TEXT FONT SIZE: 9 p.t

SAME SIZE ARTWORK
LEAFLET SIZE: 140 mm x 352 mm

20 mm

22 mm

22 mm

exposure to either sunlight or artificial ultraviolet radiation sources. In a series of in vitro and in vivo studies, adapalene did not exhibit mutagenic or genotoxic activity.

ADVERSE REACTIONS:
Some adverse effects such as erythema, scaling, dryness, pruritus and burning occur in 10 -40% of patients. Pruritus or burning immediately after application also occurs frequently. In approximately 1% or less of patients, skin irritation, burning/stinging., erythema, sunburn and acne flares have also been reported. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with the use of Adapalene Gel during clinical trials were reversible upon discontinuation of therapy.

OVERDOSAGE:
No overdosage has been reported with adapalene gel in human beings. Adapalene Gel microspheres is intended for topical use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur. The dosage for acute oral toxicity of Adapalene Gel in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

HOW SUPPLIED:
Adapalene Gel microspheres is supplied in 15g tube.

STORAGE:
Store below 30 °C. Protect from light. Do not freeze

Keep all medicines out of reach of children.

MAL 10120013AZ

Revision Date: 13/03/2023

Product Registration Holder
Glenmark Pharmaceuticals (Malaysia)
Sdn Bhn (660397-W)
D-31-02. Menara Suezcap 1,
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59200 Kuala Lumpur, Malaysia

Manufactured by:
Glenmark
PHARMACEUTICALS LTD.
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D-Road, MIDC, Satpur,
Nashik - 422 007,
Maharashtra State, India.
Ⓣ Trade Mark

PE00000 MY

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For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Adapalene Gel Microspheres 0.1% w /w

Derma MS
AQUEOUS GEL

SPACE FOR PHARMACODE

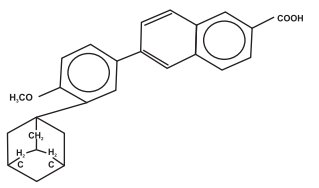
Composition:
Adapalene 0.1% w/w (As Microspheres)
In a aqueous gel base

Preservatives:
Methyl Hydroxybenzoate BP 0.1% w/w
Phenoxyethanol BP 0.25% w/w

Product Description:
A printed carton containing an insert & printed lami tube containing opaque white smooth homogenous gel.

GENERAL INFORMATION:
Adapalene Gel microspheres, containing Adapalene in a **Microsponge delivery system,** is used for the topical treatment of acne vulgaris. Each gram of Adapalene Gel microspheres contains adapalene 0.1% (1 mg), a retinoid analogue for the topical treatment of acne vulgaris, as microspheres and preservatives, viz. Methyl Hydroxybenzoate and phenoxyethanol.

The chemical name of adapalene is 6-[3-(1-adamantyl)-4 methoxyphenyl]-2-naphthoic acid. Adapalene is a white to off- white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol, and practically insoluble in water. The molecular formula of adapalene is $C_{28}H_{28}O_3$, and its molecular weight is 412.52. Adapalene has the following structural formula:



CLINICAL PHARMACOLOGY:
Pharmacodynamics:
Adapalene is a retinoid analogue for the treatment of acne vulgaris. It is a naphthoic acid Adapalenetive with a methoxyphenyl adamantyl side chain. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes, all of which represent important features in the pathology of acne vulgaris. Adapalene is a chemically stable derivatice of naphthoic acid that binds selectively to the nuclear retinoic acid receptor (RAR) subtypes RARγ (found in dermal fibroblasts), activating genes responsible for cellular differentiation; it does not bind to cytosolic retinoid acid binding proteins. Adapalene is thought to modulate keratinisation and inflammation of follicular in a reduction in microcomedones, the precursors of acne lesions

Adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. It has been suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

Analysis of cryosections, radioactive tracing, and fluorescence studies in excised human skin have shown that adapalene gel penetrates into the epidermis and dermis (especially the pilosebaceous units).

Microsponge delivery system of microspheres:

- Microsponge is a polymeric delivery system consisting of solid phase porous **microspheres (SPPM, Microsponge),** which are round microscopic particles made of synthetic polymer. Microsponge

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ICONGRAPHICS CODE:

PANTONE SHADE

PANTONE BLACK PROCESS C

Supersedes Artwork Code: PE35471

PHARMACODE:

have been incorporated into several topical prescription products in an effort tom improve performance or tolerability.

SPPMs provide a reservoir effect allowing more prolonged skin exposure to the active ingredient. The advantage of microsphere is that it releases active drug primarily into the epidermis with minimal transdermal penetration and little systemic absorption. Furthermore, the delivery vehicle consists of a porous microsphere that is capable of grandual relase of its ingredients.

- The studies of Site-specific Drug Delivery to Pilosebaceous Structures Using Polymeric Micropshere have shown the penetration properties of the microspheres in the skin depend on the size of the particles. Rolland et al (1993) and other studies have reported that adapalene-loaded microspheres (5-μm diameter) were specifically targeted to the follicular ducts and did not penetrate via the stratum corneum.

Rationale Use of Microsphere Adapalene:
Based on the result of clinical trials microsphere adapalene provided a better tolerability with minimal irritation compared to conventional adapalene, without compromising on the efficacy.

Pharmacokinetics:
The pharmacokinetics of topical adapalene has not been extensively studied. Therapeutic effects of the drug usually appear within 8 to 12 weeks of initiation of treatment. The transdermal absorption of Adapalene is low. Only trace amounts of the parent substance (<0.25 ng/mL) have been found in the plasma of acne patients following chronic topical application of adapalene gel in controlled clinical trials. The microparticles of Adapalene, being of the size 3 to 10 μm, achieve follicular targeting and action at the pilosebaceous unit without dispersing into the stratum corneum and causing irritation. Thus enhanced effect as well as safety is achieved with Adapalene microsponge delivery. Excretion of any systemically absorbed Adapalene appears to be primarily by the biliary route.

INDICATIONS FOR USE:
Adapalene Gel microsphere is indicated for the topical treatment of acne vulgaris.

DOSAGE AND ADMINISTRATION:
Adults:
Adapalene Gel microspheres is used in the topical treatment of mild to moderate acne where comedones, papules and pustules predominate. Adapalene is applied once daily at night as a 0.1% Gel microsphere to the skin that has been cleansed and dried. Other topical preparations that may cause irritation should not be used concomitantly.

During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results may be noticed within eight to twelve weeks of treatment.

Pediatric Population:
The safety and efficacy of Adapalene in pediatric patients under the age of 12 years have not been established.

USE IN SPECIAL POPULATIONS:
Pregnancy:
Category C
No teratogenic effects were seen in animal studies. There are no adequate and well controlled studies in pregnant women with topical Adapalene gel. Hence use of Adapalene is not recommended during pregnancy. Adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation:
It is not known whether topically applied Adapalene is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Adapalene Gel is administered to nursing mothers.

Pediatric use:
The safety and efficacy of Adapalene in pediatric patients under the age of 12 years has not been established.

Route of Administration: Topical

CONTRAINDICATIONS:
Hypersensitivity to adapalene or any of the components in the vehicle gel.

PRECAUTIONS:
General:

- FOR EXTERNAL USE ONLY
- Cutaneous signs and symptoms such as erythema, dryness, scaling, burning or pruritus may be experienced during treatment.
- Avoid contact with the eyes, lips, angles of the nose and mucous membranes.
- Avoid excessive exposure to sunlight, including sunlamps. It is more advisable to use sunscreen before stepping out in the sunlight.
- Concomitant use of topical products that may dry or irritate the skin, such as medicated or abrasive soaps or cleansers, soaps and cosmetics with a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime must be avoided since local irritation may occur.
- In case of hypersensitivity to any of the ingredients, discontinue the therapy.
- Do not apply to cuts, eczematous, sun burnt or abraded skin.
- Avoid exposure to UV light.

DRUG INTERACTIONS:
As Adapalene Gel microspheres might produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect and products with high concentration of alcohol, astringents, spices or lime) should be used with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol or salicylic acid in combination with Adapalene Gel microspheres.

If these preparations have been used, it is advisable not to start therapy with Adapalene Gel microspheres, until the effects of such preparations in the skin have subsided.

Since percutaneous absorption of Adapalene is negligible, any drug interactions with systemically administered drugs are unlikely.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY:
Carcinogenicity studies with adapalene have been conducted in mice (topical) and in rats (oral doses) at approximately 4 to 75 times the maximum human topical dose. In the oral study, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats and in the incidence of benign and malignant phaeochromocytomas in the adrenal medullas of male rats.

No photocarcinogenecity studies have been performed with adapalene. Animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to ultraviolet radiation or to sunlight. Patients should therefore be advised to avoid or minimize