



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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**WITHDRAWAL ASSESSMENT REPORT
FOR**

DIRACTIN

International Nonproprietary Name (INN):
ketoprofen gel (semisolid Transfersome preparation)

Procedure No. EMEA/H/C/865

Day 180 Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

This should be read in conjunction with the “Question and Answer” document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Diractin Gel, “indicated for the symptomatic treatment of mild to moderate-pain in osteoarthritis of superficial joints like the knee” is not approvable since "major objections" have been identified which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Efficacy:

- The efficacy of the drug for the proposed dose has not been sufficiently demonstrated.

II. EXECUTIVE SUMMARY

II.1 Problem statement/ About the product

Ketoprofen (ATC code M01AE03) is a non-steroidal antirheumatic drug, derivate of propionic acid. The drug exhibits anti-inflammatory, analgesic, and antipyretic activity. The mechanism of action is related to the inhibition of cyclooxygenase (COX), leading to a decrease in prostaglandin (e.g. prostaglandin E₂ and prostaglandin F_{2α}). As prostaglandins are mediators of pain, inflammation and platelet aggregation, as well as gastric protectants and regulators of renal perfusion, most of the clinical effects of ketoprofen can be adequately explained by a reduced prostaglandin formation. Ketoprofen, as most other classical NSAIDs, shows no pronounced selectivity for COX-1 and COX-2.

There are currently authorised medicinal products containing ketoprofen in gel in many European countries. The applicant states that Diractin gel contains a novel carrier-based (Transfersome) dosage form of ketoprofen for epicutaneous application, which is expected to avoid clearance of the free ketoprofen by the cutaneous microcirculation and would allow targeted delivery into deeper subcutaneous tissues.

The initially proposed indication was: “*Symptomatic treatment of inflammations and pain from osteoarthritis*”.

In the response document to the day 120 LOQ, the applicant claims: “*symptomatic treatment of mild to moderate pain in osteoarthritis of superficial joints like the knee*”.

Proposed posology:

“For external application to the knee

2.2 g DIRACTIN containing 50 mg ketoprofen. This corresponds to one completely filled dosing aid. To be applied twice a day per knee and to be spread evenly. (application area of approximately 500 cm²).

In addition the applicant is currently proposing an increase in dose: “*In case of an insufficient treatment response the dosage will be increased to 4.4 g Diractin containing 100 mg ketoprofen. This corresponds to two completely filled dosing aids.*”

For external application to other superficial joints

The quantity of DIRACTIN to be applied to other parts of the body should be adjusted proportionally according to the size of the application area”.

According to EULAR (European League Against Rheumatism) recommendations 2003: an evidence based approach to the management of knee osteoarthritis, osteoarthritis (OA) is the most common

form of arthritis in Western populations. It is characterised pathologically by both focal loss of articular cartilage and marginal and central new bone formation. OA of the knee, the principal large joint to be affected, results in disabling knee symptoms in an estimated 10% of people older than 55 years, a quarter of whom are severely disabled. Knee OA is associated with symptoms of pain and functional disability. Physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity and mortality. Current treatments aim at alleviating these symptoms by several different methods:

- Non-pharmacological treatments (for example, education, exercise, lifestyle changes)
- Pharmacological treatments (for example, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), topical treatments)
- Invasive interventions (for example, intra-articular injections, lavage, arthroplasty).

In this review, the expert committee considered that the optimal management of knee OA requires a combination of non-pharmacological and pharmacological treatment modalities. Current evidence to support the various treatments in current use, however, is very variable. Concerning pharmacological treatment, paracetamol is the oral analgesic to try first and, if successful, the preferred long term oral analgesic, while NSAIDs should be considered in patients unresponsive to paracetamol. The therapeutic place of topical applications (NSAID, capsaicin) in the treatment of osteoarthritis is not clear at present. In this document it is stated that topical NSAIDs are sometimes used and are thought to be liked by patients.

II.2 The development programme/Compliance with CHMP Guidance/Scientific Advice

There is no specific guideline on the clinical development of topical medicines for the treatment of OA. Points to Consider on Clinical Investigation of Medicinal Products Used in the Treatment of OA (CPMP/EWP/784/97) explicitly mentions that it addresses “pharmaceutical treatments of osteoarthritis only. Use of topical remedies including iontophoresis and intra-articular injections are not dealt with in this paper...”. Nonetheless, as ketoprofen e.c. is indeed a pharmaceutical treatment, the recommendations within this guideline will be taken into account as appropriate.

No CHMP scientific advice has been given for Diractin; however, national advice has been given by some European Agencies.

II.3 General comments on compliance with GMP, GLP, GCP

GMP: No specific issues during assessment of the dossier give any reasons for asking for an inspection prior to authorisation.

The GLP status of the submitted studies is not mentioned by the applicant under this section in the Non clinical Overview (Module 2.4). No information about GLP status of absorption and distribution studies is provided. Metabolism studies were conducted in accordance with GLP principles as it is indicated in Module 4.2.2.4. In the Non-clinical Toxicology Tabulated Summary (Module 2.6.7), it is stated that toxicology studies were performed in compliance with GLP standards with the exceptions of two local tolerance studies.

Given the development of ketoprofen 40 years ago, the non-clinical studies predate the introduction of GLP and it is very unlikely that they were conducted to current standards.

According to the Applicant, all studies have been designed to meet the requirements set by Good Clinical Practice Guidelines and under the guiding principals detailed in the Declaration of Helsinki. All studies were also carried out in keeping with applicable local law(s) and regulation(s).

II.4 Type of application and other comments on the submitted dossier

IDEA AG applied for a marketing authorisation for the medicinal product Diractin gel (ketoprofen) according to art. 8 (3) (full application) of a known active substance via centralised procedure, category art. 3(2)(b) “optional scope, significant innovation”.

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

Drug substance

The Drug Substance is ketoprofen. This substance is described in the Ph. Eur. monograph No. 0922I. A certificate of suitability was presented.

Ketoprofen is a white or almost white powder freely soluble in ethanol, methanol, acetone, ether, and ethyl acetate. Ketoprofen can exist as two polymorphs. The transition from the glass-like form to the regular crystalline form occurs spontaneously upon storage at room temperature within 10 days.

A chiral centre is present in ketoprofen.

Information regarding the following sections was not submitted: Description of Manufacturing Process and Process Controls; Control of Materials; Control of Critical Steps and Intermediates; Process Validation and/or Evaluation; Manufacturing Process Development; Characterisation; Elucidation of Structure and Other Characteristics.

This is acceptable as ketoprofen is described in the Ph. Eur. monograph No. 0922 and a certificate of suitability has been presented.

A list of specifications including methods is presented and conforms with the corresponding Ph. Eur. monograph

The applicant did not present validation studies as the analytical procedures used to characterise the drug substance comply with the currently valid version of the Ph. Eur. monograph for ketoprofen (0922). This is acceptable.

Batch analyses data for the drug substance is provided in the dossier including an overview of ketoprofen batches used as well as batch analysis results.

The results show that the quality of the batches manufactured to date is consistent.

Specifications are in accordance with the current European Pharmacopoeia Monograph for ketoprofen.

Ketoprofen used in the manufacturing of the Drug Product is stored and shipped in fibre drums lined with two polyethylene bags. Each polyethylene bag is individually sealed by a plastic tie. The fibre drum is sealed with a locking metal lid and suitably labelled before storage and shipping. This container closure system is adequate.

Ketoprofen is described in the current version of the European Pharmacopoeia. For the drug substance a certificate of suitability is available. The information relevant for this section has been assessed by the European Department for the Quality of Medicines (EDQM).

A re-test period of 5 years is granted in the certificate of suitability. This is acceptable

Drug Product

Description and Composition of the Drug Product

The drug product (Diractin Gel) is in the form of a light yellow semi-solid formulation for application on the skin, containing ketoprofen associated with adaptable carriers (Transfersomes), and is indicated for the symptomatic treatment of inflammation and pain in osteoarthritis.

Diractin Gel is based on an innovative drug delivery system (Transfersomes) originally described by Gregor Cevc, and thoroughly investigated ever since by many researchers. Transfersomes are lipid vesicles consisting of lipid bilayers structurally related to liposomes. In addition to phospholipids, Transfersomes present relatively high amounts of non-ionic surfactants. The drug product is packaged in 50g and 150g tubes (1g Diractin Gel contains 22.9 mg ketoprofen).

These vesicles are sufficiently deformable to overcome the primary skin barrier and too large to be taken-up by cutaneous blood microvasculature. They are intended to penetrate the skin barrier along the naturally occurring transcutaneous moisture gradient.

After penetration through the skin, the active ingredient is mainly released from the carriers deep below the skin, rather than in the skin, over a period of many hours. Drug association with Transfersomes also avoids rapid drug dissipation and influences positively drug biodistribution by shielding the associated drug molecules from undesired clearance. This minimises undesired ketoprofen clearance from the skin or from the underlying targeted tissue. The drug molecules are thus accumulated at the chosen site, which is an advantage of Transfersome-mediated drug transport into target peripheral tissue.

The postulated mechanisms are mostly theoretical and partially supported with experimental evidence.

Pharmaceutical Development

The physicochemical properties of the drug substance that could be relevant for product performance were identified and do not impact the performance of the drug product, since ketoprofen is dissolved in the gel.

The amount of drug associated to the carriers is dependent on carrier content and ionic strength.

During stability studies no incompatibilities were found between the drug and the excipients, all of which are well-established pharmaceutical preparation ingredients.

All excipients are widely used materials in pharmaceutical formulation, with a long story of safe utilisation

The selection of all proposed excipients was properly justified during formulation development and stability studies confirmed their good compatibility with ketoprofen.

The main drug product parameters/characteristics studied during the formulation development were the following:

Carrier size and size distribution - The average carrier size and size distribution was chosen so as to reliably ensure final product homogeneity.

Carrier adaptability – The adaptability of the drug carrier is a key parameter that depends mainly on the bilayer elastomechanics and permeability.

Drug release - Drug release from Transfersomes was assessed during formulation development using an *in vitro* assay.

Formulation pH - The formulation pH is controlled using a buffering system, which was optimised during formulation development.

Besides the above, other characteristics studied during the formulation development were the following: antimicrobial preservation; antioxidants; solvents; odour masking.

The formulation includes overages for the antioxidants.

Manufacturing Process Development

Manufacturing process development was well conducted and described in detail. The production of the drug product consists of three main steps: (1) Production of a concentrated liquid suspension intermediate; (2) Production of a gel intermediate; (3) Mixing of both intermediates into a final semisolid formulation

During process development, all potentially relevant instrument settings as well as different homogenisation times were tested and optimised to ensure reproducible results of the defined process.

In order to confirm the validity of production parameters and their acceptance ranges, five production scale batches were manufactured. The differences between the parameter ranges used during scaling-up and the acceptance range of the production parameters for the production-scale manufacturing were found.

Based on these studies the average carrier size in the liquid suspension intermediate at the end of homogenisation was found. The particle size of nanocarriers is one of the major characteristics that influence their pharmaceutical performance and *in vivo* fate. Therefore, the narrow acceptance ranges thus proposed are acceptable.

The acceptance criteria proposed for pH and carrier adaptability are also justified.

Container closure system

Diractin Gel is packaged in tamper evident sealed aluminium tubes (50g and 150g tubes) with an inner lacquer, together with a dosing device to ensure correct dosing. As ketoprofen is known to be light-sensitive, the aluminium tube provides adequate protection.

Compatibility of the drug product with the dosing device was addressed, as recommended by the guideline CPMP/ICH/2887/99 Rev 1.

Description of Manufacturing Process and Process Controls

The manufacturing process is well described, resulting from a well conducted development process and includes 6 steps.

The operating parameters have been established during manufacturing process development as well as during manufacturing process validation. Most characteristics of various intermediates that are routinely measured during the process are justified and acceptable.

Data obtained with 13 batches of show that the intermediate comply with the specifications.

Process Validation and/or Evaluation

Validation results show the reproducibility of the process. The assessed parameters were within the acceptance range indicating the homogeneity of the batches.

Control of Excipients

Polysorbate 80, sodium hydroxide, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dehydrate, butylhydroxytoluene, disodium edentate, methyl parahydroxybenzoate, carbomer, glycerol hydrate, benzyl alcohol, ethanol, sodium metabisulphite and purified water comply with the respective Ph.Eur. current monographs and specifications. Validation of analytical procedures and justification of specifications is covered by Ph.Eur

Phosphatidylcholine and linalol are tested according to IDEA Specifications and are properly justified.

Control of Drug Product: Specifications and Analytical Procedures

The following analytical procedures are performed on Diractin Gel: appearance; pH; viscosity; carrier size; drug release; lipid dry mass (CG); ketoprofen identification and content (HPLC); drug substance impurities; methylparaben identification and content (HPLC); butylhydroxytoluene (HPLC); EDTA (HPLC); sodium metabisulfite; microbiological quality.

The analytical procedures have been validated in accordance to ICH Q2A and ICH Q2B. Validation studies presented are acceptable.

The different specifications proposed are, in general, well justified.

Batch analysis data were obtained with three pilot and seven commercial scale batches of 50g tubes, which comply with the proposed specifications. A further three commercial scale batches of 150g tubes packaged in aluminium tubes were only used for stability purpose.

Description and specifications as well as some batch analyses results are provided for the primary packaging materials, including: inner lacquer; crimp seal (hot sealing lacquer); aluminium foil - screw cap and a dosing spatula.

Stability

Stability studies for the drug product packaged in 50g tubes have been performed on three pilot scale and three commercial scale batches.

In the described conditions, the drug product was found to be stable for the proposed shelf-life when stored in the proposed market package configuration. All quality test results are within the defined limits.

In-use Stability Studies

In-use stability study was carried out. All physical and chemical results as well as microbiological quality are within the defined limits. Results supported the proposed in-use shelf life.

III.2 Non clinical aspects

The drug product is a light yellow semi-solid formulation containing ketoprofen in vesicles : across this report it is referred as IDEA-033 or as Diractin.

The rationale of Diractin Gel formulation is the following: it contains lipid vesicles especially designed to be ultra-deformable and consequently able to overcome non-invasive, semi-permeable barriers, such as the skin, to deposit the drug to a certain depth below the application site. In addition, the vesicles are too large to be taken-up by cutaneous blood microvasculature. After penetration through the skin ketoprofen should be released from the vesicles deep below the skin, over several hours. The association of the drug with the vesicles should also avoid rapid drug dissipation shielding the associated drug molecules from undesired clearance from the underlying target tissues.

Accumulation at the chosen site should therefore be achieved and constitute an advantage of this delivery system over other pharmaceutical forms.

Since ketoprofen is marketed for many years as an anti-inflammatory drug for systemic and for topical use, the pharmacological and toxicological characteristics are known and well determined. The new aspect that should mainly be clarified in dedicated studies should be related to the innovative formulation, for which “proof of concept” studies would have been desirable.

Pharmacodynamics

The primary mechanism of action for ketoprofen is considered to be the inhibition of the COX pathway of arachidonic acid metabolism, leading to decreased production of prostaglandins. In addition to COX inhibition, ketoprofen inhibits the lipoxygenase pathway. Other properties of ketoprofen include antibradykinin and lysosomal membrane-stabilizing activities as well as the prevention of the release of lysosomal enzymes that mediate tissue destruction during inflammation (Kantor TG, 1986).

The pharmacodynamic profile of ketoprofen is considered well known and the extent and scope of the bibliographic documentation provided in this application are considered appropriate. No new pharmacodynamic neither safety pharmacology studies have been performed which is acceptable. “Proof of concept” studies with IDEA-033 should include studies showing how the innovative formulation would influence the pharmacological activity of ketoprofen, especially related to the intended therapeutic indication and pharmacokinetic studies characterising the tissue penetration profile below the site of application. Nevertheless, no pharmacology studies in any animal model of the human disease to be covered in the proposed indication of Diractin (osteoarthritis of the knee) have been conducted. It would have been appropriate to show whether and how the anti-inflammatory and the analgesic properties of ketoprofen were influenced by its binding to the vesicles. Nevertheless, sufficient information was expected to be generated in the clinical setting and therefore additional proof of concept studies were not required. The submitted application includes a revision of the pharmacological properties of ketoprofen as a NSAID, those related and unrelated to the indication, but mainly derived from its mode of action.

Pharmacokinetics

Studies with the IDEA-033 formulation aiming at characterising the systemic (plasmatic) and the tissue (below the application site) distribution of ketoprofen in IDEA-033 as compared to a conventional topical formulation (Gabrilen gel) and an immediate release oral formulation (Ketoprofen Ratiopharm) were performed in pigs. These studies can be considered as adding to the proof of concept, since the aim of the vesicles-containing IDEA-033 formulation is to achieve a more efficient and deeper penetration of ketoprofen below the site of application, thus allowing higher local concentrations and lower plasma concentrations to be achieved.

Absorption

In pigs where the IDEA-033 has been applied at different total doses and different surface area doses, the systemic *absorption* of ketoprofen was dose-dependent but not surface area-dependent. Systemic absorption of ketoprofen from IDEA-033 seemed higher than from the conventional topical formulation (Gabrilen gel) at the lower dose used but not for the higher dose (for the same surface area) as the reverse was observed. Conclusions are therefore difficult to draw. Cmax values were consistently higher for IDEA-033 than for the conventional ketoprofen gel. The results showed the advantage of topical versus oral administration on promoting higher concentrations locally while keeping systemic concentrations lower.

Distribution

The distribution profile in tissue below the application site, of ketoprofen in IDEA-033 formulation vs a conventional formulation and vs an oral formulation has been studied in hybrid pigs. IDEA-033 formulation allowed a higher level of ketoprofen to reach either the superficial or the deeper muscle layers.

The difference was lower between IDEA-033 formulation and conventional ketoprofen gel than between either topical formulation vs the oral one.

Also has been observed that PK parameters in the tissues below application depended on the dose and on the surface area of application as when a 50mg dose was applied over different areas leading to different dose/surface area, the higher dose/surface area led to higher tissue levels below the application site.

Standard deviations of mean values for all these experiments are not shown. Original data show that the standard deviations are generally very high. Due to the large variability, differences should be considered as tendencies and it should not be possible to draw final conclusions.

Muscle tissue concentration after occlusive application of IDEA-033

The application of IDEA 033 under occlusive conditions versus non occlusive conditions was also compared. However, doses (14 and 50 mg/pig) and application areas were different in the two situations and therefore not easily comparable. Additional studies and data in order to explain the effect of non occlusive, occlusive and partial occlusive dressing on muscle tissue concentrations are needed.

Synovial fluid

The penetration of IDEA-033 ketoprofen vs topical formulation applied over elbow and knee joints in the pig into the synovial fluid was also performed. Results clearly show that the concentration of ketoprofen in the synovial fluid of the treated joints was close to 5 times higher than that in the non-treated and in plasma after 2 hours of dosing. After 2 hours, at the subsequent time points, concentrations from treated and non-treated joints were similar to those in the plasma. The exposure of treated joint was therefore higher than that of non-treated, possibly due to the higher concentrations in the first hours post-application. This may suggest that an initial delivery directly to (below) the application site will occur, followed by distribution into the systemic circulation. Whether this corresponds to an added value over other topical formulations of ketoprofen has not been shown since no pharmacodynamic studies with IDEA-033 have been performed.

Metabolism-elimination

The metabolic and excretion profile of ketoprofen in IDEA-033 were not studied. Some literature data has been provided though. Ketoprofen is metabolised by CYP450, main 2C9 subfamily, and excreted as glucuronide as the only metabolite identified in bile and faeces. *In vitro*, in a study performed with a panel of human CYP450 isoforms incubated with ketoprofen EP, minor oxidation potential for the CYP2C9, around 12% after 30 minutes incubation was reported.

Unfortunately, a study of skin metabolism was not performed. Moreover, it should have been studied if the presence in the formulation of different excipients modifies the cutaneous metabolism of ketoprofen. No bioanalytical method to differentiate vesicle-bound from vesicle-free ketoprofen in the skin structure seems to be available.

Toxicology

The toxicological profile of ketoprofen is known and clinical experience exists related to the topical and oral administration. Therefore, studies performed with the IDEA-033 formulation were limited. The toxicological program dedicated to IDEA-033 included i) repeated dose toxicity studies of 2 weeks in rats, 13 weeks in rats and 26 weeks (+4weeks recovery) in minipigs by the epicutaneous route of administration, ii) in vivo genotoxicity study in rats, local tolerance studies of 10 days, 6 weeks and 26 weeks duration in rats, rabbits, pigs and minipigs, eye corrosion test in the rabbit and contact sensitization test in the guinea-pig.

Single dose toxicity

Single dose toxicity of IDEA-033 was not performed.

Repeat dose toxicity (including toxicokinetics)

In rats, after repeated cutaneous administration of IDEA-033 no new toxicological findings in addition to those already identified for NSAIDs were observed. Hemathological, gastro-intestinal and renal toxicity was observed. In addition, erythema in treated and control animals (more severe at higher dose animals) and oedema in treated animals were observed in the 2 weeks and 13 weeks study. Erythema was not described as severe. The Cmax and AUC values observed in this study were much higher than those to be reached under the conditions of clinical use.

In a 26 weeks study in pigs, where animals were treated with 2.92, 7.29 or 14.52 mg/Kg/day ketoprofen applied epicutaneously, formulated as IDEA-033 with appropriate concentrations in order to allow the same dose volume of 0.317ml/Kg to be applied, no changes in body weight gain, food consumption and organ weights were observed in treated animals as compared to controls. Dermal irritation was observed in treated and control animals

The mean Cmax and AUC increased markedly with repeated administrations suggesting duration-dependent accumulation. No gender differences were observed in PK parameters.

The Cmax and AUC values observed at week 26 are summarised in the Table below.

Dose mg/Kg/day	Cmax ng/ml		AUC ng.h/ml	
	Males	Females	Males	Females
0	n.d.	n.d.	n.d.	n.d.
2.92	182	591	2783	5656
7.29	308	322	4393	3939
14.52	898	1620	14385	21591
Humans (220mg/knee/day)	194.3		1527	

The Cmax and AUC values in males were close to those observed in humans after 220mg/knee/day. Adverse events associated with ketoprofen e.g. GI effects at least might therefore still be expected with IDEA-033 chronic administration.

Post-mortem findings corresponded to stomach lesions as the only findings reported. Pathological changes on spleen, lymph nodes or thymus were not observed as well as cell counts and morphology of bone marrow and blood.

Genotoxicity

Genotoxicity studies *in vitro* and *in vivo* including the full ICH test battery did not reveal a genotoxic concern for ketoprofen.

Carcinogenicity

Published carcinogenicity studies in rats and mice also did not reveal a carcinogenic potential. The studies are old and not conducted according to current standards and detailed information is lacking. However, due to existing clinical experience with ketoprofen, new studies are not deemed as necessary.

Reproduction Toxicity

The reproductive toxicity profile of ketoprofen has been revised and is not expected to be altered by the new formulation. The known effects of NSAIDs on premature closure of the fetal *ductus arteriosus* (Mamma K et al, 1983) as well as on retardation of labour onset justifies that use in pregnancy should be avoided. However, human data should be the main data to be considered when advising the use of diclofenac in pregnancy.

Local tolerance

Local tolerance studies addressed the ocular sensitization potential, dermal corrosion/irritation, contact sensitization potential.

The Primary Ophthalmic Irritation Test did not suggest a significant eye irritant potential of IDEA-033 in rabbits.

Concerning dermal toxicity, the studies conducted with IDEA-033 suggest that IDEA-033 can be estimated as non-irritant for the skin of pigs and the rat. In minipigs IDEA-033 exerted a mild to moderate, transient and reversible skin irritant effect. In rabbits IDEA-033 caused mild, transient, and reversible dermal irritation, which appeared to be less pronounced by either reducing the applied ketoprofen area dose from 0.24 mg ketoprofen per cm² to 0.06 mg per cm², or by reducing the dosing frequency of IDEA-033 from twice daily to once daily.

In guinea-pigs, no contact sensitizing potential was noted in animals treated with IDEA-033 or the vehicle.

A mild irritation potential in humans cannot be excluded.

Other toxicity studies

Ketoprofen is known to have phototoxic potential. Dedicated studies with IDEA-033 were not performed but protection of treated areas from light is advised. However, occlusion is expected to reduce the absorption of ketoprofen.

All of the excipients in IDEA-033 are described as well known pharmaceutical excipients already used in pharmaceutical preparations or cosmetics or as food additives or ingredients. Most substances can be regarded as essentially safe (at least under the conditions used) or already evaluated and approved with respect to possible health effects. Linalool seems to have a potential for sensitization related to the formation, by auto-oxidation, of oxidized linalool. Antioxidants can minimize the auto-oxidation. Protection from auto-oxidation will prevent the formation of sensitizing derivatives. In IDEA-033, the presence of antioxidant components in the formulation is claimed to prevent the auto-oxidation of linalool.

Ecotoxicity / environmental risk assessment

An ERA based on published data has been submitted by the applicant. However, the ERA is not complete and the data currently submitted does not exclude any potential environmental risk and the need for a phase II study.

III.3 Clinical aspects

Introduction

The applicant has developed a novel vesicle-based dosage form of ketoprofen (IDEA-033) for epicutaneous (e.c.) application to treat the signs and symptoms associated with OA and to minimise the potential for the systemic AE associated with oral administration of NSAIDs. The rationale of this approach is that this drug delivery tool would avoid clearance of the free ketoprofen by the cutaneous microcirculation because the ketoprofen binding carrier is too large to become absorbed by the skin capillaries. Theoretically, this would allow targeted delivery into deeper subcutaneous tissues, though this hypothesis has not been proven at clinical level.

Pharmacokinetics

Ketoprofen is a well known active substance with a well defined pharmacokinetic profile when administered via extravascular (i.m., p.o.) or i.v. routes. It is characterised by a short half-life (ca. 2 h), low volume of distribution (ca. 0.1 L/kg) possibly due to high protein binding (ca. 95%), 80% excretion in urine as glucuronide, rapid (ca. 1.5 h for t_{max}) and complete (ca. 90%) oral absorption.

In this application, most of the data presented rely on published literature. The applicant justifies the reference to published data in order to provide information in the relevant sections of the clinical pharmacokinetic report by stating that the pharmacokinetics of ketoprofen from Diractin is comparable to systemically administered ketoprofen.

The main PK characteristics have been either obtained from literature or determined in two clinical PK studies summarised below

Study CL-033-I-01

This was an open-label, single- and multiple-dose, 2-treatment, 1-sequence crossover study.

The primary objective of this study was to determine the single-dose bioavailability of ketoprofen from Diractin to that of a single oral dose. Secondary objectives were to determine steady-state bioavailability of Diractin following the eleventh dose and absorption linearity by comparing systemic exposure from the first and final epicutaneous doses.

Study CL-033-I-02

This was an open-label, multiple-dose, 2-treatment, parallel group study.

The objective was to compare the systemic exposure, pharmacokinetics, and urinary excretion of ketoprofen after 2 weeks of once daily (od) or bid application of IDEA-033.

In addition, blood samples for the determination of ketoprofen concentrations in plasma were taken in the two efficacy studies: after 2 weeks and end of study visit in study CL-033-**II-03** and at 6 or 12 weeks and on the end of study visit in study CL-033-**III-02** (and its extension phase).

All the analytical methods were fully validated, according to current standards, enabling to produce accurate and precise concentration results of unchanged ketoprofen. In-study validation is included in each report. However the hydrolysis step for total ketoprofen analysis should be adequately validated. In addition, the method determines free ketoprofen. However there is no evidence that ketoprofen is in the free form in plasma and not bound to the vesicles. No experimental evidence has been provided to substantiate that practically all ketoprofen determined in plasma was protein-bound, and not vesicle-bound. However this can be accepted based on logical reasoning and because it is not expected to have clinical implications.

- **Absorption**

Results from the above studies (I-01 and I-02) show a very slow ($t_{1/2} = 15.9 - 33.4$ h) and limited absorption (bioavailability relative to oral formulation is ca. 7.5%) of ketoprofen from this topical gel application. Prolongation of half-life compared to oral dosing suggests flip-flop kinetics. A ca. 2-fold accumulation at steady-state would be consistent with a twice daily administration and the reported half-life. However, since steady-state has not been achieved, these data suggest absorption non-linearity.

- **Metabolism and Elimination**

Metabolism has not been extensively studied with Diractin and the information is largely based on the extrapolation of information gathered from literature on the metabolism of ketoprofen after oral, i.v. or i.m. administration. This should be regarded with great caution due to the low but persistent plasma levels achieved with Diractin topical gel application. From study CL-033-I-02, the vast majority of total ketoprofen recovered in urine was excreted as glucuronide metabolite, i.e. more than 95% of total ketoprofen, in terms of geometric mean results. The geometric mean amount of total ketoprofen recovered in urine within 1 dosing interval corresponded to 2% or less of the dose applied epicutaneously during 1 dosing interval. Recovery of glucuronide in the urine follows known pattern of ketoprofen metabolism and excretion. This finding confirms literature reports on glucuronide excretion.

- **Dose proportionality and time dependencies**

Studies CL-033-I-01 and CL-033-I-02 and plasma concentration data from two clinical efficacy studies address the issue of time and dose dependency. Results from the two clinical efficacy studies indicate a slight but consistent decrease in exposure from week 6 or week 12 to end of study for both enantiomers, which exhibit similar concentrations. On the other hand, the assertion that mean and median values indicate dose proportionality cannot be endorsed based on the data.

As reported in several studies, total variability is extremely high. Reliable estimates of intra-individual as well as inter-individual variability have not been provided.

- **Special populations**

Concerning pharmacokinetics in special populations, it is recommended to avoid ketoprofen medication during pregnancy, although embryopathic effects have not been recorded. However, ketoprofen may have adverse effects on the foetus through its pharmacological properties, including possible premature closure of the ductus arteriosus Botalli and pulmonary hypertension, as generally known for NSAIDs. The proposed SPC adequately addresses the issue of ketoprofen medication during pregnancy.

The proposed SPC also states: “*Careful monitoring is advised in patients suffering from impaired kidney function*”. In addition, it should reflect the information provided, namely that Diractin should be contraindicated in severe renal insufficiency. The literature reported findings on cirrhotic patients warrants a mention in the SPC, which was included as follows under section 4.4 Special Warnings and Precautions: “There is insufficient knowledge about the impact of hepatic impairment on ketoprofen

plasma concentration after treatment with Diractin, as patients with hepatic impairment had been excluded from the clinical studies investigating safety and efficacy of Diractin.”.

Again, extrapolation of data from literature to clinical use of Diractin should be regarded with great caution due to the persistent and prolonged nature of low ketoprofen concentrations. The only mentions in the SPC concern pregnancy (contraindication), children (no experience) and renal impairment (careful monitoring of patients). Data from literature and from the applicant on Diractin is rather scarce and do not cover all the possible differences in special populations to ensure safe use of this medicinal product. Regarding the persistent and prolonged nature of low ketoprofen concentrations, the SPC refers, under section 4.8 Undesirable Effects: “Due to limited knowledge about the impact of low persistent ketoprofen blood levels, such as the ones achieved by chronic application of Diractin, adverse reactions should be monitored with care during the course of a long-term treatment with Diractin.”

- **Pharmacokinetic interaction studies**

Interaction information compiled by the applicant indicates some possible form of interaction with methotrexate, lithium, probenecid, aspirin and warfarin. These have been determined at much higher plasma levels than the ones reached with topical applications of ketoprofen including Diractin, which are only ca. 1% and 7% as compared to oral administration, in terms of C_{max} and AUC respectively after dose correction. The pharmacokinetic implications of the persistent nature of these low concentrations have not been addressed in the literature or in any study by the applicant. Therefore it is not granted that the interactions do not exist and the applicant should further justify the absence of this information in the SPC.

- **Discussion on clinical pharmacokinetics**

In this application, most of the data presented rely on published literature. The applicant justifies the reference to published data in order to provide information in the relevant sections of the clinical pharmacokinetic report by stating that the pharmacokinetics of ketoprofen from Diractin is comparable to systemically administered ketoprofen. This is not considered fully appropriate.

There are two important issues in this application:

- One concerns the fact that published pharmacokinetic characteristics have been determined at much higher plasma levels than the ones reached with topical applications of ketoprofen including Diractin, which are only ca. 1% and 7% as compared to oral administration, in terms of C_{max} and AUC respectively after dose correction. The pharmacokinetic implications of the persistent nature of these low concentrations in long term treatment, as opposed to large peaks followed by rapid decay after oral administration have not been addressed in the literature or in any study by the applicant. Therefore direct extrapolation is not granted and all statements on ketoprofen pharmacokinetics based on literature have to be viewed as mere hypothesis with no experimental evidence.
- The second issue concerns to the fact that the applicant resorts to published literature reporting significant ketoprofen levels in the synovial fluid and other tissues possibly involved in the inflammatory process of OA after topical application from different formulations. The applicant does not make any direct claim aimed at extrapolating these results obtained with other topical formulations to the ones obtained with Diractin, but an implication is strongly suggested. Only animal data substantiating synovial fluid accumulation are provided for this formulation. The lack of distribution data of this type obtained with Diractin makes it very difficult to assess the implications of the claimed mechanism of access to the site of action, namely that ... *“vesicles are driven by the water gradient across the skin and actively transport the associated drug across the skin for targeted delivery into deep subdermal tissues. The ultra-deformable carriers with the associated drug are too large for uptake by the cutaneous microcirculation. This limits clearance from the skin by capillaries and allows greater penetration of the drug into tissues deep below the application.”* This claim can

neither be substantiated with data from the literature, because the formulations are different nor with the applicant's own human data, which is inexistent. Animal data has a limited predictive value in this instance.

Correlation between pharmacokinetics and pharmacodynamics is not possible because plasma levels hardly reflect concentrations at the postulated site of action.

Pharmacodynamics

The pharmacology of ketoprofen is well-known. No original pharmacodynamic studies in humans have been provided. A comprehensive description of the mechanism of action has been provided by the applicant. The conclusions of the summaries are considered adequate and are supported by updated bibliography. The dosage regime proposed by the company is based on efficacy trials.

Clinical efficacy

Even though the Points to Consider on Clinical Investigation of Medicinal Products Used in the Treatment of OA (CPMP/EWP/784/97) mention that they address pharmaceutical treatments of osteoarthritis but not topical remedies, recommendations within this guideline have been taken into account, when appropriate.

- **Dose response study**

The selection of the proposed dose (50 mg b.i.d.) was based on results from study CL-033-**III-02**, summarised below.

- **Main studies**

The Applicant has provided three studies as evidence of efficacy:

- Study CL-033-**II-03**: "A double-blind, placebo-controlled evaluation of safety and efficacy of epicutaneously applied IDEA-033 (ketoprofen in vesicles) in comparison to oral celecoxib for the treatment of pain associated with osteoarthritis of the knee"
- CL-033-**III-02**: "A double-blind, placebo-controlled evaluation of dose related safety and efficacy of epicutaneously applied IDEA-033 for 3 months treatment of osteoarthritis of the knee"
- CL-033-**III-02E**: "A double-blind, dose-controlled evaluation of safety and efficacy of epicutaneously applied IDEA-033 for 12 weeks treatment of osteoarthritis of the knee following a 12 weeks placebo controlled trial".

Study CL-033-III-02E is an extension phase of study CL-033-III-02.

Study ID	Design and Study objective	Study Posology	Subjs by arm entered	Diagnosis/ Inclusion crit.	Primary Endpoint
CL-033- II-03	Phase II-III ¹ , multicentre, double-blind, randomised, placebo and active controlled Safety and efficacy of 110 mg of ketoprofen e.c. b.i.d. as compared to placebo and 200 mg celecoxib/day.	<ul style="list-style-type: none"> • 110 mg ketoprofen e.c. b.i.d. + 1 placebo capsule b.i.d. • 100 mg celecoxib capsules b.i.d. + placebo e.c., b.i.d. • placebo ec, b.i.d. + 1 placebo capsule b.i.d. 	Ketoprofen: n=138 Celecoxib: n=132 Placebo: n=127 Duration: 6 weeks	<ul style="list-style-type: none"> • OA of knee • At least 2 of: Morning stiffness < 30', crepitus, ≥ 40 yr • at least 3 on Likert's 5 point scale while not on NSAIDS 	<ul style="list-style-type: none"> • change from baseline at week 6/end of study on the VAS version of the WOMAC pain subscale • change from baseline at week 6/end of study on the VAS version of the WOMAC function subscale • patient global assessment of response to therapy measured on the 5-point Likert scale at week 6/end of the study
CL-033- III-02	Phase III, multicentre, randomised, double-blind, placebo-controlled. Elucidation of the dose-response function in efficacy and safety in order to determine the optimal dose.	<ul style="list-style-type: none"> • 25 mg ketoprofen e.c. b.i.d. per knee • 50 mg ketoprofen e.c. b.i.d. per knee • 100 mg ketoprofen e.c. b.i.d. per knee • Placebo gel, b.i.d. 	25 mg: n=223 50 mg: n=223 100 mg: n= 221 placebo: n=199 Duration: 12 weeks	<ul style="list-style-type: none"> • OA of knee • At least 2 of: Morning stiffness < 30', crepitus, ≥ 40 yr 	<ul style="list-style-type: none"> • change from baseline at week 12/end of study on the VAS version of the WOMAC pain subscale • change from baseline at week 12/end of study on the VAS version of the WOMAC function subscale • patient global assessment of response to therapy measured on the 5-point Likert scale at week 6/end of the study
CL-033- III-02E	Phase III, multicentre, randomised, double-blind, dose controlled To identify the dose-dependent safety and efficacy profile in patients with active treatment during 12 weeks and a subsequent treatment for another 12 weeks.	<ul style="list-style-type: none"> • 25 mg ketoprofen e.c. b.i.d. per knee • 50 mg ketoprofen e.c. b.i.d. per knee • 100 mg ketoprofen e.c. b.i.d. per knee 	25 mg: n=172 50 mg: n= 171 100 mg: n= 167 Duration: 12 weeks	Completed CL-033-III-02	<ul style="list-style-type: none"> • change from baseline at week 12/end of study according to the modified OMERACT-OARSI criteria²

An uncommon approach was therefore chosen; no phase II dose ranging study was performed before the confirmatory trial, as it is normally considered prudent to avoid accumulation of data at excessive doses. Instead a late phase III study intended to determine the optimal dose with respect to efficacy and safety was carried out (CL-033-III-02). This study evaluated the effect of epicutaneous ketoprofen over a range of doses (25, 50 and 100 mg b.i.d.) versus placebo, and is provided as main evidence of efficacy. In this study, the magnitude of the effect on pain was similar for the 100 mg and 50 mg doses b.i.d, so the 50 mg b.i.d. dose emerged as the one to be recommended in the SPC. An extension phase of this trial, for which purely descriptive statistics were to be provided, was also submitted.

Results from another efficacy study (II-03), considered as a phase II in USA but a phase III in Europe, was performed before the dose ranging trial, so a 110 mg b.i.d. dose was used, and is considered here as a supportive study. The populations also differed slightly in baseline pain scores, whereas in the

¹ Phase II study according to the Tabular Listing of All Clinical Studies (Module 5.2) and to Study ID number; phase II in US but phase III in EU according to study protocol.

² Additionally, 10 non-graded efficacy endpoints are detailed in the protocol.

sensitivity analyses response appeared to be related to baseline pain scores, so it was considered that no conclusions of the study with the 110 mg could be extrapolated regarding efficacy to the proposed 50 mg dose. Also, concerns regarding whether celecoxib was the optimal comparator and whether it was optimally dosed, as the SPC recommends that in case of insufficient relief of symptoms, an increased efficacy can be obtained with 200 mg b.i.d. were present. Therefore, there is only one trial (III-02) to support the intended dosing of 50 mg (study III-02).

In addition, apparently as per FDA's requirements, there are 2 additional studies ongoing in the United States. These studies are to provide 12-week controlled data against oral naproxene, and 52-week safety and efficacy data of IDEA-033 as compared to oral naproxen. According to the D120 LOQ, these results will be available on 1Q 2008. The applicant is requested to discuss whether confirmatory evidence of the 50 mg dose in comparison to what might be considered an optimal comparator will be provided. Confirmatory evidence of post-hoc analyses from a population with limited pain might also be submitted. Additionally, 52 week data and information on ethnicities will also be provided.

Main trial

As regards **pivotal trial III-02** and even though three-arm, placebo and active controlled studies are recommended in OA as phase III trials, the use of randomised parallel dose-response clinical trials as confirmatory studies, though not so frequently used, is recognised in general pieces of guidance. Unfortunately, since there is the only one pivotal trial, exceptionally compelling results in terms of external and internal validity, clinical relevance, data quality, statistical significance and internal consistency are expected. Other than this, most of the trial's characteristics, including blinding, inclusion/exclusion criteria or study endpoints (VAS version of the pain subscale as primary endpoint, function and patient's global assessment as co-primary) etc... followed the directions of the OA guidance.

Of note, it is supported that in order to improve homogeneity, inclusion was restricted to OA of the knee, though in this situation extrapolation to upper limbs is not acceptable according to the guidance, and since ketoprofen is expected to act locally, extrapolation from a superficial joint like the knee to a deep like the hip is doubtful. The applicant should restrict the indication to OA of the knee. In addition, since the benefits over inflammation are not sustained by any secondary or primary endpoints, and if any, evidence of benefit is only limited to pain (see below), the indication should be restricted to this symptom. The study duration might be adequate (12 weeks) if the extension phase is taken into account (12 more weeks), though the requirement to provide radiographic data as evidence that no deleterious effect is produced, was not provided. On the D121 response document, the applicant has performed a review which includes updated literature on the role of ketoprofen on knee structure. Taking into account the references provided, the fact that treatment duration should be limited as much as possible, and even considering the limited in vivo knowledge of the effect of PK/accumulation data in underlying tissues; the absence of data on radiographic evaluation at one year on joint degeneration, does not seem crucial at this stage. This question could be solvable with the provision of 52 week data from the American study.

Statistically significant differences for the percentage change from baseline on the pain subscale were detected for the 50 and the 100 mg dose in the ITT population, but only for the 50 mg when the baseline observation carried forward technique for imputation of missing data was used.

Table 11.4-2: Visual Analogue Scale (VAS) WOMAC pain subscale (ITT).
Mean (SD)

Treatment	Baseline Visit 2	Week 12 (End-of-study visit)	Percentage change from baseline	p
100 mg	65.67 (13.38)	28.39 (21.00)	-57.35 (29.30)	0.0383
50 mg	65.35 (14.35)	27.92 (21.28)	-57.09 (31.70)	0.0204
25 mg	64.10 (13.90)	29.88 (21.16)	-53.40 (31.10)	0.3616
Placebo	65.58 (13.18)	32.57 (32.33)	-49.53 (34.05)	-

Overall, no statistically significant effects on function or patient’s global assessment were detected. Although this should not normally be the case, as pain and function are inextricably linked and the trial was sufficiently powered to detect a difference in both, according to current guidance, if the effect on pain is sufficient and there is no evidence of a deleterious effect on function, as appears to be the case, the only implications will be in the labelling. Similar results were shown for the PP population, though strictly speaking no statistically significant differences were found for pain in the 50 mg group (p= 0.0542). Overall, differences between treatment groups were not detected for any of the relevant secondary endpoints (use of rescue medication, treatment failure due to lack of efficacy etc...).

In addition, the applicant’s predefined criteria for clinical relevance in study III-02 for pain were not met (lower limit CI for Mann-Whitney statistic below 0.56 = small, non-relevant, superiority, see applicant’s table 11.4-11 below) and there is an approximate mean difference from baseline between the 50 mg and placebo which can hardly be considered to have any therapeutic relevance (approximately 4-5 mm on the VAS 100 mm WOMAC pain subscale³, see applicant’s table 11.4-8 below).

Tabelle 11.4-11: Multivariate generalised Wilcoxon-Mann-Whitney Statistic with 95%-confidence limits for primary and co-primary variables (percent changes) in ITT-population

ITT	Pat. global assessment	Pain	Function	Stoch. order
100 mg ketoprofen in IDEA-033 e.c. vs. Placebo gel e.c.				
p-value	0.3214	0.0380	0.1308	0.0859
P	0.5278	0.5609	0.5442	
Lower	0.4729	0.5034	0.4869	
Upper	0.5827	0.6185	0.6015	
50 mg ketoprofen in IDEA-033 e.c. vs. Placebo gel e.c.				
p-value	0.0260	0.0267	0.0182	0.0115
P	0.5620	0.5649	0.5692	
Lower	0.5074	0.5075	0.5118	
Upper	0.6166	0.6223	0.6266	
25 mg ketoprofen in IDEA-033 e.c. vs. Placebo gel e.c.				
p-value	0.3034	0.2995	0.8516	0.4029
P	0.5288	0.5303	0.5054	
Lower	0.4740	0.4731	0.4484	
Upper	0.5836	0.5876	0.5625	

P = Mann-Whitney Statistic
 Lower = Lower limit of 95% confidence interval
 Upper = Upper limit of 95% confidence interval

³ 10 mm are usually considered as minimal perceptible improvements while differences of 20 mm are usually considered as the threshold of important improvements.

Table 11.4-8: Summary of Least Square Means for Absolute Changes from Baseline Values of WOMAC Pain and Physical Function Subscale and for Patient Global Assessment at Visit 5 / End of Study – ITT Population.

(Co-)Primary Efficacy Variable	100 mg ketoprofen in IDEA-033 e.c.	50 mg ketoprofen in IDEA-033 e.c.	25 mg ketoprofen in IDEA-033 e.c.	Placebo gel e.c.	p-value ^a
WOMAC Pain Subscale					
N	209	211	209	185	
LS Mean (SE)	-37.07 (1.42)	-37.27 (1.41)	-34.87 (1.42)	-32.67 (1.51)	0.1080
p-value	0.0398	0.0278	0.3014	-	
WOMAC Physical Function Subscale					
N	208	211	209	185	
LS Mean (SE)	-22.06 (1.27)	-23.69 (1.26)	-19.88 (1.27)	-19.13 (1.34)	0.6369
p-value	0.1168	0.0127	0.6894	-	
Patient Global Assessment					
N	209	211	209	185	
LS Mean (SE)	2.23 (0.08)	2.36 (0.08)	2.23 (0.08)	2.11 (0.08)	0.1987
p-value ^b	0.3180	0.0276	0.2362	-	

a: Based on the analysis of covariance (ANCOVA).

b: Pairwise comparison: IDEA-033 vs. placebo.

Additionally, a high response to placebo (77.5 % of responders according to the OMERACT OARSI RR, 86.8% for the 50 mg dose), a high amount of rescue medication (average amount of rescue medication taken by day, per days in study of 0.61 to 0.69, evenly distributed across treatment groups) and a very low compliance for study medication (99/223 patients for the 50 mg group or 77/ 199 for placebo) were evidenced. These findings raise serious concerns regarding the internal validity of the pivotal study, which seem to be almost impossible to solve.

In the response document to the day 120 LOQ, the applicant has suggested to recommend 50 mg b.i.d. as the starting dose and 100 mg b.i.d. as a dose escalation option. However, in the only dose ranging study in which several doses were studied (CL-033-III-02), the “minimum effective” dose (the clinical relevance of the findings need further consideration) was the 50 mg and indeed, the 100 mg dose did not appear to be any more efficacious than the 50 mg dose. Certainly, the dose escalation to 100 mg cannot be recommended (in fact, not all three primary or co-primary endpoints were statistically significant for both the 50 and the 100 mg dose).

The issue of dose finding and clinical relevance has not been fully resolved. The applicant has decided instead to focus on a post-hoc sensitivity analysis performed in patients with baseline WOMAC pain subscale ≤ 65 mm. The lower bound of the CI does not reach equality (0.5) for either 100 mg or 50 mg for pain. Similar results are provided for the PP population and with the BOCF technique, though the lower bound in most cases reaches equality. In this situation, the acceptability of this exploratory analysis is an important issue. Of course, a specific claim in a particular subgroup usually requires pre-specification of the corresponding null hypothesis and an appropriate confirmatory strategy (Points to consider on multiplicity issues in clinical trials, CPMP/EWP/908/99). In addition, the applicant has not justified the reasons for selecting this particular cut-off value. Therefore, there might some evidence the efficacy is in line with the one obtained with celecoxib and the product is topic what might be considered an advantage. However to concur with the arguments of the applicant there is need to obtain further clarifications has described above. Point not solved

Supportive studies

Study CL-033-III-02-E (extension phase of study CL-033-III-02). No decline in RR was evidenced from week 12 to week 24. However, since patients were recovering from a flare, there is no placebo arm or randomised withdrawal, the optimal length of treatment is not clear. As recognised by the applicant, the missing placebo-controlled data during the extension phase or of a randomised withdrawal, hampers interpretation of the results as to whether the response rate beyond 12 weeks is a result of spontaneous recovery after a flare or maintenance of efficacy. In any case, no further decrease in WOMAC pain subscale for patients in the active treatment arms from the pivotal trial, appears to have been evidenced beyond 12 week; while the decrease from week 6 to week 12 in these arms seems to be limited (less than 10 mm on the VAS scale). Furthermore, hardly any differences were evidenced between the active treatment arms and the placebo arm earlier than 12 weeks. In any case, it should be clearly stated in the SPC that treatment should be limited to 12 weeks, as there is no evidence of efficacy beyond this time. The following wording is suggested.” Treatment should not exceed 12 weeks duration”.

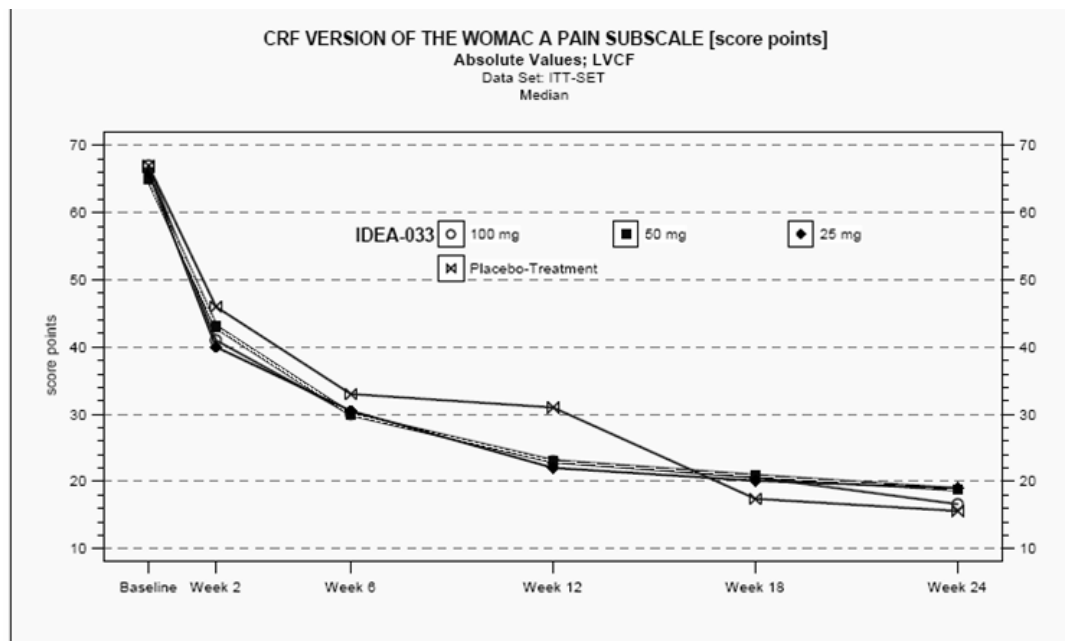


Figure 16: WOMAC Pain Changes from Baseline within study CL-033-III-02 (Week 2, 6 and 12) for patients rolled over into CL-033-III-02E (week 18 and 24). Patients on Diractin during the first phase of the study (IDEA 033: 100mg, 50mg and 25mg) remained on active treatment after week 12. Patients on Placebo were switched to active treatment at week 12.

Study CL-033-II-03. Model sensitivity was demonstrated by means of celecoxib being statistically superior to placebo on all three primary endpoints, but ketoprofen at a 110 mg dose was not statistically significant to placebo on function. The differences observed between celecoxib, at its standard dose for OA, and placebo were similar to those detected for ketoprofen at 110 mg dose, though the election of celecoxib as optimal comparator might be questionable. These differences were higher than those obtained in the pivotal trial (just over 10 mm on the VAS pain WOMAC pain subscale for celecoxib, 8 mm for ketoprofen).

Discussion and conclusion

In conclusion, a single pivotal trial supports the use of 50 mg Diractin b.i.d. in OA of the knee. In these circumstances results should be particularly compelling in terms of external and internal validity, clinical relevance, statistical significance, data quality and internal consistency. There are however,

remaining concerns regarding the clinical relevance of the findings over pain in this single pivotal trial.

Clinical safety

The safety database for Diractin gel includes four studies in the target population (OA patients) and a dermal safety study. Overall, the safety database includes 1.317 patients treated with ketoprofen gel at different doses up to 100 mg twice daily. Of them, 257 received 50 mg twice daily, which is the proposed dose for Diractin gel. Two of the studies were placebo-controlled and one of them was also controlled with oral celecoxib.

The study population was knee OA patients for three of the studies and OA patients for the long term open-label study CL-033-III-01. With respect to patients' demographic characteristics, it would have been desirable to have had a higher percentage of patients older than 75 years in order to reflect the potential target population better. In addition, most of the population was Caucasian and few patients from other origins were included. The Applicant should discuss if a different safety profile would be expected for non-Caucasian patients.

For all studies, the majority of drug related adverse events were related to the skin or application site, mainly irritation with higher erythema scores which were more common in the ketoprofen gel treatment group. Photoallergic contact dermatitis is a very well-known adverse event related with the topical administration of ketoprofen. This adverse event may be especially relevant for patients living in the South of Europe for whom exposure to sunlight is almost permanent. The measures to avoid contact with sunlight proposed by the Applicant are considered adequate and the SPC and patient information should be in accordance. However, the information given to patients should be reinforced by adding a sentence in the outer packaging, warning patients that this medicinal product has photosensitizing potential. The inclusion of other information in the "blue box" (e.g., a pictogram) can be appropriate, although the implementation of this particular action will depend on each Member State (see "Guideline on the packaging of medicinal products for human use authorised by the Community", July 2007).

In the long-term study over a treatment period of 3 months, treatment with ketoprofen in none of the three strengths (100, 50, or 25 mg) showed an increased safety risk from the previous studies. The incidence of serious AEs was also low and few of them were considered treatment-related.

Cross-sensitivity reactions with other arylpropionic acid derivatives, such as tioprofenic acid or fenofibrate, have been described. No information on these cross-sensitivity reactions has been included in the proposed SmPC. A sentence warning prescribers about this particular safety issue should be included in section 4.4 of the SmPC.

According to the data submitted, it appears that the safety profile of Diractin in the OA population is acceptable and no major safety concerns have been identified with the intended posology.

Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

IV. ORPHAN MEDICINAL PRODUCTS

Not applicable

V. BENEFIT RISK ASSESSMENT

V.1 Benefits

The pivotal trial (study III-02) was overall in accordance with the guidance on OA, though the use of a randomised parallel dose ranging design, instead of a three-arm, placebo and active controlled study is not so common. Statistically significant differences for the main endpoint (percentage change from baseline on the pain subscale) were detected for the 50 and the 100 mg dose in the pivotal trial III-02, although these differences were apparent only for the 50 mg when the baseline observation carried forward technique for imputation of missing data was used. However, no statistically significant effects on function or patient's global assessment were detected. Although this should not normally be the case as pain and function are inextricably linked and the trial was sufficiently powered to detect a difference in both, according to current guidance, if the effect on pain is sufficient and there is no evidence of a deleterious effect on function, as appears to be the case, this will only have implications in the labelling.

However, the applicant's predefined criteria for clinical relevance in study III-02 for pain were not met, so the applicant has decided to focus in a post-hoc analysis including only patients with baseline pain ≤ 65 mm VAS and to propose an increase of dose to 100 mg in case of insufficient relief of symptoms. The applicant has proposed to do so despite the fact that there is no evidence of superior efficacy of the 100 mg dose over the 50 mg.

The Applicant has submitted another efficacy study (II-03), considered as a phase II in USA but a phase III in Europe. This trial was performed before the dose ranging trial, so a 110 mg b.i.d. dose was used, and from CHMP's point of view, it can be considered only as a supportive study. An extension phase of the pivotal trial has also been submitted, in which the reponse rate did not apparently decrease from 12 to 24 weeks.

In conclusion, only a single pivotal trial is available to support the use of 50 mg Diractin b.i.d. in OA of the knee. In these circumstances results should be particularly compelling in terms of external and internal validity, clinical relevance, statistical significance, data quality and internal consistency. There are however, remaining concerns regarding the clinical relevance of the findings over pain in this single pivotal trial.

V.2 Risks

Concerning clinical safety, the majority of drug related adverse events were related to the skin or application site, mainly irritation with higher erythema scores more common in the ketoprofen gel treatment group. Photoallergic contact dermatitis is a very well-known adverse event related with the topical administration of ketoprofen. This adverse event may be especially relevant for patients living in the South of Europe for whom exposure to sunlight is almost permanent.

According to the data submitted, it appears that the safety profile of Diractin in the OA population is acceptable and no major safety concerns have been identified with the intended posology.

V.3 Balance and Conclusions

The major objection on efficacy has not been resolved. Therefore, the benefit/risk balance of Diractin gel indicated for the symptomatic treatment of mild to moderate-pain in osteoarthritis of superficial joints like the knee, remains unfavourable