COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Okitask 25 mg granules (ketoprofen (as lysine salt))

NL/H/3583/001/DC

Date: 12 January 2023

This module reflects the scientific discussion for the approval of Okitask 25 mg granules. The procedure was finalised at 15 December 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Okitask 25 mg granules from Dompé Farmaceutici S.p.A.

The product is indicated in adults aged 18 years or above in the symptomatic treatment of acute mild to moderate pain, and pain and fever associated with cold and flu.

A comprehensive description of the current indication and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product OKi 40 mg granules for oral solution which has been registered in Italy by Dompé Farmaceutici S.p.A. since 1994. The product was authorised as a line extension of OKi 80 mg granules, but was withdrawn in 2010 due to marketing reasons. In the Netherlands, no reference product was registered at the time of this procedure.

The concerned member states (CMS) involved in this procedure were Finland, Hungary and Poland.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a so called “hybrid application” since approval was sought for additional therapeutic indications compared to the reference product.

The MAH provided published clinical literature for the indications. Following comments of the involved member states, a revised indication was proposed. The assessment of proposed indications is discussed in section IV.

II. QUALITY ASPECTS

II.1 Introduction

Okitask concerns white to ivory white coated granules contained in a sachet. The sachet is a triple foil made of PET, aluminium and PE. Each sachet contains 700 mg of drug product including 25 mg ketoprofen, as 40 mg ketoprofen lysine salt. The contents of the sachet can be placed directly onto the tongue. It dissolves in saliva and can therefore be taken without water.

The excipients are: povidone K-25 (E1201), colloidal anhydrous silica (E551), hypromellose, basic butylated methacrylate copolymer, sodium laurilsulfate, stearic acid (E570), magnesium stearate (E572), aspartame (E951), mannitol (E421), xylitol (E967) and talc (E553B).

The excipients for the flavour are: glucose, sucrose, maltodextrin, maize starch, butylated hydroxyanisole, Arabic gum, natural lime flavour, natural lemon flavour and natural mint flavour.

II.2 Drug Substance

The active substance is ketoprofen lysine salt, an established active substance that is not described in the European or British Pharmacopoeia (Ph.Eur.)(BP). However the ketoprofen moiety and the lysine moiety separately are. Ketoprofen lysine salt is a white to almost white crystalline powder. It is very soluble in water, and insoluble in acetone and ethanol. Solubility of the active substance is pH dependent. Ketoprofen lysine salt shows no optical rotation. It is slightly hygroscopic, yielding only one crystal form in the manufacturing process.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Manufacturer I – Ketoprofen lysine salt is prepared in reaction of ketoprofen with a lysine solution. The starting materials are acceptable. No heavy metal catalysts or class 1 organic solvents are used in the process.

Manufacturer II – Ketoprofen lysine salt is prepared in a six step reaction. The starting materials are acceptable. No special inorganic compounds are used in the manufacturing process. The possible inorganic impurities are controlled by tests.

Quality control of drug substance

The active substance specification is established in-house by the MAH and is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for two full scale batches of each manufacturer.

Stability of drug substance

Manufacturer I – Stability data on the active substance have been provided for three batches stored at 25°C/60% RH for 12 months and at 40°C/75% RH for six months in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of two years without special storage conditions.

Manufacturer II – Stability data on the active substance have been provided for nine batches. All batches were stored at 25°C/60% RH up to 72 months, three batches were

stored at 30°C/65% RH for six months, and three batches were stored at 40°C/75% RH for six months in accordance with applicable European guidelines. Based on the stability data available, the proposed retest period of four years can be granted.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The formulation development section contains sufficient information on the justification for amount of mannitol and xylitol and identification of the critical quality attributes. The chosen amounts of the coating agents and the structure of the product are sufficiently discussed. The mechanism of disintegration of coating layers upon administration of the drug product was explained. The function of the coating has been discussed and justified. The effectivity of the taste masking is considered adequately discussed.

Two bioequivalence studies, under fasted conditions, have been performed with the test product versus the reference product. The test batches used in the bioequivalence studies were manufactured according to the finalised formulation and manufacturing process. Comparative dissolution studies with the test and reference batches used in the bioequivalence studies were provided. More than 85% of the drug is dissolved within 15 minutes for both test and reference at three different pH conditions.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. It comprises of five steps and is considered a non-standard process. The MAH has committed to continue the monitoring and the evaluation of the data regarding impurities post authorisation, to consider a further decrease of the shelf-life limit for total impurities. Process validation data on the product have been presented for three industrial scale batches in accordance with the relevant European guidelines.

Mixing times of all steps and the filling process were validated. Homogeneity of the product and coating efficiency are considered a critical attribute which were suitably validated and controlled. The proposed limits for particle size distribution are justified. Insight on the suitability of the quality controls in place is given.

Control of excipients

The three chosen flavours are non-pharmacopoeial excipients. Acceptable information on in-house specifications and applied test methods has been provided. The remaining excipients comply with pharmacopoeial requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, mean weight, uniformity of weight, uniformity of dosage units, loss on drying, dissolution, identification, drug substance

assay, purity and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from five industrial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data of six industrial scale batches have been provided. The drug product batches were stored at 25°C/60% RH (6 to 24 months), 30°C/65% RH (6 to 12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies were according to the ICH stability guideline. The product was packed in the proposed packaging. No out of specification results and significant changes were observed. A shelf life of 24 months was granted.

No photostability study has been performed. This was considered acceptable as it is very unlikely that that the product is stored outside the original packaging, which protects the product from light. It was demonstrated that the active substance from manufacturer I is photostable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Okitask 25 mg granules has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made at the time of the procedure:

- The MAH committed to continue the monitoring and the evaluation of the data regarding impurities to consider a further decrease of the shelf-life limit for total impurities if possible.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Okitask is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of OKi 40 mg granules which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ketoprofen lysine salt is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this hybrid application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Okitask 25 mg granules (Dompé Farmaceutici S.p.A., Italy) is compared with the pharmacokinetic profile of the reference product OKi 80 mg granules for oral solution – dosed as half a sachet (40 mg) (Dompé Farmaceutici S.p.A., Italy). The composition of the OKi 80 mg differs from the test product. There is a marked difference in the amount of mannitol, an excipient known to influence bioavailability. The MAH sufficiently demonstrated that varying levels of mannitol in the range at issue do not influence the human pharmacokinetics of ketoprofen lysine salt granules. The reference product used in the bioequivalence studies is therefore considered acceptable. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Study 1 – Single dose, fasting conditions, 25 mg ketoprofen (= 40 mg ketoprofen lysine salt)

Design

A single-dose, open-label, randomised, three-treatment, six-sequence, three-period cross-over bioequivalence study was carried out under fasted conditions in 24 healthy male (n=13) and female (n=11) subjects, aged 19-51 years. Each subject received a single dose (25 mg) of one of the 2 ketoprofen formulations (test with or without water, or reference with water). There were three dosing periods, separated by a washout period of 7 days. Subjects were randomly assigned to receive each of the following treatments:

- Treatment A
  - Okitask 25 mg granules with water: the treatment was applied on the tongue and allowed to dissolve in the mouth for 2 minutes, then 240 mL of tap water was swallowed and no further fluid intake was permitted for 2 hours.
- Treatment B
  - Okitask 25 mg granules without water: the treatment was allowed to dissolve in the mouth in the absence of tap water. Each volunteer's mouth was made wet by swallowing 20 mL of tap water directly before applying the treatment to the tongue, then no fluid intake was permitted for 2 hours.
- Reference treatment
  - OKi 80 mg granules for solution: 40 mg of OKi 80 mg granules for oral solution from one half of the bipartite sachet was dissolved in 190 mL of tap water plus 50 mL of tap water to rinse the glass, then no further fluid intake was permitted for 2 hours.

Blood samples were collected pre-dose and at 0.08, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, and 8 hours after administration of the products.

The design (including the blood sampling scheme) of the study is acceptable. A single-dose study under fasting condition is appropriate as there are no food restrictions. Furthermore the proposed SmPC method of administration prescribes that the test product Okitask can be taken without water and as such bioequivalence establishment of the test product without water to the reference product is essential. The washout period of 7 days is considered sufficient.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in the studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

All 24 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=24	AUC_{0-t} µg.h/mL	$AUC_{0-\infty}$ µg.h/mL	C_{max} µg/mL	t_{max} h	$t_{1/2}$ h
Treatment A	4.65 ± 0.97	4.76 ± 1.00	2.98 ± 0.93	0.50 (0.25 – 1.5)	1.59 ± 0.19
Treatment B	4.57 ± 0.98	4.69 ± 1.00	2.66 ± 0.76	0.50 (0.25 – 1.5)	1.60 ± 0.24
Reference	4.16 ± 0.74	4.26 ± 0.76	2.98 ± 0.59	0.50 (0.25 – 0.75)	1.66 ± 0.26
***Ratio A/Reference (90% CI)**	1.11 (1.06 - 1.17)	1.11 (1.06 - 1.16)	0.96 (0.87 - 1.07)	--	--
***Ratio B/Reference (90% CI)**	1.09 (1.04 - 1.15)	1.09 (1.04 - 1.15)	0.87 (0.79 – 0.97)	--	--
***Ratio A/B (90% CI)**	1.02 (0.97 - 1.07)	1.01 (0.97 - 1.06)	1.10 (0.99 – 1.22)	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
* in-transformed values

Conclusion on first bioequivalence study
Based on the pharmacokinetic parameters of ketoprofen the test product Okitask 25 mg granules without water is not bioequivalent to the reference product OKi 80 mg granules for oral solution with respect to the rate of absorption, as the 90% confidence interval for test/reference ratio of C_{max} was not contained within the acceptance range of 0.80-1.25. In contrast, the test product Okitask 25 mg granules with water was demonstrated to be bioequivalent to the reference product OKi 80 mg granules for oral solution and to the test product Okitask 25 mg granules (without water), both with respect to the rate and extent of absorption.

As the first bioequivalence study did not demonstrate bioequivalence for all parameters, the results of this study were used to calculate a larger sample size for a second bioequivalence study.

Study 2 – Single dose, fasting conditions, 25 mg ketoprofen (= 40 mg ketoprofen lysine salt)
Design
A single-dose, open-label, randomised, two-treatment, two-sequence, two-period cross-over bioequivalence study was carried out under fasted conditions in 71 healthy male (n=37) and

female (n=34) subjects, aged 19-54 years. Each subject received a single dose (25 mg) of one of the 2 ketoprofen formulations. There were two dosing periods, separated by a washout period of 5 days. Subjects were randomly assigned to receive each of the following treatments:

- Test
    - Okitask 25 mg granules: the content of an entire sachet of the test formulation was placed on the tongue and dissolved in the mouth during 3 minutes in absence of water. The mouth was wet by drinking 20 mL of mineral water directly before placing the granules on the tongue. Afterwards, no fluid intake was permitted for 2 hours.
- Reference
    - OKi 80 mg granules for oral solution bipartite sachet (half sachet of 80 mg of ketoprofen lysine salt): the content of half sachet of the reference formulation was dissolved in 190 mL of mineral water. The subject drank the entire solution immediately. Then, 50 mL of mineral water was used to rinse the glass and the rinse was drunk immediately. Afterwards, no fluid intake was permitted for 2 hours.

Blood samples were collected pre-dose and at 0.08, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, and 8.0 hours after administration of the products.

The design (including the blood sampling scheme) of the study is acceptable. A single-dose study under fasting condition is appropriate as there are no food restrictions. Furthermore the proposed SmPC method of administration prescribes that the test product Okitask can be taken without water and as such bioequivalence establishment of the test product without water to the reference product is essential. The wash-out period of 5 days should be sufficient.

Analytical/statistical methods

The methods used in the studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable. Bio-equivalence between the proposed product and Oki 80 mg granules for oral solution was not considered to be indisputably shown due to the fact that the applied quality control sample concentrations did not cover the whole calibration range. However, the MAH has provided sufficient additional information to assure that their bioanalytical results are sufficiently robust to conclude bioequivalence from this pivotal bioequivalence study.

Results

After the first dosing, one subject withdrew consent to study participation for personal reasons and another subject was discontinued due to intake of disallowed concomitant medication as therapeutic countermeasure against an adverse event (back ache) during the wash-out interval of period I. Therefore 69 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ketoprofen under fasted conditions.

Treatment N=69	AUC_{0-t} µg.h/mL	$AUC_{0-\infty}$ µg.h/mL	C_{max} µg/mL	t_{max} h	$t_{1/2}$ h
Test	4.82 ± 1.02	4.93 ± 1.07	2.77 ± 0.82	0.50 (0.25 – 1.0)	1.66 ± 0.23
Reference	4.62 ± 1.08	4.77 ± 1.13	3.16 ± 0.75	0.25 (0.25 – 0.75)	1.87 ± 0.31
Ratio A/Reference (90% CI)	1.05 (1.03 - 1.07)	1.05 (1.02 - 1.07)	0.86 (0.82 – 0.91)	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

Conclusion on second bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Okitask 25 mg granules without water is considered bioequivalent with a half sachet of OKi 80 mg granules for oral solution.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Clinical efficacy

The MAH applied for the indications of the innovator product OKi 40 mg granules for solution:

- pain of various kinds and origins, in particular, headache, toothache, neuralgia and menstrual, muscular and osteoarticular pain and [Okitask] is indicated in adults and adolescents from 15 years of age.

Efficacy was shown for these indications in the earlier marketing application, although the indication for adolescents was not pursued in the end.
Additionally, four extra indications were applied for:

- common cold and flu symptoms,
- sore throat,
- migraine,
- tension headache.

The MAH provided literature studies for each of the extra indications. The publications submitted in support of the additional indications are discussed below. Following comments

of the involved member states, the indication was shortened to: "Okitask is recommended in the symptomatic treatment of acute mild to moderate pain, and pain and fever associated with cold and flu in adults aged 18 years or above" as such a short general indication covers sore throat and other forms of mild-moderate pain and reflects the recommendation made in the updated EMA Guideline on pain.

Common cold and flu symptoms

The MAH put forward two arguments to support the additional indication:

1. The beneficial effect of ketoprofen in the treatment of common cold and flu is considered established (table 3).

Table 3. Authorised ketoprofen product and approved indications in EU countries

EU MS	The Netherlands	Finland	France	Italy
Product	Rilies 25 mg tablet	Ketorin 25 mg tablet	Toprec 25 mg tablet	OKi 80 mg granules for oral solution
Active ingredient	Ketoprofen	Ketoprofen	Ketoprofen	KLS
MA Number	RVG 14148	12388	3308106	028511095
Indications	Fever and pain with flu, colds and after vaccination, headache, toothache, muscle pain, pain after jaw surgery, menstrual pain.	Temporary pain and feverish conditions caused by viruses such as the common cold and influenza symptoms (fever, headache, muscle and joint pain, sore throat, arthritis pain, menstrual cramps and toothache.	The symptomatic treatment of painful conditions of mild to moderate intensity and/or fever.	Paediatric population: short-term symptomatic treatment of inflammatory conditions associated with pain, with or without fever, such as those affecting the osteoarticular system, postoperative pain and otitis.
Authorisation date	October 1991	June 1996	June 1988	November 1994

2. Additional placebo controlled data which underpinned a positive United States' Federal Drugs Administration (FDA) assessment for ketoprofen 25 mg (equivalent to KLS 40 mg) in the treatment of fever.
    - The FDA has previously approved Actron 25 mg (ketoprofen) tablets (Bayer), for "the temporary relief of pain, dysmenorrhea, headache and fever". For the approval, reference is made to two pivotal clinical studies investigating antipyretic effect, one in a fever model induced by endotoxin, and one in a natural fever model (upper respiratory infection), comparing ketoprofen,

paracetamol and placebo. Summaries of the two studies are presented in Table 4 and Table 5. An anti-fever effect of 25 mg ketoprofen has been shown in both studies. In one study the fever was experimentally induced. The other study was in a natural setting i.e. upper respiratory infection (table 4 and 5). There were no significant differences in demographics nor mean baseline body temperature among the treatment groups in either study. In terms of the average and maximum temperature reduction, there was a statistically significant difference showing that ketoprofen reduced pyrexia over placebo. It was concluded that ketoprofen is an effective antipyretic at over–the-counter dosage levels based on the results from both induced and natural fever models.

Table 4. A single-dose, double blind, randomised parallel group, single centre study into the effect of ketoprofen in induced pyrexia in 120 subjects

Drug & strength	6h average T elevation mean (°F)	8h average T elevation mean (°F)	8h max T elevation mean (°F)
Ketoprofen 25 mg	0.69*	0.71*	1.50*
Acetaminophen 650 mg	0.70*	0.72*	1.47*
Placebo	1.41	1.35	2.57

*p<0.05

Table 5. A single-dose, double blind, randomised parallel group, fourteen centre study into the effect of ketoprofen in natural pyrexia secondary to upper respiratory infection in 112 subjects

Drug & strength	6h average T elevation mean (°F)	8h average T elevation mean (°F)	8h max T elevation mean (°F)
Ketoprofen 25 mg	1.2*	1.0*	2.1*
Acetaminophen 650 mg	1.1*	1.1*	2.2*
Placebo	-0.2	-0.3	0.8

*p<0.05

Note: Ketoprofen 12.5 mg was also included in these studies but has not been included in the summary tablets above as the product is not relevant for this application.

It is noted that the two studies referred to were not performed with the reference product. Moreover the results presented are from an indirect source i.e. an assessment report of the FDA. However it is argued that the anti-fever effect of ketoprofen is acceptable based on the class effect argument. The new arguments submitted by the MAH confirm this.

Sore throat

Three studies investigating the use of ketoprofen against a sore throat were presented by the MAH. Two studies used ketoprofen granules (Ruperto, 2011 and Passàli, 2001) and one

used ketoprofen 20 mg transdermal tape (Ozaki et al., 2001). The study with transdermal tape is not assessed for the efficacy of Okitask granules since the route of administration is different.

In the study by Ruperto (2011) the granule sachet could not be masked, in contrast to paracetamol and placebo which were also administered. As a result the test product was administered on an open-label basis. Efficacy evaluation of ketoprofen seemed comparable with paracetamol. The study by Passàli (2001) was single-blinded and a placebo-arm was lacking. Therefore there was no assay sensitivity, which is essential in clinical trials in pain. The observed statistical difference on the time course of pain, as measured by the Visual Analogue Scale, is a few millimetres: the clinical relevance of this result is questioned. Furthermore, a much higher dose than the recommended dose for Okitask was used (160 mg in the study versus 2-3 dd 25 mg as proposed for Okitask). In conclusion, the study did not provide support for efficacy with the proposed posology for Okitask.

In response, the MAH referred to the study by Moore et al (1996). This study was a prospective non-comparative open-label multicentre cohort study of at least 5 days of treatment with ketoprofen 75 to 150 mg daily for relief of pain or fever. The primary objective of the study was to evaluate safety of ketoprofen. 1009 patients had Ear-Nose-Throat disorders (otitis, sinusitis, tonsillitis), 978 dysmenorrhoea, and 2081 musculoskeletal pain. The analysis of the Global Clinical Impression shows that in over 80% of patients a marked therapeutic effect was obtained. The MAH also pointed at the systemic effect of ketoprofen.

Sore throat is described as an inflammation related symptom associated with cold and flu. While alleviation of 'pain associated with sore throat' might be considered demonstrated, this alleviation is considered not to be due to an inflammatory mode of action but to the analgesic effect of ketoprofen. In this context it was recommended to shorten the indication to: 'symptomatic treatment of acute mild to moderate pain' as this also covers sore throat and other forms of mild-moderate pain. Such a short general indication also reflects the recommendation made in the updated EMA Guideline on pain.

Migraine

The MAH provided three studies to investigate the use of ketoprofen against migraine. Two studies had a different route of administration: rectal (Kangasniemi, 1992) and intramuscular (Karabetsos, 1997). These studies were not considered relevant.

One double-blind, placebo-controlled, randomised, cross-over study was considered suited for assessment (Dib et al., 2002). The study used oral ketoprofen (75 mg and 150 mg) in a dual-release formulation, consisting of a scored wafer containing two superimposed layers of active ingredient, one of which is released immediately and the other is encapsulated in a slow-release support. Both showed some effect in migraine. However, it is uncertain whether the results can be bridged to ketoprofen granules. And as such the efficacy of ketoprofen granules in migraine has not been demonstrated. Furthermore, the proposed posology for treatment of migraine with Okitask is one sachet (25 mg ketoprofen) with a

maximum of three sachets (75 mg) a day. The proposed posology for efficacy in migraine is not sufficient substantiated by the data from the study by Dib, using posology of 75 mg and 150 mg ketoprofen.
It is concluded that this study shows limited efficacy of ketoprofen in migraine. Therefore, migraine was removed from the proposed indication.

Tension headache
When 'migraine' was removed from the indication, 'tension headache' was added. Several published clinical studies in tension headache have subsequently been discussed (Steiner and Lange, 1998; Mehlisch et al., 1998; Dahlöf and Jacobs, 1996; Lange and Lentz, 1995; van Gerven et al., 1996). These studies show efficacy of ketoprofen in 'tension headache'. However, (tension) headache is not specified in the indication. The short general indication 'symptomatic treatment of acute mild to moderate pain' also covers headache.

Overall conclusions on clinical efficacy
The data provided show efficacy of ketoprofen in several pain models. The anti-fever is considered sufficiently established. The indication "Okitask is recommended in the symptomatic treatment of acute mild to moderate pain, and pain and fever associated with cold and flu" is acceptable. For additional information, see *Steps taken after the finalisation of the initial procedure – Summary* at the end of this document.

IV.4 Clinical safety

The MAH provided a sufficient discussion on the adverse events associated with NSAIDs, ketoprofen and ketoprofen lysine salt, including numbers of reports of adverse events. There is some evidence that ketoprofen formulated as lysine salt may cause less gastrointestinal adverse events than other (oral) formulations of ketoprofen. Nevertheless, gastrointestinal adverse events remain. For the elderly, a dose adjustment is recommended. NSAIDs in general are associated with medication overuse headache. This is reflected in the SmPC. Overall, Okitask 25 mg granules can be safely used.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Okitask 25 mg granules.

Table 6. Summary table of safety concerns as approved in RMP

Important identified risks	• Cardiovascular and cerebrovascular events (heart failure, myocardial infarction, cerebrovascular accident) • Gastrointestinal bleeding, ulceration and perforations • Severe skin reactions (Stevens-Johnson syndrome, epidermal necrolysis) • Use during first and second trimester of pregnancy

Important potential risks	None
Missing information	• Potential for off-label use in adolescents under 18 years of age • Use in breastfeeding

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product OKi 40 mg granules for oral solution. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. The data provided show efficacy of ketoprofen in several pain models. The anti-fever effect is considered sufficiently established. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of: a pilot test with four participants, followed by two rounds with ten participants each. The 21 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Okitask 25 mg granules has a proven chemical-pharmaceutical quality and is a hybrid form of OKi 40 mg granules for oral solution. OKi is a well-known medicinal product with an established favourable efficacy and safety profile. Bioequivalence has been shown with and without water in compliance with the requirements of European guidance documents.

Four additional indications were applied for: common cold and flu symptoms, sore throat, migraine and tension headache. In the Board meetings of 10 March 2016 and 24 November 2016, the application was discussed. The Board came to a positive conclusion for the anti-fever effect of ketoprofen. The proposed indication migraine was not considered approvable. The indications sore throat and tension headache are covered by the general indication 'acute mild to moderate pain' and are therefore not specified in the wording of

the indication. The issues regarding quality aspects and bioequivalence were adequately addressed by the MAH.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Okitask 25 mg granules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 December 2016.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Type of modifi-cation	Date of start of the procedure	Date of end of the procedure	Approval/ non approval
NL/H/3583/001/E/001	Repeat use procedure to register the product in Bulgaria, Spain, France, Lithuania, Latvia, and Portugal.	E	5-12-2018	7-6-2019	Approval
NL/H/3583/001/IB/001/G	- a change to the ASMF holder's name, the address remains the same - a minor change to the manufacturing process where charcoal is used as a processing agent - a minor change to the specification, whereby the Total Organic Carbon has been an 'off-line' test, it is now an 'online' test and included on the specification for purified water - a minor change to the specific rotation analytical method, where the sample amount and solvent are increased in proportion, and therefore the concentration of the solution is unchanged. The tests are considered equivalent. - a minor change to the immediate packaging - where by the length of the joint between polyethylene bag joints has been changed.	IB	12-3-2018	13-6-2018	Approval
NL/H/3583/1-2/IB/004	Amendment of fever-indication. In addition, some editorial changes and changes in line with SmPC guideline and excipient guideline are introduced. **Indication**: "recommended in the symptomatic treatment of acute mild to moderate pain, and pain and fever associated with cold and flu." **was changed to**: "recommended in the short-term symptomatic treatment of acute mild to moderate pain, and/or fever"	IB	26-8-2019	18-12-2019	Approval
NL/H/3583/1-2/IB/005	To extend the shelf-life of the finished product as packaged for sale from 24 months to 36 months when stored in the original packaging in order to be protected against light and moisture.	IB	5-11-2019	4-12-2019	Approval
NL/H/3583/001/IA/006	The MAH requested the elimination of dissolution test as IPC performed on the Intermediate coated Ketoprofen lysine salt (KLS) taking into account that: - on the basis of the historical data acquired until now, no out of specification and/or out of trends occurred on the dissolution test performed on the KLS Intermediate. - according to the Ph.Eur./USP monograph, for the single dosage unit, the dissolution test should be performed	IA	12-12-2019	11-1-2020	Approval

	only at release of the drug product.				
NL/H/35831-2/II/007/G	Type II: To change the Particle Size Distribution specification limits of the active substance ketoprofen lysine salt. Type IA: To delete the non-significant parameter Heavy Metals from the specifications of the active substance ketoprofen lysine salt used in the manufacturing process of the active substance.	II + IA	20-1-2020	18-5-2020	Approval
NL/H/3583/1-2/IB/008	Addition of the Elemental Impurities Risk Assessments for the ketoprofen containing granules and tablets (Finished Product) to Section 3.2.P.5.5 of the dossier, as committed during RUP.	IB	15-2-2020	16-3-2020	Approval
NL/H/3583/1-2/IB/009	To add the Certificate of Analyses (COA's) for ketoprofen lysin salt Reference Standards and ketoprofen lysin salt Working Standard to the Dompé Farmaceutici S.p.A. section 3.2.S.5 of the dossier, as committed during RUP.	IB	15-2-2020	16-3-2020	Approval
NL/H/3583/1-2/IB/010	Name change in Poland	IB	15-2-2020	11-5-2020	Approval
NL/H/3583/001/IA/011/G	Change in the name and/or address of the MAH	IA	18-3-2020	17-4-2020	Approval
NL/H/3583/1-2/IA/012	To update sections 4.2 and 4.4 of the SmPC and section 2 and 3 of the PL to implement the signal recommendations on EMA/PRAC/201784/2020 adopted at the 14-17 April 2020 PRAC meeting.	IA	28-10-2020	4-11-2020	Approval
NL/H/3583/1-2/IB/013/G	Change in the name of the medicinal product to Okitask Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location.	IB + IA	24-11-2020	24-12-2020	Approval
NL/H/3583/001/IB/014/G	To tighten the active substance (ketoprofen lysin salt) specification limits To extend the re-test period of the active substance from 48 months to 60 months.	IB	25-3-2021	27-5-2021	Approval
NL/H/3583/1-2/IB/015/G	To extend the re-test period of the active substance from 48 months to 60 months Minor changes to the restricted part of the ASMF	IB	31-3-2021	18-6-2021	Approval
NL/H/3583/001/IB/016/G	Minor change in the manufacturing process Change in the batch size of the finished product Deletion of a non-significant in-process test	IB	31-3-2021	30-4-2021	Approval
NL/H/3583/1-2/R/001	Renewal	R	30-4-2021	11-8-2021	Approval
NL/H/3583/001/E/002	Repeat use procedure to register the product in Croatia, Greece, Romania and Slovenia.	E	18-11-2021	17-1-2022	Approval
NL/H/3583/1-2/II/017	Quality changes in active substance	II	18-3-2022	29-6-2022	Approval
NL/H/3583/001/IB/018/G	Minor changes in the manufacturing process of the active substance	IB	18-3-2022	15-4-2022	Approval

NL/H/3583/1-2/IB/020	To change the (invented) name of the medicinal product in Spain from Sprintafen to Okidol.	IB	11-4-2022	6-7-2022	Approval
NL/H/3583/001/IB/021/G	Deletion of a non-significant in-process test Change to in-process tests or limits applied during the manufacture of the finished product	IB	2-6-2022	11-8-2022	Approval
NL/H/3583/001/IB/022	Change in the holding time for intermediate	IB	12-7-2022	11-8-2022	Approval
NL/H/3583/1-2/IB/024	Change in the name in CMS Romania.	IB	16-8-2022	6-9-2022	Approval