IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Okitask 25 mg Coated Granules in Sachet
KETOPROFEN LYSINE
PA23072/001/001

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

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6303/001/DC and UK/H/6309/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 06th February 2019 under procedure number IE/H/0959-0960/001/DC

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA23072/001/001-002 (previously PA1186/024/001-002)
Marketing Authorisation Holder: Dompé Farmaceutici S.p.A (previously Chefaro Ireland DAC)

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

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

Based on the review of the data on quality, safety and efficacy, the 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, PGF2a 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).

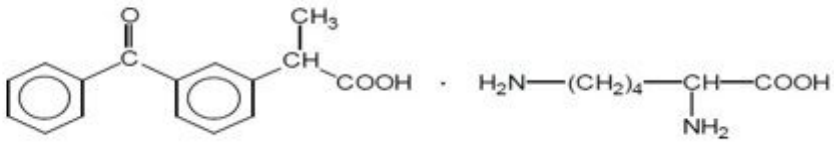
Ketoprofen 25 mg Film-Coated Tablets are packaged in opaque, aluminium/polyamide/aluminium/polyvinyl chloride blisters, in pack sizes of 8, 10, 15, 16 and 20 film-coated tablets. Not all pack sizes may be marketed.

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 biologicalaspects

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 surfacewater) for ketoprofen lysine salt (0.6 µg/L) exceeded the action limit of 0.01 µg/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 (logKow) 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:

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

Treatment	**AUC0-t µg/mL/h**	**AUC0-∞ µg/mL/h**	**Cmax µg/mL**	**tmax h**	**t½ h**
Test T	4.53 ± 1.35	4.64 ± 1.40	3.61 ± 1.17	0.38	1.64 ± 0.17

(with water)				0.08 – 1.0	
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. OVERALL CONCLUSIONS

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.

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.

VI. REVISION DATE

September 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/6303 and 6309/001/DC to IE/H/0959-0960/001/DC	N/A	N/A	N/A	Approved 06/02/2019