required for applications of this type.

Efficacy
Bioequivalence has been demonstrated between the applicant’s Ketoprofen/Omeprazole 200mg/20mg modified-release capsules and Ketoprofen 200mg Capsules and Omeprazole 20mg Capsules administered individually, in patients in both fed and fasted conditions. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200mg/20mg strength can be extrapolated to the 150mg/20mg and 100mg/20mg strengths also.

Safety
No new or unexpected safety concerns arise from these applications.

Product Literature
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.
Risk Benefit Assessment
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with ketoprofen and omeprazole is considered to have demonstrated the therapeutic value of the compounds. The risk benefit 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

The following table lists non-safety updates to the Marketing Authorisations for Axorid 100mg/20mg, 150mg/20mg and 200mg/20mg modified release capsules (PL 15142/0090-0092, UK/H/1068/0002-004/DC that have been approved by the MHRA since the products were first licensed. This is not a complete list of the post-authorisation changes that have been made to the Marketing Authorisations.

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To add a pack size of 10 capsules in a 60 ml bottle. As a consequence changes have been made to section 6.5 of the Summaries of Product Characteristics (SmPCs), (Nature and contents of container), Patient Information Leaflet (PIL) and labelling.</td>
<td>UK/H/1068/002-004/IB/008</td>
<td>SmPCs PIL Labelling</td>
<td>16 August 2010</td>
<td>06 September 2010</td>
<td>Approval</td>
<td>No</td>
</tr>
<tr>
<td>To update Sections 2, 4.2, 4.3, 4.5, 4.6, 5.2 and 6.3 of the SmPCs to include information on the reduced AUC of omeprazole when given together with enzalutamide and in line with the Quality Review of Documents template (QRD) template. Consequently, the PIL has been updated.</td>
<td>UK/H/1068/002-004/II/023</td>
<td>SmPCs PIL</td>
<td>03 February 2016</td>
<td>31 March 2016</td>
<td>Approval</td>
<td>Yes (Annex 1.1)</td>
</tr>
</tbody>
</table>
Annex 1.1

Our Reference: PL 15142/0090, Application 0037
PL 15142/0091, Application 0038
PL 15142/0092, Application 0038

Product(s): Axorid 100 mg/20 mg modified-release capsules
Axorid 150 mg/20 mg modified-release capsules
Axorid 200 mg/20 mg modified-release capsules

Marketing Authorisation Holder: Meda Pharmaceuticals Limited
Active Ingredient(s): Ketoprofen, Omeprazole.

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/1068/002-004/II/023

Reason:
To update Sections 2, 4.2, 4.3, 4.5, 4.6, 5.2 and 6.3 of the Summary of Product Characteristics (SmPCs) to include information on the reduced area under the plasma concentration curve (AUC) of omeprazole when given together with enzalutamide and in line with the Quality Review of Documents (QRD) template (reference is made to Question 3.16, CMDh/132/2009/Rev.36). Consequently, the Patient Information Leaflet (PIL) has been updated.

Supporting Evidence
1. The results of a published phase I drug interaction study that investigated the effects of oral enzalutamide (approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC)) on the pharmacokinetics of co-administered drugs was submitted. The published study (Pharmacokinetic Drug Interaction Studies with Enzalutamide - Jacqueline A. Gibbons et al - Clin Pharmacokin May 2015) is summarised below.
2. Revised SmPC
3. Revised Patient Information Leaflet

Evaluation
1. Phase I drug interaction study.
Method: A single-sequence crossover design was used to determine the effects of enzalutamide 160mg/day on the pharmacokinetics of a single oral dose of sensitive substrates for CYP2C8 (pioglitazone 30 mg), CYP2C9 (warfarin 10 mg), CYP2C19 (omeprazole 20 mg), or CYP3A4 (midazolam 2 mg).

Results: Enzalutamide reduced the AUC∞ of oral S-warfarin, omeprazole, and midazolam by 56, 70, and 86 %, respectively. Therefore, the results showed that enzalutamide is a moderate inducer of CYP2C9 and CYP2C19 and a strong inducer of CYP3A4.

Study Conclusion: It is recommended to avoid concomitant use of enzalutamide with narrow therapeutic index drugs metabolized by CYP2C9, CYP2C19, or CYP3A4, as enzalutamide may
decrease their exposure. The European Centralised SmPC for Xtandi 40mg soft capsules (enzalutamide: Astellas) was amended in November 2015 to include the findings from the above PK interaction study.

The PK study findings and the subsequent amendment to the Xtandi SmPC are considered adequate evidence to support the change proposed in Section 4.5 of the Axorid SmPCs.

**Conclusion**

The proposed changes to the Axorid SmPCs and PIL are considered acceptable and there are no objections to approval.

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

**Decision**

Approved on 31 March 2016