



Public Assessment Report

Decentralised Procedure

Ketoprofen 25 mg Granules

Ketoprofen 25 mg Film-Coated Tablets

(ketoprofen (as ketoprofen lysine salt))

Product Licence No.: PL 02855/0310 and PL 02855/0305

European Procedure No.: UK/H/6303 and 6309/001/DC

Omega Pharma Limited

LAY SUMMARY

Ketoprofen 25 mg Granules Ketoprofen 25 mg Film-Coated Tablets

ketoprofen (as lysine salt)

This is a summary of the Public Assessment Report (PAR) for Ketoprofen 25 mg Granules (PL 02855/0310; UK/H/6303/001/DC) and Ketoprofen 25 mg Film-Coated Tablets (PL 02855/0305; UK/H/6309/001/DC). It explains how the applications for Ketoprofen 25 mg Granules and Ketoprofen 25 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 Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets.

For practical information about using Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets, patients should read the package leaflets or contact their doctor or pharmacist.

What are Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets and what are they used for?

These applications are for hybrid medicines. This means that these medicines are similar to a reference medicine already authorised in the EU called OKi 40 mg granules for oral solution in sachet (Dompé Farmaceutici S.p.A., Italy), albeit with certain differences.

The reference product is indicated for the relief of pain of various kinds and origins, in particular, headache, toothache, neuralgia, menstrual, muscular and osteoarticular pain. While Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets are indicated to be used to relieve mild to moderate pain and fever associated with cold and flu, rheumatic and muscular pain, headache, toothache and period pain in adults 18 years and over.

In addition, these hybrid products differ from the reference product in pharmaceutical form. The pharmaceutical form of the reference product is granules for solution in sachet, whilst the pharmaceutical form for Ketoprofen 25 mg Granules is coated granules in sachet and the pharmaceutical form for Ketoprofen 25 mg Film-Coated Tablets is film-coated tablets.

How do Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets work?

These medicines contain the active ingredient ketoprofen (as ketoprofen lysine salt) which belongs to a group of medicines called "Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)". Ketoprofen acts by blocking the chemical substances that normally cause inflammation in the body. Ketoprofen lysine salt is a salt of ketoprofen which is absorbed quicker by the body.

How are Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets used?

The pharmaceutical form of Ketoprofen 25 mg Granules is coated granules in sachet and that for Ketoprofen 25 mg Film-Coated Tablets is film-coated tablets; the route of administration for both medicines is oral.

These medicines can only be obtained with a prescription.

The patient should always take either of these medicines exactly as described in the package leaflet or as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

How to use Ketoprofen 25 mg Granules

This product is for short term use only. The patient should take the lowest dose for the shortest time necessary to relieve their symptoms. The recommended dose is 1 sachet up to 3 times a day as required.

The patient should wait at least four hours before taking another sachet.

The patient should not exceed the recommended dose.

The contents of the sachet must only be placed onto the tongue and swallowed. The patient can take Ketoprofen 25 mg Granules with or without water.

If symptoms persist or the pain worsens, or if any new symptoms occur, the patient should consult their doctor or a pharmacist.

Use in the elderly

Ketoprofen 25 mg Granules should be used with caution in the elderly. The patient should not take more than 1 sachet of Ketoprofen 25 mg Granules in 24 hours.

Use in children and adolescents under the age of 18 years

Ketoprofen 25 mg Granules should not be used in children and adolescents under the age of 18 years.

For further information on how Ketoprofen 25 mg Granules are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare product Regulatory Agency (MHRA) website.

How to use Ketoprofen 25 mg Film-Coated Tablets

This product is for short term use only. The patient should take the lowest dose for the shortest time necessary to relieve their symptoms.

The recommended dose is 1 tablet up to 3 times a day as required.

The patient should wait at least four hours before taking another tablet.

The recommended dose should not be exceeded.

The patient should swallow the tablet whole, with water if necessary.

If symptoms persist or the pain worsens, or if any new symptoms occur, the patient should consult his/her doctor or pharmacist.

Use in the elderly

Ketoprofen 25 mg Film-Coated Tablets should be used with caution in the elderly. An elderly patient should not take more than one Ketoprofen 25 mg Film-Coated Tablet in a period of 24 hours.

Use in children and adolescents under the age of 18 years

Ketoprofen 25 mg Film-Coated Tablets should not be used in children and adolescents under the age of 18 years.

For further information on how Ketoprofen 25 mg Film-Coated Tablets, refer to the package leaflet and Summary of Product Characteristics available on the MHRA website.

What benefits of Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets have been shown in studies?

Because Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets are hybrid medicines, studies in healthy volunteers consist of tests to determine that these medicines are therapeutically equivalent to the reference medicine.

What are the possible side effects of Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets?

Like all medicines, these medicines can cause side effects, although not everybody gets them.

Side effects may include:

Common (may affect up to 1 in 10 people)

- poor digestion (dyspepsia), nausea (feeling sick), abdominal pain, vomiting.

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflets or the Summaries of Product Characteristics (SmPCs) available on the MHRA website.

Why were Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets approved?

It was concluded that, in accordance with EU requirements, Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Table have been shown to be therapeutically equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that the products can be approved for use.

What measures are being taken to ensure the safe and effective use of Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets?

A Risk Management Plan (RMP) has been developed to ensure that Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflets, 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 Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets

Marketing Authorisations for Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets were granted in the UK to Omega Pharma Limited on 31 January 2019.

The full PAR for Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets follows this summary.

This summary was last updated in April 2019.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Ketoprofen 25 mg Granules (PL 02855/0310; UK/H/6303/001/DC) and Ketoprofen 25 mg Film-Coated Tablets (PL 02855/0305; UK/H/6309/001/DC) could be approved.

Ketoprofen is recommended, in adults aged 18 years and over, for the symptomatic treatment of acute mild to moderate pain such as rheumatic and muscular pain, headache, toothache, menstrual pain, and for pain and fever associated with common cold and flu symptoms.

The Reference Member State (RMS) for these procedures was the UK and the Concerned Member States (CMSs) were Ireland and Estonia.

Ketoprofen 25 mg Granules and Ketoprofen 25 mg Film-Coated Tablets contain the active ingredient ketoprofen (as ketoprofen lysine salt), which is a derivative of propionic acid and is a Non-Steroidal Anti-Inflammatory Drug (NSAID) with analgesic, anti-inflammatory and antipyretic actions. The mechanism of action of NSAIDs is related to the reduction in prostaglandin synthesis caused by inhibition of the enzyme cyclooxygenase. More specifically, NSAIDs inhibit the transformation of arachidonic acid into cyclic endoperoxides, PGG₂ and PGH₂, the precursors of prostaglandins PGE₁, PGE₂, PGF_{2a} and PGD₂, prostacyclin PGI₂ and thromboxanes (TxA₂ and TxB₂). Inhibition of prostaglandin synthesis may also interfere with other mediators such as quinines, causing an indirect action in addition to the direct action.

The applications were submitted under Article 10(3) of Directive 2001/83/EC, as amended, claiming to be hybrid medicinal products. The European Reference Product is OKi 40 mg granules for oral solution (Dompé Farmaceutici S.p.A., Italy), which was granted a product licence in Italy on 14 December 2001. The applications also refer to OKi 40 mg granules for oral solution (80 mg bipartite sachet, each half sachet containing 40 mg ketoprofen lysine salt corresponding to 25 mg ketoprofen; Dompé Farmaceutici S.p.A., Italy), as the 40 mg originator product is not currently marketed.

At the time of assessment of the proposed products, the indications for the reference product OKi 80 mg granules for solution were "Pain of various kinds and origins, in particular, headache, toothache, neuralgia and menstrual, muscular and osteoarticular pain".

The proposed applications do not fall within the strict definition of Article 10(1) of Directive 2001/83/EC, as amended, because the applications have sought approval with additional therapeutic indications compared to the reference product (OKi 40 mg granules for solution). For this reason, the legal basis for these applications falls under Article 10(3) of Directive 2001/83/EC, as amended, with the new target indications supported by published clinical literature presented in the dossiers.

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

Data from one bioequivalence study was submitted with these applications. This study was conducted in line with current Good Clinical Practice (GCP).

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

The RMS and CMSs considered that the applications could be approved at the end of procedure (Day 210) on 07 January 2019. After a subsequent national phase, licences were granted in the UK on 31 January 2019.

II QUALITY ASPECTS

II.1 Introduction

Ketoprofen 25 mg Granules are white to ivory granules. Each sachet of granules contains 25 mg ketoprofen (as lysine salt).

Ketoprofen 25 mg Film-coated Tablets are round, convex, 7 mm diameter, blue film-coated tablets, with a non-functional score line on one side. The score line is not intended for breaking the tablet. Each film-coated tablet contains 25 mg ketoprofen (as lysine salt).

Ketoprofen 25 mg Granules

In addition to the active substance ketoprofen, Ketoprofen 25 mg Granules also contain the pharmaceutical excipients povidone (E1201), colloidal anhydrous silica (E551), hypromellose, basic butylated methacrylate copolymer, sodium laurilsulfate, stearic acid (E570), magnesium stearate (E572), aspartame (E951), mannitol (E421), xylitol (E967), talc (E553B) and flavour (which contains glucose, sucrose, maltodextrin, maize starch (E1450), butylated hydroxyanisole (E320), arabic gum, lime flavour, lemon flavour and mint flavour).

Ketoprofen 25 mg Granules are packaged in opaque, polyethylene/aluminium sachets, in pack sizes of 8, 10, 15, 16 and 20 sachets. Not all pack sizes may be marketed.

Ketoprofen 25 mg Film-Coated Tablets

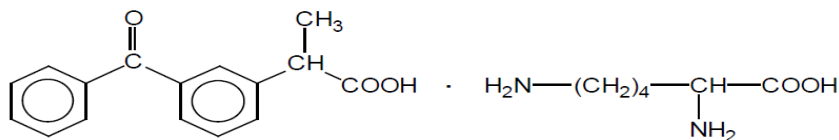
In addition to the active substance ketoprofen, Ketoprofen 25 mg Film-Coated Tablets also contain pharmaceutical excipients in the tablet core and coating, namely mannitol (E421), crospovidone, sodium laurilsulfate, colloidal anhydrous silica, sodium stearyl fumarate, polyvinyl alcohol (E1203), macrogol, titanium dioxide (E171), talc (E553B), brilliant blue (E133) and quinoline yellow (E104).

Ketoprofen 25 mg Film-Coated Tablets are packaged in opaque, aluminium/polyamide/aluminium/polyvinyl chloride blisters, in pack sizes of 8, 10, 15, 16 and 20 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 ACTIVE SUBSTANCE

rINN: Ketoprofen lysine salt
 Chemical Name: DL-lysine, mono (3-benzoyl- α -methylbenzene acetate)
 Structure:



Molecular Formula: $C_{16}H_{14}O_3 \cdot C_6H_{14}N_2O_2$
 Molecular Weight: 400.49 g/mol

Appearance: White or almost white crystalline powder
 Solubility: Ketoprofen lysine salt is very soluble in water, insoluble in acetone and ethanol.

Ketoprofen lysine salt is not the subject of a European Pharmacopoeia monograph.

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 specifications 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 specifications. Batch analysis data are provided that comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

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

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

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished products. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

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

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results:

- 1 a shelf-life of 3 years for Ketoprofen 25 mg Granules, with no special storage conditions, is acceptable.
- 2 a shelf life of 3 years for Ketoprofen 25 mg Film-Coated Tablets, with the special storage instructions 'Store in the original packaging in order to protect against light and moisture.' is acceptable.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of ketoprofen 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.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology

No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

The applicant has provided an Environmental Risk Assessment in accordance with EMEA/CHMP/SWP/4447/00 corr 2.

A Phase 1 calculation of the Predicted Environmental Concentration in surface water ($PEC_{\text{surfacewater}}$) for ketoprofen lysine salt ($0.6 \mu\text{g/L}$) exceeded the action limit of $0.01 \mu\text{g/L}$ at which a Phase II assessment is necessary. In addition, the applicant has provided an experimentally derived figure of 3.31 for the log n-octanol/water partition coefficient ($\log K_{ow}$) for ketoprofen lysine salt, which is below the limit (>4.5) for further persistence, bioaccumulation and toxicity (PBT) assessment.

The applicant has not provided suitable justification for the absence of a Phase II investigation for ketoprofen lysine salt. The applicant has committed to provide an updated ERA post authorisation; this is considered acceptable.

III.6 Discussion on the non-clinical aspects

The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

In accordance with the regulatory requirements, data from one bioequivalence study have been submitted with these applications. This study was conducted in line with current Good Clinical Practice (GCP). The applications are also supported with published clinical literature presented in the dossiers.

IV.2 Pharmacokinetics

In support of the applications, the applicant submitted the results of one bioequivalence study.

This study was an open-label, randomised single-dose, two-period, two-stage crossover study to compare the test product Ketoprofen lysine salt (KLS), 40 mg immediate release tablets, (corresponding to 25 mg ketoprofen; Dompé S.p.A., Italy) versus the reference product OKi granules for solution (containing 40 mg KLS corresponding to 25 mg ketoprofen, Dompé S.p.A., Italy) after oral administration to healthy volunteers, under fasting conditions.

The subjects were given a single dose of either treatment following an overnight fast of at least 10 hours. The test product was administered with 240 ml of water. The content of half sachet of the reference formulation was dissolved in 190 ml of water. The subject drank the entire solution immediately. The glass was then rinsed with 50 ml of water and the subject drank the rinse immediately. Following the administration of either treatment, no further fluid intake was permitted for 2 hours. Blood samples were collected before and up to 8 hours after each administration. The washout period between the treatment periods was at least 4 days.

Since bioequivalence was demonstrated after stage 1, the study, according to the protocol, was terminated, and stage 2 was not performed.

A summary of the pharmacokinetic results is presented below:

Results

Table 1 PK parameters and statistics of ketoprofen (25 mg, N=30)

Treatment	AUC _{0-t} µg/mL/h	AUC _{0-∞} µg/mL/h	C _{max} µg/mL	t _{max} h	t _{1/2} h
Test T (with water)	4.53 ± 1.35	4.64 ± 1.40	3.61 ± 1.17	0.38 0.08 – 1.0	1.64 ± 0.17
Reference R	4.12 ± 1.35	4.22 ± 1.39	3.40 ± 1.38	0.25 0.25 – 0.50	1.64 ± 0.17
*Ratio T/R (94.12% CI**)	1.11 1.04 - 1.17	1.11 1.04 - 1.17	1.08 0.98 - 1.20	NA	NA

* Ratio of geometric least-squares mean values

** 94.12% CI was calculated as study was set-up according to a two-stage design

In line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**)', the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference products.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data have been submitted for these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data from the clinical study submitted with these applications, no new safety data were submitted. The safety data submitted showed that the test product was well-tolerated. No new or unexpected safety issues were raised from these data.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended for these applications.

V USER CONSULTATION

A user consultation with target patient groups on each of the PILs has been performed on the basis of a bridging report making reference to Ketoprofen Lysine Salt 40 mg granules (Dompé Farmaceutici S.p.A., Italy). The bridging report submitted by the Marketing Authorisation Holder is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ketoprofen is considered to have demonstrated the therapeutic value of the compound.

The benefit/risk for both products is, therefore, considered to be positive.

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

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

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

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

Application type	Scope	Product information affected	Date of start of the procedure	Date of end of procedure	Outcome	Assessment report attached Y/N