SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ACITRETIN 10 PHARMC Capsules

ACITRETIN 25 PHARMC Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACITRETIN 10 PHARMC - Each capsule contains 10 mg acitretin

ACITRETIN 25 PHARMC- Each capsule contains 25 mg acitretin

Sugar free.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

ACITRETIN 10 PHARMC - Hard gelatin capsule containing a yellow powder with a white to off-white body and a brown cap printed in black with “A 10” on the capsule body.

ACITRETIN 25 PHARMC - Hard gelatin capsule containing a yellow powder with a yellow to light yellow body and a brown cap printed in black with “A 25” on the capsule body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe extensive psoriasis and local or generalised pustular psoriasis and severe disorders of keratinization such as congenital ichthyosis, pityriasis rubra pilaris, Darier’s disease and other disorders of keratinization resistant to all other forms of therapy.

Experience for use in the above conditions is limited.

The quantity of a prescription should only cover treatment for one month to ensure regular monitoring.

4.2 Posology and method of administration

Posology

Adults

Because there are differences in the absorption and rate of metabolism of acitretin, the dosage must be individually adjusted. The capsules should be taken preferably once daily with a meal, or with some milk. The following will serve as guidelines:

The initial daily dose

25 mg (1 capsule; 25 mg) or 30 mg (3 capsules; 10 mg) for about two to four weeks may give satisfactory therapeutic results.

The maintenance dose

Must be based on clinical efficacy and tolerability. In general, a daily dosage of 25 - 50 mg taken for a further six to eight weeks, achieves optimal therapeutic results. It may be necessary in some cases to increase the dose up to a maximum of 75 mg per day (3 capsules; 25 mg). Therapy can be terminated in patients with psoriasis whose lesions have resolved sufficiently. Relapses should be treated as described above.

In disorders of keratinization

A continuous maintenance is mostly needed with the dose at the lowest possible level. This may be less than 20 mg/day and should not exceed 50 mg daily.

Combined treatment

When ACITRETIN PHARMC is used in combination with other types of therapy, it may be possible, depending on the patient's individual response, to reduce the dosage of ACITRETIN

PHARMC. Standard topical treatments except keratolytics which should be stopped, can generally be continued, and do not interfere with ACITRETIN PHARMC.

Method of administration

For oral use only.

4.3 Contraindications

Pregnancy and lactation:

ACITRETIN PHARMC is highly teratogenic and must not be used by females who are pregnant or who intend becoming pregnant. ACITRETIN PHARMC is contraindicated in all women of childbearing potential unless the following precautions are strictly observed:

1. Before therapy with ACITRETIN PHARMC is instituted, patients of childbearing potential must be examined for pregnancy and told clearly and in detail by the medical practitioner about the precautions to be taken, the risks involved, and the possible consequences should pregnancy occur during the course of treatment or within three years of discontinuing therapy.
2. Having excluded pregnancy, any woman of childbearing potential must practise effective contraception for at least one month before treatment, during the treatment period and for at least three years following its cessation.
3. The same effective and uninterrupted contraceptive measure must be taken every time therapy is repeated, independently of the intervening period and must be continued for three years afterwards.
4. Should pregnancy occur, in spite of these precautions, during treatment with ACITRETIN PHARMC or up to three years after its discontinuation, there is a high risk of severe malformation of the foetus (e.g., exencephaly).
5. The woman is reliable and capable of understanding the risks, of complying with effective contraceptive measures and confirms that she has understood the warnings.
6. Therapy should not begin until the second or third day of the next normal menstrual period.
7. A negative pregnancy test result must be obtained within two weeks before commencement of

treatment. (It is advisable to perform additional pregnancy tests at monthly intervals during therapy.)

Women of childbearing potential must not receive blood from patients treated with ACITRETIN PHARMC. ACITRETIN PHARMC must not be given to nursing mothers.

- Hypersensitivity to acitretin or to any of the inactive excipients (see section 6.1)
- ACITRETIN PHARMC is also contraindicated in patients with severely impaired liver and kidney functions and in patients with chronic abnormally elevated blood lipid values.
- The effect of microdosed progesterone preparations or “minipills” may be diminished by interaction with acitretin and should not be used.
- Hypervitaminosis A.
- Children less than 18 years of age or until bone development is complete.
- Treatment for longer than 12 months, as limited safety and efficacy data are available.
- Since both acitretin, as contained in ACITRETIN PHARMC, and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated. Supplementary treatment with antibiotics such as tetracyclines is therefore contraindicated (see section 4.5).
- An increased risk of hepatitis has been reported following the concomitant use of methotrexate and etretinate. Consequently, the concomitant use of methotrexate and ACITRETIN PHARMC is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

The following musculo-skeletal changes have been reported after long-term systemic retinoid treatment: hyperostosis, including vertebral hyperostosis and bridging of vertebral bodies; exostoses; extra-skeletal calcifications, including soft tissue calcifications; calcification of the anterior spinal ligament and calcification of tendons and ligaments especially ankles, knees and pelvis; periosteal thickening; disk narrowing; cortical bone resorption; osteoporosis; thinning of bones; fractures; premature epiphyseal closure and painless muscle stiffness.

Less frequently, severe skin reactions, including erythema multiforme and toxic epidermal necrolysis may occur.

Less frequently, patients may experience photosensitivity reactions.

Transient and usually reversible elevation of transaminases and alkaline phosphatases have been observed. Elevation of serum triglycerides and serum cholesterol has occurred, especially in high-risk patients (disturbances of lipid metabolism, diabetes, obesity, alcoholism). An associated risk of atherogenesis cannot be ruled out if these disturbances persist.

Hepatic function should be monitored before and every one to two weeks for the first two months after starting treatment with ACITRETIN PHARMC and then every three months during treatment. If pathological values for hepatic function are found, monitoring should be repeated at weekly intervals. If they fail to return to normal or if they deteriorate, ACITRETIN PHARMC must be withdrawn. It is then advisable to continue monitoring hepatic function for at least three months.

Serum cholesterol and serum triglycerides (fasting values) must be monitored in high-risk patients (disturbances of lipid metabolism, diabetes, obesity, alcoholism) and in long-term treatment.

In diabetics, retinoids can either improve or worsen glucose tolerance. Blood-sugar levels should be checked more frequently than usual in the early stages of treatment.

Benign intracranial hypertension has been reported with ACITRETIN PHARMC. Since tetracyclines can also cause an increase in intracranial pressure, their combination with ACITRETIN PHARMC is contraindicated (see section 4.3).

In adults receiving long-term treatment, appropriate examinations should periodically be performed in view of possible ossification abnormalities. In the event of ossification disorders, ACITRETIN PHARMC should be discontinued.

Any patient complaining of atypical musculo-skeletal symptoms during treatment with ACITRETIN PHARMC should be promptly and fully investigated to exclude acitretin induced bone changes or extra-skeletal calcification.

The effects of UV light are enhanced, therefore excessive exposure to sunlight and the unsupervised use of sunlamps should be avoided. Patients should not donate blood either during or for at least three years following discontinuation of ACITRETIN PHARMC.

ACITRETIN PHARMC is contraindicated in pregnant women and women of childbearing potential (see section 4.3).

Contraception

As a minimum requirement, female patients of childbearing potential must use at least one highly effective method of contraception (i.e., a user-independent form), or two complementary user-dependent forms of contraception. Contraception should be used for at least 1 month prior to starting treatment, throughout treatment and continue for at least 3 years after stopping treatment with acitretin, even in patients with amenorrhea.

Prescribing and dispensing restrictions

For women of childbearing potential, the prescription duration of ACITRETIN PHARMC should ideally be limited to 30 days in order to support regular follow up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of ACITRETIN PHARMC should occur on the same day.

This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medicine.

Male patients

The available data suggest that the level of maternal exposure from the semen of the patients receiving ACITRETIN PHARMC is not of a sufficient magnitude to be associated with the teratogenic effects of ACITRETIN PHARMC. Male patients should be reminded that they must not share their medicine with anyone, particularly not females.

Additional precautions

Patients should be instructed never to give this medicine to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 3 years following discontinuation of acitretin because of the potential risk to the foetus of a pregnant transfusion recipient.

Educational material

In order to assist prescribers, pharmacists and patients in avoiding foetal exposure to acitretin the Marketing Authorisation Holder will provide educational material to reinforce the warnings about the teratogenicity of acitretin, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Psychiatric disorders

Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids, including acitretin. Particular care should be taken in patients with a history of depression. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Awareness by family or friends may be useful to detect mental health deterioration.

Decreased night vision has been reported with acitretin therapy. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored (see section 4.8).

Treatment with high dose retinoids can cause mood changes including irritability, aggression, and depression.

Very rare cases of Capillary Leak Syndrome/retinoic acid syndrome have been reported from world-wide post marketing experience.

Very rare cases of exfoliative dermatitis have been reported from world-wide post marketing experience.

ACITRETIN PHARMC should only be prescribed by healthcare professionals who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with acitretin therapy.

Acitretin is highly teratogenic. The risk of giving birth to a deformed child is exceptionally high if acitretin is taken before or during pregnancy, no matter for how long or at what dosage. Foetal exposure to acitretin always involves a risk of congenital malformation.

Primary contraceptive method is a combination hormonal contraceptive medicine, or an intrauterine device and it is recommended that a condom or diaphragm (cap) is also used. Low dose progesterone-only medicines (minipills) are not recommended due to indications of possible interference with their contraceptive effect.

Patients should be warned of the possibility of alopecia occurring (see section 4.8).

Paediatric population

Since there have been occasional reports of bone changes in children, including premature epiphyseal closure, skeletal hyperostosis and extra osseous calcification after long-term treatment with etretinate, these effects may be expected with acitretin. ACITRETIN PHARMC therapy in children is therefore, contraindicated (see section 4.3). If, in exceptional circumstances, such therapy is undertaken the child should be carefully monitored for any abnormalities of musculoskeletal development and growth parameters and bone development must be closely monitored.

4.5 Interactions with other medicines and other forms of interaction

Alcoholic beverages must not be ingested during treatment with ACITRETIN PHARMC by women of childbearing age as etretinate can be formed with concurrent ingestion of acitretin and ethanol. Etretinate formation from acitretin is enhanced by the ingestion of alcoholic beverages. Alcoholic beverages should also be avoided for 2 months after cessation of acitretin therapy.

Concomitant administration of vitamin A and other retinoids must be avoided because hypervitaminosis A could arise.

In investigations on the effect of acitretin, as contained in ACITRETIN PHARMC, on the protein binding of anticoagulants of the coumarin type (warfarin), no interaction was detected.

In concurrent treatment with phenytoin, it must be remembered that acitretin partially reduces the protein binding of phenytoin.

Further interactions between acitretin and other substances e.g., digoxin, cimetidine, combined oestrogen/progesterone oral contraceptives, have not been observed so far. The effect of microdosed progesterone preparations or “minipills” may be diminished by interaction with acitretin and should not be used.

An increased risk of hepatitis has been reported following concomitant use of methotrexate and ACITRETIN PHARMC. Combined use of these medicines is contraindicated (see section 4.3).

ACITRETIN PHARMC should not be used during pregnancy and lactation (see section 4.3).

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential

Acitretin is highly teratogenic. Its use is contraindicated in women who might become pregnant during or within 3 years of the termination of treatment. The risk of giving birth to a deformed child is extremely high if acitretin is taken before or during pregnancy, no matter for how long or at what dosage.

Acitretin is therefore contraindicated in every woman of childbearing potential unless each of the following conditions is met:

1) The patient is suffering from a severe disorder of keratinisation which is resistant to standard therapies.

2) The patient can be relied on to understand and follow the physician's instructions.

3) The patient is capable of taking the stipulated contraceptive measures reliably and without fail.

4) It is absolutely essential that every woman of childbearing potential who is to undergo treatment with acitretin uses effective contraception (preferably 2 complementary methods) without interruption for four weeks before, during and for 3 years after the discontinuation of treatment with acitretin. The patient should be instructed to immediately contact a doctor in case of suspected pregnancy.

Even female patients who normally do not practice contraception because of a history of infertility should be advised to do so, while taking acitretin.

5) Therapy should not commence until the second or third day of the next normal menstrual period.

6) At the start of therapy, a negative pregnancy test result (minimum sensitivity of 25 mIU/mL) must be obtained up to three days before the first dose is given. During therapy, pregnancy tests should be arranged at 28-day intervals. A negative pregnancy test not older than 3 days is mandatory before prescription is made at these visits. After stopping therapy, pregnancy tests should be performed at 1-3 monthly intervals for a period of 3 years after the last dose is given.

7) Before therapy with acitretin is instituted, the healthcare professional must give patients of childbearing potential detailed information about the precautions to be taken, the risk of very severe foetal malformation, and the possible consequences if pregnancy occurs during treatment with acitretin or within 3 years of discontinuing therapy.

8) The same effective and uninterrupted contraceptive measures must be taken every time therapy is repeated, however long the intervening period may have been, and must be continued for 3 years afterwards.

9) Should pregnancy occur, despite these precautions, there is a high risk of severe malformation of the foetus (e.g., cranio facial defects, cardiac and vascular or CNS malformations, skeletal and thymic defects) and the incidence of spontaneous abortion is increased. This risk applies especially during treatment with acitretin and 2 months after treatment. For up to 3 years after acitretin discontinuation, the risk is lower (particularly in women who have not consumed alcohol) but cannot be entirely excluded due to possible formation of etretinate. Therefore, before instituting acitretin the treating healthcare professional must explain clearly and in detail what precautions must be taken. This should include the risks involved and the possible consequences of pregnancy occurring during acitretin treatment or in the 3 years following its cessation.

10) Women of childbearing age must not consume alcohol (in drinks, food or medicines) during treatment with acitretin and for 2 months after cessation of acitretin therapy (see section 4.4, 4.5 and 5.2).

Pregnancy

ACITRETIN PHARMC is contraindicated in pregnant woman (see section 4.3).

Breastfeeding

ACITRETIN PHARMC is contraindicated in breastfeeding women (see section 4.3).

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Decreased night vision has been reported with ACITRETIN PHARMC therapy.

Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The frequency of adverse reactions listed below is defined using the following convention: frequent; less frequent or frequency unknown (cannot be estimated from the available data).

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequency unknown	Vulvo-vaginitis due to *Candida albicans*
Immune system disorders	Frequency unknown	Hypersensitivity
Nervous system disorders	Frequent	Headache
	Less frequent	Dizziness, peripheral neuropathy, benign intracranial hypertension
Eye disorders	Frequent	Drying of and inflammation of mucous membranes (e.g., conjunctivitis, xerophthalmia)
	Less frequent	Blurred vision, night blindness, ulcerative keratitis
Ear and labyrinth disorders	Frequency unknown	Impaired hearing, tinnitus
Vascular disorders	Frequency unknown	Flushing, Capillary Leak Syndrome/Retinoic Acid Syndrome
Respiratory, thoracic and mediastinal disorders	Frequent	Drying of and inflammation of mucous membranes (e.g., epistaxis and rhinitis)
	Frequency unknown	Dysphonia
Gastrointestinal disorders	Frequent	Dry mouth, thirst, stomatitis, gastrointestinal disorders (e.g.,

MedDRA system organ class	Frequency	Adverse reactions
		abdominal pain, diarrhoea, nausea, vomiting)
	Less frequent	Gingivitis
	Frequency unknown	Dysgeusia, rectal haemorrhage
Hepato-biliary disorders	Less frequent	Hepatitis, jaundice
Skin and subcutaneous tissue disorders	Frequent	Cheilitis, pruritus, alopecia, skin exfoliation (all over the body, particularly on the palms and soles), skin fragility, sticky skin, dermatitis, abnormal hair texture, brittle nails, paronychia, erythema
	Less frequent	Rhagades, bullous dermatitis, photosensitivity reaction
	Frequency unknown	Pyogenic granuloma, madarosis, dryness of the skin may be associated with scaling, thinning, erythema (especially of the face), hair thinning and frank alopecia, granulomatous lesions, sweating, rhagades of the corner of the mouth, madarosis, angioedema, urticaria, exfoliative dermatitis
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, myalgia
	Less frequent	Bone pain, exostosis (maintenance treatment may result in progression of existing spinal hyperostosis, in appearance of new hyperostotic

MedDRA system organ class	Frequency	Adverse reactions
		lesions and in extra-skeletal calcification, as has been observed in long-term systemic treatment with retinoids)
General disorders and administration site conditions	Frequent	Peripheral oedema
	Frequency unknown	Malaise, drowsiness
Investigations	Frequent	Liver function test abnormal (transient, usually reversible elevation of transaminases and alkaline phosphatises), abnormal lipids (during treatment with high doses of acitretin, reversible elevation of serum triglycerides and serum cholesterol has occurred, especially in high-risk patients and during long-term treatment. An associated risk of atherogenesis cannot be ruled out if these conditions persist)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In the event of acute overdosage, ACITRETIN PHARMC must be withdrawn at once. Further treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 13.4.2 Dermatological preparations - other.

Pharmacotherapeutic group: Antipsoriatics, retinoids for treatment of psoriasis

ATC code: D05BB02

Acitretin is a synthetic aromatic analogue of retinoic acid and the free acid derivative and the main metabolite of etretinate. In preclinical investigations for safety of acitretin, no relevant mutagenic or carcinogenic effects were found. Acitretin and etretinate were found to be teratogenic in animals, even at low doses.

In psoriasis and disorders of keratinization, acitretin brought about a more normal epidermal cell proliferation, differentiation, and cornification. The action of acitretin is purely symptomatic; the mechanism of action is yet largely unknown.

5.2 Pharmacokinetic properties

Absorption

Acitretin reaches maximum plasma concentration one to four hours after ingestion of the medicine. Bioavailability of a single dose is approximately 60 %, but this may vary from one patient to another (36 - 95 %).

Distribution

Acitretin is highly bound to plasma proteins, penetrates readily into body tissue and is excreted via bile and urine as polar metabolites.

Biotransformation

Acitretin is metabolised by isomerization into its 13-*cis* isomer (*cis* acitretin), by glucuronidation and cleavage of the side chain.

Elimination

The elimination half-life is 50 to 70 hours and *cis* acitretin is 60 hours. From the longest elimination half-life observed for acitretin (70 hours), one can predict that more than 99 % of the medicine would be eliminated within 36 days after the last dose of long-term therapy.

Furthermore, plasma concentrations of acitretin and *cis* acitretin were below the sensitivity limit of the assay (< 6 ng/ml) within four weeks following cessation of treatment. No indication for a deep compartment is present.

Etretinate has been detected in up to 50 % of patients treated with acitretin. Etretinate has a long elimination half-life (approximately 120 days) due to deposition in adipose tissue.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Maltodextrin

Microcrystalline sodium

Sodium ascorbate

Capsule shell

Gelatin

Iron oxide red (E172)

Iron oxide yellow (E172) – ACITRETIN PHARMC 25 mg only

Purified water

Sodium lauryl sulphate

Titanium dioxide

Black printing ink

Iron oxide black (E172)

Propylene glycol (E1520)

Shellac glaze

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from moisture.

6.5 Nature and contents of container

ACITRETIN 10 PHARMC- Each carton contains 1, 2, 3, 5, 6 or 10 PVC/PVDC/aluminium blister strips containing 10 capsules/strip.

ACITRETIN 25 PHARMC - Each carton contains 1, 2, 3, 5, 6 or 10 PVC/PVDC/aluminium blister strips containing 10 capsules/strip.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special precautions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharmacorp (Pty) Ltd.

29 Victoria Link

Route 21 Corporate Park

Irene, 0178

RSA

8. REGISTRATION NUMBER(S)

ACITRETIN 10 PHARMC: 53/13.4.2/0683

ACITRETIN 25 PHARMC: 53/13.4.2/0684

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 October 2023

10. DATE OF REVISION OF THE TEXT : N/A