SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

RET-AVIT GEL 0.05%, 0.025%
RET-AVIT CREAM 0.05%, 0.025%

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tretinoin 0.05% w/w.
Tretinoin 0.025% w/w.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

RET-AVIT GEL: Pale yellow clear gel, characteristic odour.
RET-AVIT CREAM: Pale yellow, homogeneous emulsion, characteristic odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acne vulgaris.

4.2 Posology and method of administration

RET-AVIT is for cutaneous use only.

The generally accepted dosage is: lightly apply to the entire affected area once a day in the evening before bedtime. For people with light or sensitive skin, it is recommended to apply the preparation once a day or every other day, depending on how the skin reacts.

Do not exceed the recommended dose

Do not swallow. For external use only.

Before treatment, you should clean the skin with lukewarm water and/or gentle soap, dry the skin gently without rubbing it and wait for 20-30 minutes before applying the medicine. Do not wash the treated area more than twice per day. Wash your hands after the treatment.

Apply a small amount of RET-AVIT and cover only the affected areas. You can use cotton wool or clean cotton swabs. Avoid accumulation of too much RET-AVIT in skin folds, such as the area where the nose meets the face. Do not apply to a cracked or eczematous area, to the eyes, eyelids, nostrils or mouth.

If RET-AVIT comes into contact with these areas, wash them thoroughly with water.

Duration of treatment – the results of the treatment are visible after two to three

weeks, but it may take six to eight weeks to achieve maximum results. The minimal duration of treatment is three months.

After applying of RET-AVIT, the skin may feel warm or sting slightly for a while. If these sensations continue or become worse, consult your doctor.

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

Patients treated with RET-AVIT 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 RET-AVIT 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 RET-AVIT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

4.3 Contraindications

RET-AVIT is contraindicated in individuals with a history of hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Use should be discontinued if hypersensitivity to any of its ingredients is noted.

RET-AVIT 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 RET-AVIT should not be used in patients with acute eczema.

RET-AVIT should not be used to treat rosacea and perioral dermatitis.

RET-AVIT is contraindicated in pregnancy (see section 4.6) and in women planning a pregnancy.

4.4 Special warnings and precautions for use

Application of excessive amounts of product 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 RET-AVIT. 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.

RET-AVIT 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.
Due to the high concentration of alcohol in RET-AVIT GEL, the product is flammable. Do not smoke a cigarette or be exposed to fire until the applied gel is completely dry.

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 RET-AVIT. Before applying RET-AVIT to areas treated with these products, it is advisable to allow the irritant effects of such preparations to subside.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of topically applied tretinoin in 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 RET-AVIT 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.

<u>Pregnancy</u>
RET-AVIT 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.

<u>Breast-feeding</u>

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In clinical studies of RET-AVIT, 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: Erythrema, 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 RET-AVIT 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

RET-AVIT 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 product 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*.

RET-AVIT 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, RET-AVIT 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 RET-AVIT 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 RET-AVIT, 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 RET-AVIT, 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 RET-AVIT.

5.3 Preclinical safety data

Local tolerance, repeat dose testing and dermal sensitisation studies with RET-AVIT 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 RET-AVIT (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 RET-AVIT 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

RET-AVIT CREAM: Oleic acid decylester, Cetostearyl alchohol, Glycerol monostearate SE, Sorbitol solution 70%, Cetomacrogol 1000, Lanolin anhydrous, Dimethicone 350, Sorbic acid, Butylate hydroxytoluene (BHT), Potassium sorbate, Purified water.

RET-AVIT GEL: Purified water, Cremophor RH 40, Isopropyl alcohol, Softigen 767, Carbomer 980, Butylated hydroxytoluene, Methyl hydroxybenzoate, Sodium propyl hydroxybenzoate, Hydrochloric acid, Sodium hydroxide.

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

Aluminium tube with internal protective lacquer with aluminium plug and screw cap containing 20 of gel or cream.

6.6 Special precautions for disposal

None

7 LICENCE HOLDER AND MANUFACTURER

CTS CHEMICAL INDUSTRIES LTD
POB 385, KIRYAT-MALACHI, ISRAEL

This leaflet format has been determined by the Ministry of Health and the content has been updated in 11/2020.