Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zorac 0.05 %, gel.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

Tazarotene ..... 0.05 g

Excipients with a well known effect:
Butylhydroxyanisole..... 0.05 g
Butylhydroxytoluene..... 0.05 g

For 100 g of gel

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel.
Zorac is a colourless to light yellow, translucent to homogeneous cloudy, gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the topical treatment of mild to moderate plaque psoriasis involving up to 10% body surface area.

4.2 Posology and method of administration

Zorac gel is available in two concentrations.
To initiate a treatment with Zorac, it is advisable to start with Zorac 0.05% in order to evaluate the skin response and tolerance before progressing to Zorac 0.1% if necessary.
Treatment with the lower concentration gel is associated with a somewhat lower incidence of local adverse events *(see sections 4.8, Undesirable effects and 5,. Pharmacological Properties).*
Treatment with the higher concentration gel gives a faster and numerically higher response rate. The physician should choose the concentration to be used based on clinical circumstances and the principle of using the least concentration of drug to achieve the desired effect.
Individual variations with respect to efficacy and tolerability are possible. It is thus advisable for patients to consult their physician on a weekly basis when initiating therapy.

A thin film of the gel should be applied once daily in the evening; care should be taken to apply it only to areas of affected skin, avoiding application to healthy skin or in skin folds. Treatment is limited to 10% body surface area (approximately equivalent to the total skin area of one arm).

If the patient experiences more drying or irritation, an effective greasy emollient (without pharmaceutically active ingredients) can be applied to the areas of the skin to be treated to improve tolerability. Healthy skin around the psoriatic plaques can be covered by using zinc paste, for example, to prevent irritation.

Usually, the treatment period is up to 12 weeks. Clinical experience, particularly on tolerability, is available on periods of use of up to 12 months.

4.3 Contraindications

- Hypersensitivity to any ingredient of the medication(s).
- Pregnancy or in women planning a pregnancy *(see section 4.6, Pregnancy and lactation).*
- Breast-feeding mothers.
- Since there is, as yet, no clinical experience, Zorac should not be used in the treatment of psoriasis pustulosa and psoriasis exfoliativa, and the gel should not be applied to intertriginous areas, to the face or to hair-covered scalp.

4.4 Special warnings and precautions for use

Care should be taken to ensure that Zorac is applied only to psoriatic lesions, as application to normal, eczematous or inflamed skin or skin affected by other pathologies may cause irritation.
Patients should be advised to wash their hands after application of the gel to avoid accidental transfer to the eyes.

If psoriatic areas on the skin of the hands are being treated, particular care should be taken to ensure that no gel is transferred to facial skin or the eyes.

If skin irritation develops, treatment with Zorac should be interrupted.

The safety of use on more than 10% of the body surface area has not been established. There is limited experience of application to up to 20% of the body surface area.

Patients should be advised to avoid excessive exposure to UV light (including sunlight, use of a solarium, PUVA or UVB therapy) during treatment with Zorac *(see section 5.3 Preclinical safety data).*

No therapeutic studies using Zorac under occlusion or concomitantly with other antipsoriatic agents (including tar shampoos) have been carried out. To minimise interference with absorption and to avoid unnecessary spreading of the medication, topical application of emollients and cosmetics should not be applied within 1 hour of applying Zorac.

The safety and efficacy of Zorac have not been established in patients under the age of 18 years.

This medicinal product contains butylhydroxyanisole and butylhydroxytoluene and therefore may cause local skin reactions (e.g. contact dermatitis) or irritation to the eyes and mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of pharmaceutical and cosmetic preparations which cause irritation or have a strong drying effect should be avoided.

4.6 Pregnancy and lactation

Pregnancy
Zorac gel is contraindicated in women who are or may become pregnant (*See section 4.3, Contraindications*). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the foetus. Women of child-bearing potential should be warned of the potential risk and use adequate birthcontrol measures when Zorac gel is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for human chorionic gonadotropin (hCG) should be obtained within 2 weeks prior to Zorac gel therapy, which should begin during a normal menstrual period.

Although in animals no malformations were observed after dermal application, skeletal alterations were seen in the foetuses, which may be attributable to systemic retinoid effects. Teratogenic effects were observed after oral administration.

Lactation
Although no data are available on the excretion of tazarotene in human milk, animal data indicate that excretion into milk is possible. For that reason Zorac gel should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The most frequently reported adverse reactions in controlled clinical trials of Zorac in the treatment of psoriasis were pruritus (incidence 20-25%), burning, erythema, and irritation (10-20%), desquamation, non-specific rash, irritant contact dermatitis, skin pain, and a worsening of psoriasis (5-10 %).
More rarely observed were stinging and inflamed and dry skin (1-3 %).
The incidence of adverse reactions appears to be concentration-related and dependent on duration of use.
The higher concentration gel (0.1%) may cause up to 5% more cases of severe skin irritation than the lower concentration gel (0.05%), especially during the first 4 weeks of use.
Furthermore skin discoloration might occur.

4.9 Overdose

Excessive dermal use of Zorac may result in marked redness, peeling, or local discomfort.
Inadvertent ingestion of Zorac is a theoretical possibility. In such a case, the signs and symptoms associated with hypervitaminosis A (severe headache, nausea, vomiting, drowsiness, irritability, and pruritus) may occur. However, it is likely that these symptoms would prove to be reversible.

5 PHARMACOLOGICAL PROPERTIES

Both gels have demonstrated therapeutic effects as early as 1 week after commencement of a course of treatment. A good clinical response was seen in up to 65% of the patients after 12 weeks of treatment.
The therapeutic effect of the higher concentration gel is more rapidly apparent and the efficacy more marked.

In various studies in which patients were also evaluated for 12 weeks following cessation of therapy, it was found that patients continued to show a certain clinical benefit, however, no difference between the higher and lower concentrations with regard to this effect was observed.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {group TOPICAL ANTIPSORIATIC AGENT. ATC-code: D05AX05}

Tazarotene, a member of the acetylenic class of retinoids, is a prodrug which is converted to its active free form, tazarotenic acid, by de-esterification in the skin area.
Tazarotenic acid is the only known metabolite of tazarotene to have retinoid activity.

The active metabolite specifically regulates gene expression, thus modulating cell proliferation, hyperplasia, and differentiation in a wide range of tissues, as has been demonstrated in *in vitro* and *in vivo* trials.

The exact mechanism of action of tazarotene in psoriasis is, as yet, unknown. Improvement in psoriatic patients occurs in association with restoration of normal cutaneous morphology, and reduction of the inflammatory markers ICAM-1 and HLA-DR, and of markers of epidermal hyperplasia and abnormal differentiation, such as elevated keratinocyte transglutaminase, involucrin, and keratin 16.

5.2 Pharmacokinetic properties

a) General characteristics

Absorption
Results of a pharmacokinetic study of single topical application of 0.1% ^{14}C-tazarotene gel show that approximately 5% is absorbed when applied to normal skin under occlusion.

After a single topical application of tazarotene gel to 20% body surface area for 10 hours in healthy volunteers, tazarotene was not detectable in the plasma. Maximum plasma levels for the active metabolite tazarotenic acid of 0.3 ± 0.2 ng/ml (for the 0.05% strength) and 0.5 ± 0.3 ng/ml (0.1% gel) were measured after approximately 15 hours. The AUC was 40% higher for the 0.1% gel compared with the 0.05% gel. Thus, the two strengths of the gel are not strictly dose proportional with respect to systemic absorption.

Repeated topical application of the 0.1% gel over 7 days led to maximum plasma levels for tazarotenic acid of 0.7 ± 0.6 ng/ml after 9 hours.

Biotransformation
After dermal application, tazarotene undergoes esterase hydrolysis to form its free acid, tazarotenic acid, and oxidative metabolism to form inactive sulphoxide and sulphone derivatives.

Elimination
Secondary metabolites of tazarotenic acid (the sulphoxide, the sulphone and an oxygenated derivative of tazarotenic acid) have been detected in human urine and faeces. The elimination half-life of tazarotenic acid after dermal application of tazarotene is approximately 18 hours in normal and psoriatic subjects.

After intravenous administration, the half-life of tazarotene was approximately 6 hours and that of tazarotenic acid 14 hours.

b) Characteristics after use in patients

After single topical application of 0.1% ^{14}C-tazarotene gel for 10 hours to psoriatic lesions (without occlusion), 4.5% of the dose was recovered in the stratum corneum and 2.4% in the epidermal/dermal layers. Less than 1% of the dose was absorbed systemically. More than 75% of drug elimination was completed within 72 hours.

In a small five patient study, repeated topical application of tazarotene 0.1% gel over 13 days results in a mean peak plasma level of tazarotenic acid of 12 ± 8 ng/ml. These patients had psoriatic lesions on 8-18% of body surface area. In a larger 24 psoriatic patient study, tazarotene 0.05% and 0.1% gels were applied for 3 months and yielded a Cmax of 0.45 ± 0.78 ng/ml and 0.83 ± 1.22 ng/ml, respectively.

In a 1 year clinical study with 0.05% and 0.1% tazarotene gel, tazarotene was detected in 3 out of 112 patients at plasma concentrations below 1 ng/ml, while its active metabolite tazarotenic acid was found in 31 patients. Only four patients had plasma concentrations of tazarotenic acid greater than or equal to 1 ng/ml (maximum 2.8 ng/ml).

5.3 Preclinical safety data

Subacute / Chronic toxicity

The safety of daily dermal application of tazarotene gel was tested in mouse, rat and mini-pig over periods of up to one year. The main observation was reversible skin irritation. In the case of the mini-pig, an incomplete healing of the dermal irritation was observed after an 8 week recovery period. The rat appears to be the most sensitive species to tazarotene, as is the case with other retinoids. Here, dermal application induced severe skin reactions and clinically significant retinoid-like systemic effects. No adverse systemic effects were observed in the other species.

After oral administration of 0.025 mg/kg/day for 1 year in the cynomolgus monkey, no toxic effects were observed. At higher doses, typical symptoms of retinoid toxicity were seen.

Reproductive toxicity

Safety of use during pregnancy has not been established. Teratogenic and embryotoxic effects were observed after oral administration in the rat and rabbit. In dermal application studies during foetal development, skeletal alterations and decreased pup weight at birth and at the end of the lactation period were observed.

Animal tests suggest that tazarotene or its active metabolite is excreted in breast milk and passes the placenta barrier. No effects on fertility are reported after topical application in the male and female rat.

Mutagenicity / carcinogenicity

No evidence of a mutagenic potential of tazarotene has been reported in *in vitro* and *in vivo* trials.

In long term investigations of the effects of dermal and oral administration in animals, no carcinogenic effects were observed.
There was an increased incidence of photocarcinogenic effects in the hairless mouse when exposed to UV light after topical application of tazarotene.

Local tolerability

Tazarotene gel has a considerable irritative potential on skin in all animal species investigated.
Instillation of tazarotene gel in the eye of the rabbit resulted in irritation with marked hyperaemia of the conjunctiva, but there was no corneal damage.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Macrogol 400
Hexylene glycol
Carbomer 974P
Trometamol
Poloxamer 407
Polysorbate 40
Ascorbic acid
Butylhydroxyanisole (E320)
Butylhydroxytoluene (E321)
Disodium edetate
Purified water

6.2 Incompatibilities

Tazarotene is susceptible to oxidising agents and may undergo ester hydrolysis when in contact with bases.

6.3 Shelf Life

3 years.
After first opening of the container: 6 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Aluminium tube, internally lacquered, epoxyphenolic, with white polypropylene cap.
Pack sizes: 10 g, 15 g, 30 g, 50 g, 60 g, and 100 g gel.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
County Mayo
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0148/061/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 July 1997

Date of last renewal: 03 December 2006

10 DATE OF REVISION OF THE TEXT

April 2008