

Public Assessment Report

Decentralised Procedure

Atralin Gel

UK/H/0858/01/DC

UK Licence N^o: PL 20288/0001

QuadraMed Ltd

LAY SUMMARY

The MHRA today granted QuadraMed Ltd a Marketing Authorisation (licence) for the medicinal product Atralin Gel. This is a prescription-only medicine (POM) that is used for the treatment of acne vulgaris.

Tretinoin is a metabolite of Vitamin A.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Atralin Gel outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Atralin Gel
Type of Application	Art 8.3 Known active
Active Substance	Tretinoin
Form	Gel
Strength	0.05%w/w
MA Holder	QuadraMed Ltd, MG House, Rumbolds Hill, Midhurst, West Sussex, GU29 9BY, UK
RMS	UK
CMS	Sweden
Procedure Number	UK/H/0858/01/DC
Timetable	Day 210 – 8 August 2007

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atralin 0.05% w/w Gel.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tretinoin 0.05% w/w.

Excipients: butylhydroxytoluene (E321), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), ethyl parahydroxybenzoate (E214), butyl parahydroxybenzoate, and isobutyl parahydroxybenzoate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pale yellow gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate *acne vulgaris*.

4.2 Posology and method of administration

Atralin Gel is for cutaneous use only.

Atralin Gel should be applied once daily, after washing in the evening, to the skin where acne lesions appear, using enough to lightly cover the entire affected area. Application of excessive amounts of gel will not provide incremental efficacy, but may increase the potential for irritation.

The gel should be applied using clean finger tips, cotton wool or a gauze swab, avoiding the mucous regions of the eyes, mouth, and nose.

A transitory feeling of warmth or slight stinging may be noted on application.

Therapeutic results may be noticed after two weeks, but four or more weeks of therapy are required before consistent beneficial effects are observed.

Patients treated with Atralin Gel may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied. Astringent toiletries should be avoided.

Children

Use of Atralin Gel in children under 10 years of age has not been investigated.

Elderly

Safety and effectiveness in a geriatric population have not been established. Clinical studies of Atralin Gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

4.3 Contraindications

Atralin Gel is contraindicated in individuals with a history of sensitivity reactions to any of its components. Use should be discontinued if hypersensitivity to any of its ingredients is noted.

Atralin Gel is contraindicated in patients with a personal or familial history of cutaneous epithelioma.

Tretinoin has been reported to cause severe irritation on eczematous skin and Atralin Gel should not be used in patients with acute eczema.

Atralin Gel should not be used to treat rosacea and perioral dermatitis.

Atralin Gel is contraindicated in pregnancy.

4.4 Special warnings and precautions for use

Application of excessive amounts of gel will not provide increased efficacy, but may increase the potential for irritation. Even at the recommended usage, the skin of certain individuals may become excessively dry, red, or swollen. If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use altogether. Excessive skin dryness may also be experienced; if so, use of an appropriate moisturizer during the day may be helpful.

Unprotected exposure to excessive sunlight or UV exposure, including sunlamps and solaria, should be minimized during the use of Atralin Gel. Patients with sunburn should be advised not to use the product on the affected areas until fully recovered because of heightened susceptibility to additional

irritation to patients under treatment with tretinoin. Patients who may have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Use of sunscreen products and protective clothing over treated areas are recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.

Atralin Gel should be kept away from the mucous regions of the eyes, mouth, and nose. If contact with these areas occurs, wash carefully with water.

There is evidence that, at least in some animal models, tretinoin may have photocarcinogenic potential, although some studies have suggested that tretinoin inhibits photocarcinogenesis. The relevance of this finding to use in man is uncertain. It is however advisable that patients avoid or minimise exposure to sunlight.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of other topical or oral retinoid medications is to be avoided. The use of medicated or abrasive soaps and cleansers, products that have a strong drying effect, and products with high concentrations of alcohol, alpha-hydroxy acids or astringents should be used with caution because of possible interaction with tretinoin. Caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulphur, resorcinol, or salicylic acid with Atralin Gel. Before applying Atralin Gel to areas treated with these products, it is advisable to allow the irritant effects of such preparations to subside.

4.6 Pregnancy and lactation

There are no adequate data from the use of topically applied tretinoin in women. Animal studies with topically applied Atralin Gel did not show any toxicity to reproduction (see section 5.3), although literature data indicate that high doses of topically applied tretinoin may be fetotoxic.

Atralin Gel should not be used in pregnancy.

It is not known whether tretinoin is secreted in breast milk. Caution should be exercised when Atralin Gel is administered to breastfeeding mothers

4.7 Effects on ability to drive and use machines

None known. The topical administration of Atralin Gel is not considered likely to affect the patient's ability to drive or use machines.

4.8 Undesirable effects

In clinical studies of Atralin Gel, the majority of adverse events were associated with the system organ class Skin and Subcutaneous Tissues. The majority of these events (such as erythema, burning, stinging, dryness and peeling) were mild in intensity occurred early during therapy and generally decreased over the course of therapy.

Common (>1/100):

Skin: Erythema, reddening, peeling, scaling, exfoliative dermatitis, dry skin, pruritus, warmth, burning, rashes, stinging reaction or pain.

Temporary hypo- and hyper-pigmentation.

Uncommon (1/100–1/1000):

Skin: Blistering and crusting of the skin, oedema

Eyes: Eye irritation.

True contact allergy to cutaneous tretinoin is rare. Increased susceptibility to sunlight or other UVB sources has been reported. Studies of Atralin Gel in volunteers indicate a low potential for the induction of allergic contact dermatitis, photoallergy or phototoxicity.

4.9 Overdose

Atralin Gel is intended for cutaneous use only. If medication is applied excessively, marked redness, peeling, or discomfort may occur. Oral ingestion of large amounts of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A (e.g. dry skin, pruritus, arthralgias, vomiting, anorexia).

If the gel is accidentally ingested, and if this ingestion is recent, measures to promote rapid gastric emptying should be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Retinoids for topical use in acne.

ATC Code: D10AD01

The precise mechanism of action of tretinoin in the treatment of acne is not known. However, biochemical and pharmacological profile studies have clearly demonstrated that tretinoin is a potent modulator of cellular differentiation and keratinisation processes which are abnormally present in the pathology of *acne vulgaris*.

Atralin Gel has been investigated in a total of 960 patients. Of these, 674 patients were included in two large randomised, placebo (vehicle) controlled, investigator blinded studies of safety and efficacy. These studies were of 12 weeks duration and included male and female mild to moderate *acne vulgaris* patients from 10 to 65 years of age.

In the two clinical studies described above, Atralin Gel was shown to be significantly more effective than its vehicle in reducing both inflammatory and non-inflammatory lesions associated with *acne vulgaris*. For the combined study populations, at 12 weeks Atralin Gel produced a mean percentage reduction in inflammatory and non-inflammatory acne lesions of 33.2% and 38.9%, respectively, compared to 18.4% and 19.7%, respectively, for vehicle ($p < 0.001$). The analysis of the dichotomized global severity score at Week 12 resulted in a significant treatment effect in favour of Atralin Gel, compared to its vehicle ($p=0.002$).

The adverse event profile observed in the studies was consistent with the known profile for topical tretinoin products – See section 4.8.

Relapse rates following treatment of acne with topical tretinoin have not been studied.

5.2 Pharmacokinetic properties

Tretinoin is a metabolite of Vitamin A. Systemic absorption was evaluated in a total of twenty-eight male and female acne patients, 13 to 37 years of age. The plasma concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid and 4-oxo-13-*cis*-retinoic acid, ranged from 0.6 to 6.2 ng/mL and were essentially unaltered after fourteen daily applications of 4 g daily doses of Atralin Gel, relative to baseline levels.

In a Phase III twelve-week study of 936 acne patients, the plasma concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid and 4-oxo-13-*cis*-retinoic acid were evaluated at Baseline and Week 12. The plasma concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid and 4-oxo-13-*cis*-retinoic acid, ranged from 0.5 to 5.3 ng/mL and were essentially unaltered after twelve weeks of daily application of Atralin Gel.

5.3 Preclinical safety data

Local tolerance, repeat dose testing and dermal sensitisation studies with Atralin Gel revealed only minor signs of irritation at the application sites.

There is no evidence of genotoxicity of tretinoin in standard in vitro and in vivo tests.

The weight of evidence indicates that topically applied tretinoin is not carcinogenic. In a lifetime study of CD-1 mice treated with a proprietary topical tretinoin product, a low incidence of skin tumours occurred at doses of 100 and 200 times the estimated clinical dose. No such tumours were seen in the study controls, but the incidence in treated animals fell within the historic control range for CD-1 mice.

In animal studies topically applied Atralin Gel (at doses higher than the proposed human dose) has not produced any measurable effect on systemic levels of tretinoin or its metabolites; nor did it have any teratogenic effects. Topically applied Atralin Gel did not produce evidence of fetotoxicity in the rat. However, literature data suggest that very high levels topically applied tretinoin may cause fetotoxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water
Glycerol
Soluble collagen
Sodium hyaluronate
Carbomer 940
Butylhydroxytoluene
Octoxynol 9
Trolamine
Methyl parahydroxybenzoate
Propyl parahydroxybenzoate
Ethyl parahydroxybenzoate
Butyl parahydroxybenzoate
Isobutyl parahydroxybenzoate
Benzyl alcohol
Phenoxyethanol

6.2 Incompatibilities

None known.

6.3 Shelf life

Three years.

After opening: three months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Collapsible epoxy-lined aluminium tube with polypropylene cap containing 20 or 45 g of gel.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

QuadraMed Limited

MG House

Rumbolds Hill

Midhurst

West Sussex

GU29 9BY

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20288/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

Module 3

BAR CODE

Package leaflet: information for the user

Atralin 0.05% w/w Gel

(Tretinoin)

Read all of this leaflet before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets severe, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Atralin Gel is and what it is used for
2. Before you use Atralin Gel
3. How to use Atralin Gel
4. Possible side effects
5. How to store Atralin Gel
6. Further information

1. What Atralin Gel is and what it is used for

Atralin Gel is a medicine used on the skin for the treatment of acne.

2. Before you use Atralin Gel

Do not use Atralin Gel:

- **If you are allergic** (*hypersensitive*) to tretinoin or to any of the other ingredients of Atralin Gel. If you experience an allergic reaction the first time you use Atralin Gel, do not use it again
- **If you have had a skin cancer**, or if any other member of your family has had one
- **If you suffer from eczema** – inflamed, dry, itchy, red scaly skin

- **If you have acne rosacea** – which may cause redness of the forehead, cheeks, nose and chin
 - **If you have perioral dermatitis** - irritation of the skin around the mouth.
 - **Do not use Atralin Gel on children under 10 years of age**
- If any of these apply to you, go back to your doctor without using Atralin Gel.

Take special care with Atralin Gel:

- **If you have sunburn or red, itchy peeling skin**, don't use Atralin Gel on those areas until they have fully recovered.
- **You must avoid too much sun** when you are using Atralin Gel. You should also avoid other sources of UV light, such as sunbeds or ultraviolet sunlamps. If you cannot avoid sunlight (for example, if you work outdoors) protect skin treated with the gel:
 - **use a sunblock or sunscreen** with a sun protection factor (SPF) of 15 or higher
 - **wear a broad-brimmed hat.**
 - **wear clothes over treated skin** that will protect it from the sun.
- **Cold and windy weather may irritate skin** treated with Atralin Gel.
- **You can use a moisturiser during the day**, as Atralin Gel can cause a little dryness of the skin.
- **You may still use other skin products like cosmetics** during the day, but make sure that your skin is cleaned thoroughly first before applying Atralin Gel.

Using other medicines

- **Do not use harsh (astringent) skin care products** such as skin peeling products, or products which have a strong drying effect on the skin (for example, products which contain a lot of alcohol).
- **If you have been using other skin products for acne** (including ones you may have bought yourself without a doctor's prescription) or if you have been using a skin peeling product, allow the effects of these medicines to wear off before starting to use Atralin Gel. Consult your doctor before you apply any other medicines to your skin while you are using Atralin Gel.

Pregnancy and breast-feeding
If you are pregnant or think you may be pregnant, do not use Atralin Gel. Using Atralin Gel whilst pregnant may be harmful to the child. Talk to your doctor, who will discuss treatments.

If you are breast-feeding, tell your doctor about your treatment with Atralin Gel. You may still be able to breast-feed your child. You may still take this medicine if your doctor considers it necessary.

Driving and using machines

Atralin Gel is unlikely to affect your ability to drive or operate machinery.

Important information about some of the ingredients of Atralin Gel

Atralin Gel contains butylhydroxytoluene which may cause local skin reactions (eg contact dermatitis, an inflammation of the skin) and may cause irritation to the eyes and skin, particularly the nostrils and the skin around the mouth. Atralin Gel also contains parahydroxybenzoates, which may cause allergic reactions (possibly delayed).

3. How to use Atralin Gel

When and how much to use

Always use Atralin Gel as your doctor has instructed you. Check with your doctor or pharmacist if you are unsure.

Normally your doctor will tell you to apply Atralin Gel **once a day, in the evening, after you have washed your face**. Only the affected areas of the skin. All of the affected area should be treated, not just the spots.

- **Thoroughly wash and dry the affected area** before applying Atralin Gel.
- **Apply a small amount of Atralin Gel** to the affected areas of the skin. All of the affected area should be treated, not just the spots. Use about the size of a pea, using clean fingertips or cotton wool or gauze.
- **Lightly cover the affected area.** Applying more Atralin Gel will not make it work more effectively. If you use too much then you may make the skin red, causing peeling and discomfort. If this happens, you should stop using Atralin Gel until these symptoms have gone away.
- **Keep away from your eyes, nostrils and mouth** when applying Atralin Gel. Wash with water if the gel gets into them. Do not allow the gel to collect in the folds of the skin around your eyes or nose.

After you have applied Atralin Gel, your skin may feel warm or sting slightly for a while. If these feelings persist, or if they get worse, consult your doctor.

Do not apply Atralin Gel to skin that is cracked, weeping or eczematous.

When your acne has improved (this may take more than 4 weeks) your doctor may tell you that you can apply Atralin Gel less frequently.

Children

Do not use Atralin Gel on children under 10 years of age

If you forget to apply Atralin Gel

If you accidentally forget an application, just make the next application as normal. Do not apply an extra dose to make up for the missed one.

If you swallow Atralin Gel

Atralin Gel is only for use on the skin. If any gel is swallowed, contact your doctor or nearest hospital casualty department immediately.

If you use more Atralin Gel than you should

If you accidentally apply too much Atralin Gel, it is unlikely to do you any harm. However, always try to exactly follow the instructions for use.

4. Possible side effects

Like all medicines, Atralin Gel can cause side effects although not everybody gets them.

Common effects

(seen in between one in 10 and one in 100 users)

Reddening, peeling or scaling of the skin, which may be swollen. Dry skin, itching, warmth or a burning sensation, rashes, pain or a stinging sensation may occur. Temporary changes (increase or decrease) in skin pigmentation may occur.

If any of these symptoms is severe, or if you get crusts, blisters, swelling or a burning sensation on the skin, **stop using the gel and consult your doctor immediately**.

Uncommon effects

(seen in between one in 1,000 and one in 100 users)

Irritation of the eye and swelling, blistering and crusting of the skin.

Very rare effects

(seen in up to one in 10,000 users)

Contact allergy has been reported with medicines containing tretinoin.

If any of the side effects gets severe, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Atralin Gel

Keep out of the reach and sight of children. Do not use Atralin Gel after the expiry date which is stated on the carton and the crimp of the tube. The expiry date refers to the last day of that month.

After first opening the gel should be stored for a maximum of three months. It is important that you record the date of opening on the container labelling.

Do not store above 25°C.

Medicines should not be disposed of in waste water or household rubbish. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Atralin Gel contains

The active substance is tretinoin.

Atralin Gel contains 0.05% tretinoin by weight. The other ingredients are water, glycerol, soluble collagen, sodium hyaluronate, carbomer 940, butylhydroxytoluene (E321), octoxynol 9, trolamine, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), ethyl parahydroxybenzoate (E214), butyl parahydroxybenzoate, isobutyl parahydroxybenzoate, benzyl alcohol and phenoxyethanol.

What Atralin Gel looks like and contents of the pack

Atralin Gel is a transparent yellow gel available in tubes of 20 g and 45 g.

Marketing Authorisation Holder:

QuadraMed Limited
MG House
Rumbolds Hill
Midhurst
West Sussex
GU29 9BY

Tel: 01730 812302

Fax: 01730 816792

e-mail: info@quadramed.org.uk

Manufacturer:

DPT Laboratories, Ltd
San Antonio
Texas 78215
USA

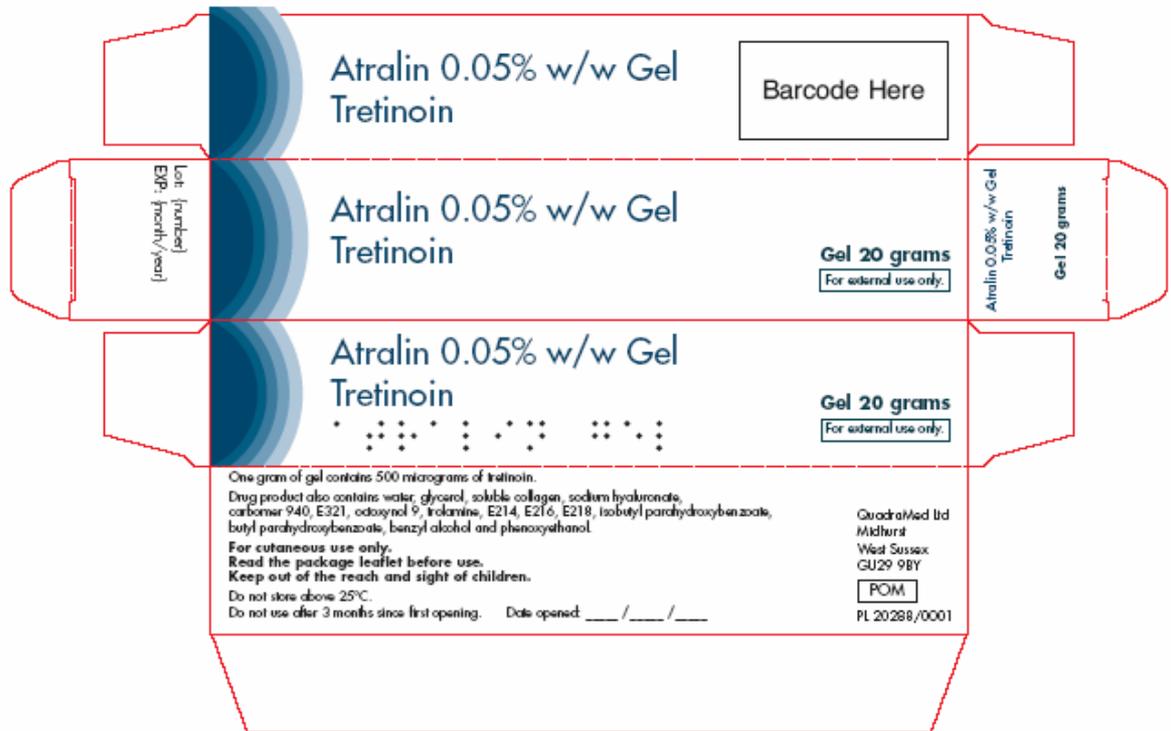
The Manufacturer responsible for release in Europe is:

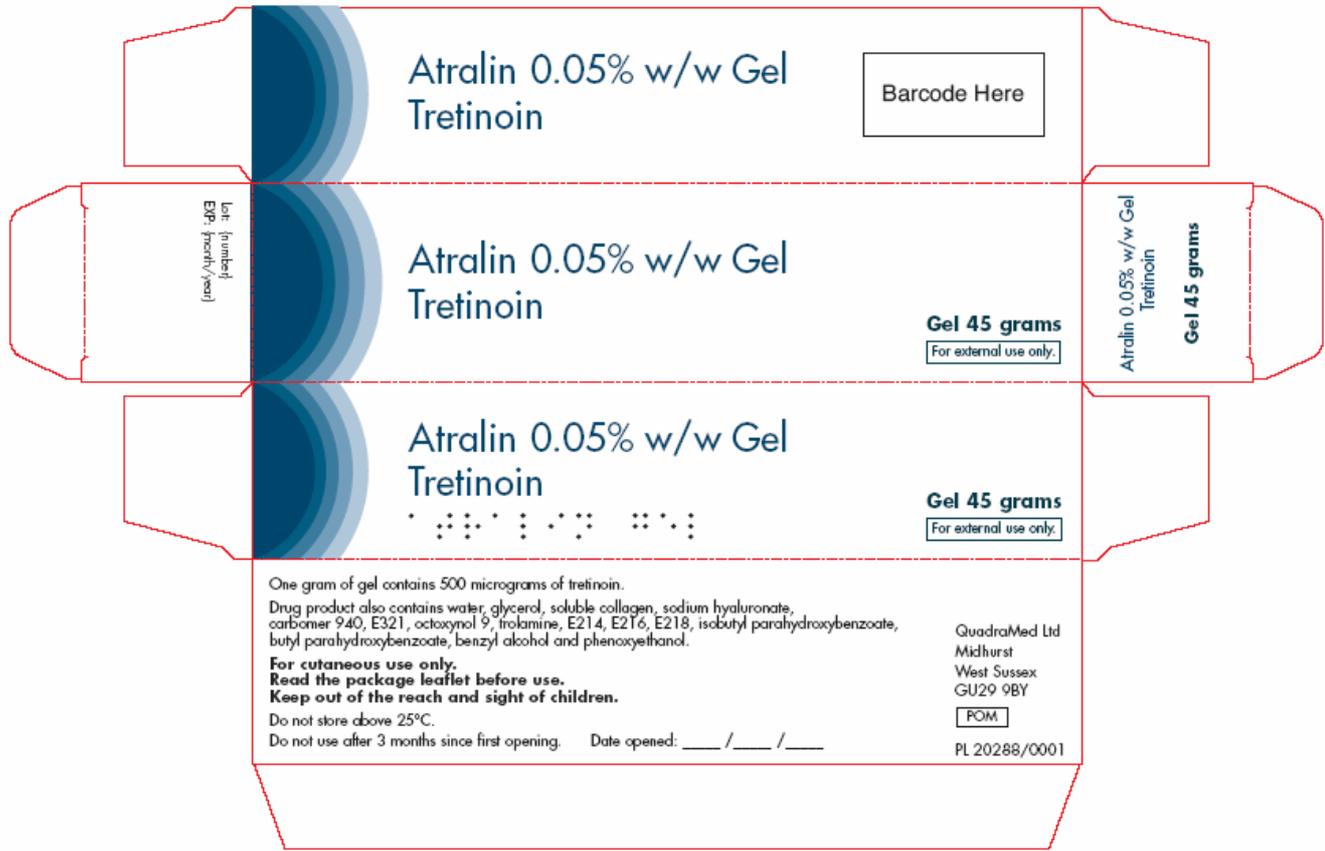
Brecon Pharmaceuticals Ltd
Pharos House
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This leaflet was last approved in:

Module 4

Labelling







Atralin 0.05% w/w Gel
Tretinoin

Gel 20 grams
For external use only.



One gram of gel contains 500 micrograms of tretinoin.
Drug product also contains water, glycerol, soluble collagen, sodium hyaluronate, carbomer 940, E321, octoxynol 9, triolamine, E214, E216, E218, isobutyl parahydroxybenzoate, butyl parahydroxybenzoate, benzyl alcohol and phenoxyethanol.
For cutaneous use only.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not store above 25°C.

QuadraMed Ltd
Midhurst
West Sussex
GU29 9BY

POM

PL 20288/0001



Atralin 0.05% w/w Gel
Tretinoin

Gel 45 grams
For external use only.



One gram of gel contains 500 micrograms of tretinoin.
Drug product also contains water, glycerol, soluble collagen, sodium hyaluronate, carbomer 940, E321, octoxynol 9, triolamine, E214, E216, E218, isobutyl parahydroxybenzoate, butyl parahydroxybenzoate, benzyl alcohol and phenoxyethanol.
For cutaneous use only.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not store above 25°C.

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POM

PL 20288/0001

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Atralin 0.05 % w/w Gel in the treatment of mild to moderate acne is approvable.

Acne vulgaris is a chronic disease of sebaceous follicles that is multifactorial in aetiology and varies in severity as evidenced by lesion type, size, number, scarring and post-inflammatory pigmentary changes. Acne occurs more frequently on the face, but can also occur on other sites such as shoulders, back, and chest. There are two main types of acne lesions: non-inflammatory and inflammatory. Non-inflammatory lesions are the open or closed comedones. Inflammatory lesions are divided into papules, pustules and nodules/nodulocystic lesions, depending on the severity and location of the inflammation within the dermis.

In westernized societies, acne vulgaris is a nearly universal skin disease afflicting 79% to 95% of the adolescent population. In men and women older than 25 years, 40% to 54% have some degree of facial acne, and clinical facial acne persists into middle age in 12% of women and 3% of men (Arch Dermatol 2002 Dec;138(12):1584-90).

A variety of drug products, topical and systemic, are currently available to treat acne. Typical treatment regimens for acne include the following:

Mild acne: topical retinoids, benzoyl peroxide, azelaic acid, topical antibiotics

Moderate acne: combination of topical treatments, oral antibiotics

Severe acne: oral antibiotics, oral retinoids.

Atralin Gel is a topical tretinoin intended for use in acne vulgaris. The product is an oil-free and fat-free gel; the applicant claims that the product is alcohol free to minimise drying. The posology is once daily.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP 'close-out letters' issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites. The applicant claims that all clinical trials for Atralin Gel have been performed in accordance to Good Clinical Practice.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Atralin Gel
Name(s) of the active substance(s) (INN)	Tretinoin
Pharmacotherapeutic classification (ATC code)	D10AD01 Retinoids for topical use in acne
Pharmaceutical form and strength(s)	0.05%w/w
Reference numbers for the Mutual Recognition Procedure	UK/H/0858/01/DC
Reference Member State	United Kingdom
Member States Concerned	Sweden
Marketing Authorisation Number(s)	PL 20288/0001
Name and address of the authorisation holder	Quadramed Limited, MG House, Rumbold's Hill, Midhurst, West Sussex, GU29 9BY, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

The EDMF procedure has been used to submit data for tretinoin drug substance.

The drug substance specification and master file are compliant with Ph Eur and regulatory requirements.

P Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

During assessment, the applicant satisfactorily addressed points relating to the optimisation of the formulation, the viscosity of the gel and the control of particle size of the drug substance.

The product specifications cover appropriate parameters for this dosage form and are considered to comply with the general ICH and Ph Eur requirements for gels, as well as the specific BP monograph for tretinoin gel.

Satisfactory validations of the analytical methods have been presented. Batch analysis has been performed on 5 batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of three years with special storage condition "Do not store above 25°C" for the drug product is considered acceptable.

The proposed in-use shelf-life of three months is also considered acceptable.

III.2 PRE-CLINICAL ASPECTS

Pharmacology

No new non-clinical pharmacological studies were provided to support this application. As the pharmacology of tretinoin is well documented, the applicant supplied a satisfactory review of the relevant published literature.

Pharmacokinetics

No new specific non-clinical pharmacokinetic data have been provided for the proposed formulation. However non-clinical toxicokinetic studies in the rat and minipig have revealed minimal elevation in plasma levels of all-*trans*-retinoic acid following tretinoin doses of up to 0.075mg/kg/day in minipigs and 0.5mg/kg/day in rats \equiv 2.5 times and 16.5 times the applicant's anticipated maximum human dose of Atralin Gel (2.0g/person/day) respectively.

Toxicology

No evidence of genotoxicity is reported following a battery of tests on the active according to ICH guidelines. Carcinogenicity studies have not been performed, which is justified due to minimal systemic exposure and extensive clinical experience with tretinoin. No reproductive toxicity was revealed following a segment I and II study in the rat, although literature data indicate that high doses of topically applied tretinoin may be fetotoxic.

Reactions seen in skin irritancy studies demonstrated that the proposed product is not an irritant. Two of the excipients used in Atralin Gel: Pancogene® Marin and Octoxynol-9, are not described in the European Pharmacopoeia (Ph. Eur.).

III.3 CLINICAL ASPECTS

Pharmacokinetics

The applicant has investigated the possibility of systemic absorption of Tretinoin in 3 clinical studies. These studies were conducted in patients suffering from acne vulgaris. Subjects were aged 10 to 53 years and were treated with large doses of tretinoin gel (4 g once daily for 14 days) in the 2 phase II studies and the dose intended for licensing (~0.5 g once daily for 12 weeks) in the phase III study.

Pharmacodynamics

The phototoxic, photo allergic and contact sensitisation potential of Atralin Gel was evaluated in 3 phase I studies. No subjects had a phototoxic reaction and no subjects showed evidence of photo allergic potential. The contact sensitisation study showed what is already known for tretinoin, that it is irritating to the skin when applied topically. This is adequately reflected in the proposed SPC.

Clinical efficacy

The clinical efficacy of Atralin Gel has been evaluated in two clinical studies. Study 735.126.CL009 was a multi-centre, investigator-blinded, controlled, randomised, 3-arm, safety, efficacy study in subjects with mild to moderate acne vulgaris. Subjects applied study medication once daily prior to bedtime for 12 weeks. Nine hundred thirty-six subjects aged 10 years and older were enrolled of which 805 completed the study. Patients were randomised in a 2:2:1 ratio to one of three treatment groups: Atralin Gel (375), Retin-A Micro (376) 0.1%; or Atralin Gel Vehicle (185). For the purposes of this application the Retin-A Micro is of limited relevance as this product is not available within the EU; therefore, this study should be regarded as a 2-arm vehicle controlled study for evaluation of efficacy.

The primary efficacy endpoints in this study were the percent reduction in at least two of the three lesion groups (inflammatory, non-inflammatory and total lesions) at week 12 and the dichotomised global severity at week 12. The study showed superiority of Atralin Gel to vehicle. These results were statistically significant.

Inflammatory, non-inflammatory and total lesions were counted from the face – excluding the nose – at baseline and week 12. After a modification to the original protocol, lesions from the nose were included in the counts. This introduced a problem as it resulted in nasal counts missing from some subjects at baseline. The applicant has provided 2 analyses: one where the available baseline nasal lesion counts were added to the baseline facial counts in both groups and the second where the available baseline nasal lesion counts were added to the baseline facial counts only for the vehicle group and assuming that the whole facial count was the facial count at baseline for the Atralin Gel group. With these analyses, the applicant has tried to minimise bias in favour of the Atralin Gel group. The results are reassuring as both analyses were in favour of the Atralin Gel group and were statistically significant.

Study 20.CLN.126.0418 was a multicentre, investigator-blinded, controlled, randomised, 2-arm, efficacy study in subjects with mild to moderate acne vulgaris. Six-hundred-one subjects were enrolled at 23 sites. All enrolled subjects were randomised (1:1) to receive either Atralin Gel or Atralin Gel vehicle. Subjects applied study medication once daily prior to bedtime for 12 weeks.

The primary efficacy endpoints were the absolute reduction from baseline to week 12 (in contrast to study 735.126.CL009) in inflammatory and non-inflammatory lesion counts and the inter-group differences in the dichotomised Global Severity assessments at week 12. The lesion counts were taken from the facial area and the nose.

Atralin Gel was superior to vehicle for both primary efficacy endpoints and this result was statistically significant. This was not the case for the Acne-QoL scores where there was no statistically significant difference between the two treatment groups.

The results of the two pivotal studies are reassuring as they have proven superiority of Atralin Gel to its vehicle. The dose and dosing regimen utilised in these studies have been justified by reference to public literature and current clinical practice.

Clinical safety

A total number of 960 subjects were exposed to Atralin Gel. The duration of exposure varied from a single application in phase I studies to multiple applications over 12 weeks. Subjects applied 0.5 g once daily (dose intended for clinical use) to 4 g once daily (dose intended for maximum exposure in pharmacokinetic studies). Tretinoin was generally tolerated with 11 patients withdrawing from the studies due to adverse events. The adverse events seen are anticipated following application of topical tretinoin and mainly involved skin disorders such as irritation, rash, pruritis. There also appeared to be a dose response effect, with AEs such as 'dry skin', 'burning sensation', 'erythema' occurring more frequently in the Retin-A Micro 0.1% group.

The applicant has provided long term safety data from published literature. From the safety data submitted with this application, no new safety concerns have arisen.

Pharmacovigilance system

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The applicant has provided justification for the absence of a Risk Management Plan. Topical tretinoin is a well established treatment for acne and has been in clinical use for over 30 years.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Efficacy and safety of Atralin Gel in the treatment of acne vulgaris has been investigated in two studies. Atralin Gel appears to be an efficacious product with an acceptable level of safety. The risk benefit balance is considered positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome