SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<TRADE NAME> <STRENGTH> Gel

<REGARDING THE APPROVAL>

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains <STRENGTH> of tretinoin

Excipient with known effect:

<REGARDING THE APPROVAL>

For the full list of excipients, see section 6.1.

1. PHARMACEUTICAL FORM

Gel

<REGARDING THE APPROVAL>

1. CLINICAL PARTICULARS
   1. Therapeutic indications

Treatment of mild to moderate *acne vulgaris*.

* 1. Posology and method of administration

Method of administration:

Tretinoin gel is for cutaneous use only.

Tretinoin 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 fingertips, cotton wool or a gauze swab, avoiding the mucous regions of the eyes, mouth, nose and open wounds.

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 tretinoin gel may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied. Astringent toiletries should be avoided.

**Paediatric population**

Use of tretinoin 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 tretinoin gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

* 1. Contraindications

Tretinoin 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.

Tretinoin 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 tretinoin gel should not be used in patients with acute eczema.

Tretinoin gel should not be used to treat rosacea and perioral dermatitis.

Tretinoin gel is contraindicated in pregnancy (see section 4.6) and in women planning a pregnancy.

* 1. 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 tretinoin 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.

Tretinoin 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.

Excipients with known effects:

This medicine contains benzyl alcohol. Benzyl alcohol may cause allergic reactions and mild local irritation.

This medicine contains 10 mg benzyl alcohol in each 2 g tube, 100 mg benzyl alcohol in each 20 g tube, and 225 mg benzyl alcohol in each 45 g tube, which are equivalent to 5 mg/g. Benzyl alcohol may cause allergic reactions and mild local irritation.

This medicinal product contains parahydroxybenzoates which may cause allergic reactions (possibly delayed).

This medicine contains butylhydroxytoluene (E321) which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

* 1. 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 tretinoin gel. Before applying tretinoin gel to areas treated with these products, it is advisable to allow the irritant effects of such preparations to subside.

* 1. Fertility, pregnancy and lactation

There are no adequate data from the use of topically applied tretinoin in pregnant women. Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, topically administered retinoids are generally assumed to result into low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure.

Animal studies with topically applied tretinoin 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.

Pregnancy

Tretinoin gel is contraindicated (see section 4.3) in pregnancy, or in women planning a pregnancy. If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

Breast-feeding

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

* 1. Effects on ability to drive and use machines

None known. The topical administration of tretinoin gel is not considered likely to affect the patient’s ability to drive or use machines.

* 1. Undesirable effects

The frequency of undesirable effects is described as follows:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1 000 to <1/100)

Rare (≥1/10 000 to <1/1 000)

Very rare (<1/10 000)

Not known (cannot be estimated from the available data).

|  |  |  |
| --- | --- | --- |
| System Organ Class | Frequency | Adverse event |
| Skin and subcutaneous tissue disorders | Common | Erythema, reddening, peeling, scaling, exfoliative dermatitis, dry skin, pruritus, warmth, burning, rashes, stinging reaction or pain, temporary hypo- and hyper- pigmentation |
| Uncommon | Blistering and crusting of the skin, oedema |
| Eye disorders | Uncommon | Eye irritation |

In clinical studies of tretinoin 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.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Health Product Vigilance Center; HPVC

* 1. Overdose

Tretinoin 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.

1. PHARMACOLOGICAL PROPERTIES
   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, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increases turnover of follicular epithelial cells causing extrusion of the comedones. 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.

Tretinoin 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, tretinoin 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 tretinoin gel produced a mean percentage reduction in inflammatory and noninflammatory 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 tretinoin 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.

* 1. Pharmacokinetic properties

Tretinoin is a metabolite of Vitamin A. After topical application of tretinoin- based formulations, the majority of tretinoin remains on the surface or in the outer layers of the skin. The absorbed dose of tretinoin following application of Tretinoin is extremely small, having no significant effect on endogenous levels of retinoids. Systemically circulating tretinoin is greater than 95% protein bound. 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 [13-cis-RA] and 4-oxo-13-cisretinoic acid [13-cis-4-oxo-RA], ranged from 0.6 to 6.2 ng/mL and were essentially unaltered after fourteen daily applications of 4 g daily doses of tretinoin 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 [13-cis-RA] and 4-oxo-13-cis-retinoic acid [13-cis-4-oxo-RA] were evaluated at Baseline and Week 12. The plasma concentrations of tretinoin and its metabolites, 13- cis-retinoic acid [13-cis-RA] and 4-oxo-13-cis-retinoic acid [13-cis-4-oxo- RA], ranged from 0.5 to 5.3 ng/mL and were essentially unaltered after twelve weeks of daily application of tretinoin gel.

* 1. Preclinical safety data

Local tolerance, repeat dose testing and dermal sensitisation studies with tretinoin 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 tretinoin 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 tretinoin gel did not produce evidence of fetotoxicity in the rat. However, literature data suggest that very high levels topically applied tretinoin may cause fetotoxicity.

1. PHARMACEUTICAL PARTICULARS
   1. List of excipients

<REGARDING THE APPROVAL>

* 1. Incompatibilities

None known.

* 1. Shelf life

<REGARDING THE APPROVAL>

* 1. Special precautions for storage

<REGARDING THE APPROVAL>

* 1. Nature and contents of container

<REGARDING THE APPROVAL>

* 1. Special precautions for disposal

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION HOLDER

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION NUMBER(S)

<REGARDING THE APPROVAL>

1. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<REGARDING THE APPROVAL>

1. DATE OF REVISION OF THE TEXT1

<REGARDING THE APPROVAL>