Bundesamt für Sicherheit
im Gesundheitswesen

Public Assessment Report

Scientific discussion

Finacea 150 mg/g Gel
Azelaic acid

AT/H/0167/001/DC

This module reflects the scientific discussion for the approval of Finacea. The procedure was finalised on 21-01-2009. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This decentralised application concerns the medicinal product Finacea 15% Gel (active ingredient: azelaic acid) which is a topical preparation proposed for the treatment of papulopustular rosacea. The legal basis for these submissions is article 8.3 (i.e. full dossier with administrative, quality, pre-clinical and clinical data) - azelaic acid is a known active substance.
Azelaic acid is the active ingredient of Skinoren 20% Cream and Skinoren 15% Gel. Skinoren 15% Gel has been approved in several European Member States via national procedures or mutual recognition procedures (MRPs) for the relief of mild to moderate papularpustular acne of the facial area and topical treatment of papulopustular rosacea. Skinoren 15% Gel and Finacea 15% Gel is the same medicinal product.

II. QUALITY ASPECTS

II.1 Introduction

Finacea 150 mg/g Gel is a gel, which is presented in an aluminium tube with internal epoxide coating and polyethylene screw cap.

II.2 Drug Substance

The active substance in Finacea is azelaic acid. The specification of the active substance meets the current scientific requirements. The adequate quality of the active substance has been shown by submitting the appropriate control data. The stability of the active substance has been tested under ICH conditions. The results of the stability studies support the established retest-period.

II.3 Medicinal Product

Finacea contains the following excipients:
1 mg benzoic acid /g Gel, 0.12 g propylene glycol /g Gel, lecithin, triglycerides (medium chain), polysorbate 80, carbomer 980, sodium hydroxide, disodium edetate and purified water.
The manufacturer responsible for batch release is Intendis Manufacturing S.p.A., Via E. Schering 21, 20090 Segrate, Italy.
The development of the product has been sufficiently made and deemed appropriate. The usage of all the excipients has been described.
The release specification includes the check of all parameters relevant to this pharmaceutical form. Appropriate data concerning the control of the finished product support the compliance with the release specifications.
The packaging of the medicinal product complies with the current legal requirements.
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, with a shelf life of 3 years without special storage conditions.
The pharmaceutical quality of Finacea has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Azelaic acid, the active substance of Finacea 15% Gel, is a naturally occurring dicarboxylic acid, present in animals, humans and plants. It is a natural constituent in whole grain cereals such as wheat, rye, and barley. Azelaic acid is also endogenously formed from longer chain dicarboxylic acids, metabolism of oleic acid, and ω-oxidation of C9 monocarboxylic acid. Endogenous plasma concentration and daily urinary excretion of azelaic acid are highly dependent on dietary intake and endogenous metabolism.

III.2 Pharmacology

The experiments presented by the applicant try to explain the possible mode(s) of actions of AzA in the treatment of acne. No pharmacodynamic studies have been performed with Skinoren Gel for the indication rosacea. The in vitro action of AzA as a scavanger of oxygen radicals might contribute to the antiinflammatory properties in acne and rosacea.
Nevertheless, the presented tests allow the conclusion that the safety pharmacology of AzA does not give any cause for concern, especially when AzA is used topically.

III.3 Pharmacokinetics

The dossier contains a series of studies in which ^{14}C - AzA was administered intravenously or via the intragastric route in rats, rabbits, dogs and monkeys. The results from these studies are summarized below:

- AzA is almost completely absorbed after intragastric application.
- AzA is metabolically degraded by ß- oxidation in the mitochondria, leading to dicarboxylic acids, which are by C2 - units shorter (pimelic acid and glutaric acid).
- Both AzA and its metabolites are rapidly excreted with the urine.

In an in vitro skin penetration experiment, using hairless mouse skin, the skin retention and the percutaneous absorption of ^{14}C - AzA were investigated. Skinoren Cream was compared with two hydrogel formulations. The results of these experiments would suggest that the highest dose fraction was delivered to the viable skin layers by the hydrogel formulation the composition of which is best comparable to the claimed formulation. Since the number of experiments was low and the variation between the single experiments was high, these differences should not be overestimated.

The presented studies on percutaneous absorption of single doses in rats and dogs were done in small groups of 4 rats or 4 dogs and were not performed according to GLP; they are just confirming the fact that the systemic absorption of azelaic acid from Finacea gel is low.

III.4 Toxicology

The data from the single dose toxicity studies show that the acute toxicity of systemically applied AzA is very low, especially after intragastric administration, and there was no increase in toxicity when AzA was applied in form of Skinoren Cream. The main conclusion from these studies is that systemically applied AzA is rather atoxic.

Most repeated dose toxicity studies were performed according to GLP regulations. The results of all studies together show that dermal applied AzA (Skinoren Cream) is atoxic even in very high doses and that orally applied AzA can also be given in high doses until toxic signs occur.

The results of reproduction toxicity studies show that even high doses of systemically applied AzA are embryotoxic only at maternal toxic doses while they are devoid of teratogenic effects. Concerning reproduction toxicity, a high level of safety can be derived from these studies with respect to the dermal application of therapeutic doses of AzA in man.

The mutagenicity testing program included two independent Ames tests, a test for gene mutations in Chinese hamster V79 cells and a test for chromosomal aberrations in human lymphocytes. In vivo studies comprised a dominant lethal assay in mice the mouse micronucleus test. All studies together do not give evidence of any mutagenic potential for azelainic acid.

The applicant's rationale for not performing life-time carcinogenicity studies is acceptable, especially since AzA is not a new active substance and long term clinical experience with the topical administration of AzA is available.
The applicant performed a 26 weeks Tg.AC Mouse dermal carcinogenicity study; results do not provide evidence of a carcinogenic potential of Finacea gel in male and female Tg.AC mice.

The results of the preclinical studies performed on local tolerance are well in line with what was seen in the clinical studies - AzA 15% gel appeared to be slightly irritating, has no phototoxic potential and its potential to cause sensitisation or photosensitisation reactions - if any - is low.

III.5 Ecotoxicity/environmental risk assessment

NA

III.6 Discussion on the non-clinical aspects

The non-clinical data presented by the applicant are considered adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rosacea is a chronic inflammatory dermatosis mostly involving the centrofacial area. It is a common disorder in fair-skinned Caucasian but occurs only rarely in dark-skinned persons. It most commonly becomes manifest between the ages of 30 to 50 years. The clinical picture of rosacea can in part resemble acne; therefore, rosacea is sometimes erroneously referred to as acne rosacea. However, pathogenetically rosacea and acne are different disease entities.

IV.2 Pharmacokinetics

Various pharmacokinetic studies with AzA (cream and gel formulation) were performed by the applicant, dating back to the 1980ies. The applicant could demonstrate that AzA is penetrating through the skin, but that the systemic load after topical administration is low.
Given the nature of the substance, the submitted pharmacokinetic data is adequate.

IV.3 Pharmacodynamics

The applicant has submitted some literature dealing with the mode of action of AzA, dermal safety was investigated in five phase I studies. It has been shown that the AzA 15% gel formulation is mildly irritating, has no phototoxic potential and its potential to cause sensitisation or photosensitisation reactions - if any - is low.
The presented data on human pharmacodynamics are not very extensive but are regarded as sufficient.

IV.4 Clinical efficacy

Two identical, 12-week, multicenter, double-blind, randomized, vehicle-controlled studies and one 15-week active-controlled study vs. metronidazole 0.75% gel (Metrogel®) were conducted to evaluate efficacy and safety of AzA 15% gel in patients with moderate, stage 2, papulopustular facial rosacea . A total of 915 rosacea patients were included; 457 of them were randomised to treatment with AzA 15 % Gel.

With respect to the primary study parameter "Count and percent reduction in inflammatory lesions", at the end of the study medication the two vehicle-controlled studies showed a net benefit in favour of AzA 15% Gel of 17.9 % (AzA Gel: 58.1 %, Vehicle: 40.2 %; 95 % Confidence Interval 9.34 to 26.45, p 0.0001) in Study A03125 and of 12.0 % (AzA Gel: 50.7 %, Vehicle: 38.7 %; 95 % Confidence Interval 1.89 to 22.2, p 0.0208) in Study A03126.
A net benefit of 17.9 % or 12.0 % versus vehicle control is a moderate effect, which lies within the expectations to a topical therapy of rosacea with a rather mild drug. Anyway it can be stated that the benefit effect of AzA Gel versus vehicle control has been shown in the two vehicle – controlled rosacea studies.

In addition to the two vehicle – controlled studies the applicant has compared AzA 15 % Gel versus metronidazole 0.75 % gel in study A08681 in a total of 251 patients (124 on AzA Gel and 127 on metronidazole gel). Taking again the count and percent reduction in inflammatory lesions at the end of study medication, there was a net benefit in favour of AzA Gel of 16.9 % (AzA Gel: 72.7 %, metronidazole gel: 55.8 %; 95 % Confidence Interval 8.0 to 25.7, p=0.0002). The applicant is claiming superiority in the efficacy of AzA Gel versus metronidazole. In order to make a full comparison of the therapeutic values of AzA Gel versus metronidazole gel in rosacea, one has to consider both the efficacy and the safety.

In summary, the efficacy of AzA 15 % Gel in patients with mild to moderate papulopustular facial rosacea (stage 2 rosacea) has been adequately documented both in two vehicle-controlled studies and in one active comparator- controlled study.

IV.5 Clinical safety

AEs seen in the rosacea studies correspond with the AEs known from AzA 15% gel in acne patients and from postmarketing experience. Like other topical treatments, AzA 15% gel appeared to be slightly irritating. The AEs are predominantly cutaneous, mild to moderate and transient.
The safety profile of AzA 15% gel for the treatment of papulopustular stage 2 rosacea is acceptable.

IV.6 Discussion on the clinical aspects

The efficacy of Finacea 15% Gel in the claimed indication "*For the topical treatment of papulopustular rosacea* " has been demonstrated adequately in two vehicle controlled studies and in one active comparator (metronidazole 0.75% gel) controlled study. The safety of Finacea 15% Gel is acceptable; there are predominantly cutaneous adverse events. The nonclinical issues are adequately reflected in the SPC.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The pharmaceutical quality of Finacea has been adequately shown.

Based on the provided data the benefit:risk ratio for Finacea 15% Gel in the treatment of papulopustular rosacea is positive.

User consultation

As stated above, Skinoren 15% Gel and Finacea 15% Gel is the same medicinal product. Skinoren 15% Gel has been approved in several European Member States via mutual recognition procedures - AT/H/0124/01 (Skinoren 15% Gel) and AT/H/0125/01 (Azelainsäure "Schering" 15% Gel) - for the treatment of mild to moderate papular-pustular acne and of papulopustular rosacea.

The PIL for Skinoren Gel 15% has undergone user testing performed by *CHC (Consumer Health Care – Science & Services GmbH)*, Germany for Intendis GmbH. The Summary Outcome Report is dated 29. October 2007.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The applicant claims, that the difference between the PIL of Skinoren 15% Gel and Finacea 15% Gel is minor: the only change is the omission of the indication concerning acne and the information about the duration of treatment and possible side effects (for this indication), because Finacea 15% Gel is only to be used by patients suffering from rosacea. There are no further changes. Design, layout, style of writing, complexity of message and language used are identical for both PILs.

The applicant refers to the "Guidance for the Pharmaceutical Industry on the use of Bridging Studies to demonstrate compliance with article 59(3) of Council Directive 2001/83/EC (MHRA, Dec. 2006)" and therefore claims that it is not necessary to test the PIL of Finacea 15% Gel again, because the PIL of Skinoren 15% gel was tested successfully.
We consider the user test for Skinoren 15% Gel to be acceptable Finacea 15% Gel.

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected Y/N	Date of start of procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)
Changes to an existing pharmacovigilance system as described in the DDPS.	AT/H/0167/001/IA/002/G	N	14.07.2010	13.08.2010	Approved	N
Variation related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	AT/H/0167/001/II/001	Y	14.06.2010	27.10.2010	Approved	N
Change in test procedure for the immediate packaging of the finished product: Minor changes to an approved test procedure	AT/H/0167/001/IA/003	N	14.12.2010	13.01.2011	Positive	N