# Approved Professional Information for Medicines for Human Use: SUPATANE 8 mg & 16 mg

**SUPATANE is teratogenic and should not be taken by pregnant women, women intending to become pregnant, or sexually active women in their fertile years, not using at least two methods of contraception, as severe malformations may occur during pregnancy.**

## SCHEDULING STATUS

S5

## 1. NAME OF THE MEDICINE

**SUPATANE 8 mg hard gelatin capsules**

**SUPATANE 16 mg hard gelatin capsules**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SUPATANE 8 mg hard gelatin capsule.

Each hard gelatin capsule contains 8 mg isotretinoin.

SUPATANE 16 mg hard gelatin capsule.

Each hard gelatin capsule contains 16 mg isotretinoin.

Sugar free

Excipients with known effect:

Contains soya-bean oil (refined).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard gelatin capsules

SUPATANE 8 mg

Hard gelatin capsule, size 3 cap with an orange body and cap, containing an orange waxy paste.

SUPATANE 16 mg

Hard gelatin capsule, size 1 cap with a white body and green cap, containing an orange waxy paste.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**Severe recalcitrant nodular acne**

SUPATANE is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflamed lesions with a diameter of 5 mm or greater. The nodules may become suppurative or haemorrhagic. “Severe”, by definition, means “many” as opposed to “few or several” nodules.

**Because of significant adverse effects associated with its use, SUPATANE should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics.**

A single course of therapy has been shown to result in complete and prolonged remission of disease in many patients. If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course, because experience has shown that patients may continue to improve while off SUPATANE.

## 4.2 Posology and method of administration

**The initial diagnosis and prescription of SUPATANE should be performed by a dermatologist with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.**

**The therapeutic response to SUPATANE and its adverse events are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy.**

### Posology

***Standard dosage***

Therapy should be started at a dose of 0,4 mg/kg daily. For most patients the dose ranges from 0,4 – 0,8 mg/kg per day. Patients with very severe disease, or with truncal acne may require higher daily doses up to 1,6 mg/kg.

The therapy duration in individual patients therefore varies as a function of the daily dose. Complete remission of the acne is often achieved by a therapy course of 16 - 24 weeks. In patients who show a severe intolerance to the recommended dose, treatment may be continued at a lower dose, with consequent increase in therapy duration.

In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the case of a definite relapse, a renewed course of SUPATANE therapy should be given with the same daily dose as previously. Since further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, re-treatment should not be initiated until after this period.

***Concurrent topical therapy***

Concurrent administration of other keratolytic or exfoliative anti-acne agents is not indicated. Nor is concurrent radiation therapy with ultraviolet light indicated. Patients should avoid exposure to the sun. Adjuvant therapy with mild topical medicines may be given, as required.

**Special populations**

***Adults including adolescents and the elderly:***

Isotretinoin therapy should be started at a dose of 0,4 mg/ kg daily. The therapeutic response to isotretinoin and some of the adverse effects are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy. For most patients, the dose ranges from 0,4 – 0,8 mg/ kg per day.

Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. The duration of treatment will depend on the individual daily dose. A treatment course of 16 - 24 weeks is normally sufficient to achieve remission.

In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the event of a definite relapse a further course of isotretinoin therapy may be considered using the same daily dose and cumulative treatment dose. As further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, a further course of treatment should not be considered until at least this period has elapsed.

***Renal impairment***

In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 8 mg/day). The dose should then be increased up to 0,8 mg/ kg/day or until the patient is receiving the maximum tolerated dose (see section 4.4).

***Patients with intolerance***

In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequences of a longer therapy duration and a higher risk of relapse. In order to achieve the maximum possible efficacy in these patients the dose should normally be continued at the highest tolerated dose.

**Paediatric population**

SUPATANE should not be used for the treatment of prepubertal acne and is not recommended in children less than 12 years of age due to a lack of data on efficacy and safety.

**Method of administration**

SUPATANE is for oral administration.

The capsule should be swallowed whole.

SUPATANE should be taken with food, once or twice daily.

**4.3 Contraindications**

***Pregnancy and lactation***

**SUPATANE may not be given to breastfeeding mothers.**

**SUPATANE causes foetal malformations. These foetal malformations have been documented and include hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent external auditory canals), microphthalmia, cardiovascular abnormalities, facial dysmorphia, thymus gland abnormalities, parathyroid gland abnormalities with parathyroid hormone deficiency and cerebellar malformations. There is also an increased risk of spontaneous**

**abortion. It's use is therefore contraindicated, not only in women who are pregnant, or who may become pregnant while undergoing treatment, but also in all woman of childbearing potential, unless an effective contraceptive is used, without any interruption, for one month prior to therapy, the duration of therapy and for at least one month after discontinuation of therapy.**

Even female patients who normally do not employ contraception because of a history of infertility (except in the case of hysterectomy) or who claim absence of sexual activity, must be advised to use effective contraceptive measures while taking SUPATANE, following the guidelines. It is recommended that two reliable forms of contraception be used simultaneously.

**SUPATANE is contraindicated in women of child-bearing potential unless the female patient meets all the following conditions:**

- **the patient must have severe nodular acne, resistant to standard therapies**
- **she must be reliable in understanding and carrying out instructions**
- **she must be informed by her doctor of the hazards of becoming pregnant during, and one month after, treatment with SUPATANE**
- **she must be warned of the possibility of contraception failure**
- she must confirm that she has understood the precautions.
- she must be capable of complying with the mandatory effective contraceptive measures.
- she must use effective contraception, without any interruption, for 1 month before starting SUPATANE therapy, during therapy and for 1 month following discontinuation of therapy.

Careful consideration must be given in each individual case to the efficacy of the contraceptive methods chosen, particularly in the first cycle of hormonal contraception when additional methods are advised.

- She must have a negative result from a reliable pregnancy test within 11 days prior to the start of therapy. Monthly pregnancy testing during treatment is strongly recommended.
- She must start SUPATANE therapy only on the 2nd or 3rd day of the next normal menstrual period.
- In the event of relapse treatment, she must also use the same uninterrupted and effective contraceptive measures, 1 month prior to, during, and for 1 month after SUPATANE therapy, and the same reliable pregnancy evaluations should be followed.
- She must fully understand the precautions and confirm her understanding and her willingness to comply with reliable contraceptive measures as explained to her.

**Should pregnancy occur, in spite of these precautions, during treatment with SUPATANE, or during the first month after discontinuation, there is an extremely high risk of severe malformation of the foetus (involving in particular, the central nervous system, the heart and the large blood vessels), even after exposure for short periods only. Every possible precaution must be taken to ensure that the patient is not pregnant at the time of commencement of, during the course of, and for one month after discontinuation of therapy.**

**In order to assist prescribing physicians and patients in avoiding foetal exposure to isotretinoin, the manufacturer provides a Pregnancy Prevention Programme consisting of the following material to reinforce the warnings about the medicine's teratogenicity and emphasise the mandatory need for reliable contraception in female patients of childbearing potential:**

- **Patient Information Brochure**

- **Brochure on Birth Control**
- **Female Patient Information and Consent Form**
- **Physician's Guide to Prescription**
- **Physician's Checklist for Prescription to Females**
- **The pregnancy prevention information should be given to patients both orally and in writing.**

**The Patient Information Brochure must be provided to all patients. In addition, all female patients must receive the Brochure on Birth Control and the Female Patient Information and Consent Form.**

SUPATANE is also contraindicated in:

- Hypersensitivity to isotretinoin or soya-bean oil to any of the excipients listed in section 6.1.
- SUPATANE contains soya-bean oil. If you are allergic to peanut or soya, do not use this medicine.
- Pre-existing hypervitaminosis A
- Hepatic insufficiency
- Patients with excessively elevated blood lipid values
- Supplementary treatment with tetracyclines is contraindicated (see section 4.5).

## 4.4 Special warnings and precautions for use

**Teratogenic effects**

SUPATANE is a powerful human teratogen inducing a high frequency of severe and life-threatening birth defects.

**SUPATANE is strictly contraindicated in:**

- Pregnant women (see section 4.3)
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.3).

Patients should be reminded that SUPATANE is a scheduled medicine and not a cosmetic agent and that it is a criminal act to transfer it to, or share it with, any person not in possession of a valid prescription. SUPATANE should only be prescribed by medical practitioners who are experienced in the use of systemic retinoids and who understand the risk of teratogenicity associated with isotretinoin therapy.

**Pregnancy Prevention Programme**

SUPATANE is TERATOGENIC

Females of childbearing potential, as well as female patients who normally do not employ contraception because of a history of infertility, should be instructed that they must not be pregnant when SUPATANE therapy is initiated, and that they should use effective contraception while taking SUPATANE without any interruptions for 1 month prior to therapy, the duration of therapy and for 1 month after discontinuation of therapy. Two reliable forms of contraception should be used simultaneously. Micro-dosed progesterone preparations (minipills) may be an inadequate method of contraception during SUPATANE

therapy. Although other hormonal contraceptives are effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as injectable/implantable contraceptive medicines.

These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with SUPATANE.

Therefore, it is important that women of childbearing potential use two effective forms of contraception simultaneously. They should also sign a Consent Form prior to beginning SUPATANE therapy (see boxed section 4.3).

Isotretinoin is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

- She has severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic anti-bacterial- and topical therapy (see section 4.1).
- The potential for pregnancy must be assessed for all female patients.
- She understands the teratogenic risk.
- She understands the need for rigorous follow-up on a monthly basis.
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the entire duration of treatment and for 1 month after the end of treatment. At least one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception including a barrier method should be used.
- Individual circumstances should be evaluated in each case, when choosing the contraception method, involving the patient in the

discussion, to guarantee her engagement and compliance with the chosen measures.

- Even if she has amenorrhea, she must follow all of the advice on effective contraception.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy or if she might be pregnant.
- She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and 1 month after stopping treatment.
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of isotretinoin.

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The prescriber must ensure that:

- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.
- The patient understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception including a barrier method, for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment.

- Negative pregnancy test results have been obtained before, during and 1 month after the end of treatment. The dates and results of pregnancy tests should be documented.
- If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred o a physician specialised or experienced in teratology for evaluation and advice.
- If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the foetus. This risk persists until the product has been completely eliminated, which is within one month following the end of treatment.

**Contraception**

Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional.

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 including a barrier method. Contraception should be used for at least 1 month prior to starting treatment, throughout treatment and continue for at least 1 month after stopping treatment with isotretinoin, even in patients with amenorrhea.

Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

**Pregnancy testing**

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL are recommended to be performed, in the first 3 days of the menstrual cycle as follows.

*Prior to starting therapy*

At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test and its date and result recorded. This test should ensure the patient is not pregnant when she starts treatment with isotretinoin. In patients without regular menses, the timing of this pregnancy test should reflect the sexual activity of the patient and should be undertaken approximately 3 weeks after the patient last had unprotected sexual intercourse. The prescriber should educate the patient about contraception.

*Follow-up visits*

Follow-up visits should be arranged at 28-day intervals. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity, recent menstrual history (abnormal menses, missed periods or amenorrhea) and method of contraception. Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

*End of treatment*

One month after stopping treatment, women should undergo a final pregnancy test.

**Prescribing and dispensing restrictions**

For women of childbearing potential, the prescription duration of SUPATANE 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 SUPATANE should occur on the same day. Dispensing of isotretinoin should occur within a maximum of 7 days of the prescription.

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 medication.

**Male patients**

The available data suggest that the level of maternal exposure from the semen of the patients receiving SUPATANE, is not of a sufficient magnitude to be associated with the teratogenic effects of SUPATANE. Male patients should be reminded that they must not share their medication 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 1 month following discontinuation of isotretinoin 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 isotretinoin the Marketing Authorisation Holder will provide educational material to reinforce the warnings about the teratogenicity of isotretinoin, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

**Psychiatric disorders**

Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.
Awareness by family or friends may be useful to detect mental health deterioration.

**Skin and subcutaneous tissues disorders**

Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7-10 days, and usually does not require dose adjustment.

Exposure to intense sunlight or to UV rays should be avoided. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used.

Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on isotretinoin for a period of 5 - 6 months after the end of the treatment because of the risk of hypertrophic scarring in atypical areas and post inflammatory hyper or hypopigmentation in treated areas. Wax depilation should be avoided in patients on isotretinoin for at least a period of 6 months after treatment because of the risk of epidermal stripping.

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase (see section 4.5).

Patients should be advised to use a skin moisturising ointment or cream and a lip balm from the start of treatment as isotretinoin is likely to cause dryness of the skin and lips.

There have been post-marketing reports of severe skin reactions (e.g. erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) associated with isotretinoin use. As these events may be difficult to distinguish from other skin reactions that may occur (see section 4.8), patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If a severe skin reaction is suspected, isotretinoin treatment should be discontinued.

**Allergic reactions**

Anaphylactic reactions have been reported, in some cases after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

**Eye disorders**

Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

Decreased night vision has also been reported and the onset in some patients was sudden (see section 4.7). Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of isotretinoin maybe necessary.

**Musculo-skeletal and connective tissue disorders**

Myalgia, arthralgia and increased serum creatine phosphokinase values have been reported in patients receiving isotretinoin, particularly in those undertaking vigorous physical activity (see section 4.8). In some cases, this may progress to potentially life-threatening rhabdomyolysis.

Bone changes including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments have occurred after several years of administration at very high doses for treating disorders of keratinisation. The

dose levels, duration of treatment and total cumulative dose in these patients generally far exceeded those recommended for the treatment of acne.

**Benign intracranial hypertension**

Cases of benign intracranial hypertension have been reported, some of which involved concomitant use of tetracyclines (see section 4.3 and section 4.5). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop benign intracranial hypertension should discontinue isotretinoin immediately.

**Hepatobiliary disorders**

Liver enzymes should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Transient and reversible increases in liver transaminases have been reported. In many cases these changes have been within the normal range and values have returned to baseline levels during treatment. However, in the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.

**Renal insufficiency**

Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, isotretinoin can begiven to patients with renal insufficiency. However, it is recommended that patients are started on a low dose and titrated up to the maximum tolerated dose (see section 4.2).

**Lipid Metabolism**

Serum lipids (fasting values) should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Elevated serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment and may also respond to dietary measures.

Isotretinoin has been associated with an increase in plasma triglyceride levels. Isotretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur (see section 4.8). Levels in excess of 800 mg/dL or 9 mmol/L are sometimes associated with acute pancreatitis, which may be fatal.

**Gastrointestinal disorders**

Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing severe (haemorrhagic) diarrhoea should discontinue isotretinoin immediately.

**High Risk Patients**

In patients with diabetes, obesity, alcoholism or a lipid metabolism disorder undergoing treatment with isotretinoin, more frequent checks of serum values for lipids and/or blood glucose may be necessary. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during isotretinoin therapy.

**Excipients: Soya-bean oil**

SUPATANE contains soya-bean oil. If you are allergic to peanut or soya, do not use this medicine (see section 4.3).

**4.5 Interaction with other medicines and other forms of interaction**

Patients should not take vitamin A as concurrent medication due to the risk of developing hypervitaminosis A.

Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported with concomitant use of isotretinoin and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see section 4.3 and section 4.4).

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase (see section 4.4).

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

**Pregnancy is an absolute contraindication to treatment with isotretinoin (see section 4.3). Women of childbearing potential have to use effective contraception during and up to one month after treatment. If pregnancy does occur in spite of these precautions during treatment with SUPATANE or in the month following, there is a great risk of very severe and serious malformation of the foetus (see section 4.3).**

The foetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia),cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot,

transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.

If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

**Breastfeeding**

Isotretinoin is highly lipophilic, therefore the passage of isotretinoin into human milk is very likely. Due to the potential for adverse effects in the child exposed via mothers' milk, SUPATANE is contraindicated during breastfeeding (see section 4.3).

**Fertility**

Isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardise the formation and development of the embryo on the part of the men taking isotretinoin.

**4.7 Effects on ability to drive and use machines**

SUPATANE could potentially have an influence on the ability to drive and use machines.

Reported cases of decreased night vision have occurred during isotretinoin therapy and in some instances have persisted after therapy (see section 4.4 and section 4.8). Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating machines.

Drowsiness, dizziness and visual disturbances have been reported. Patients should be warned that if they experience these effects, they should not drive, operate machinery or take part in any other activities where the symptoms could put either themselves or others at risk.

## 4.8 Undesirable effects

### Summary of safety profile

Some of the side effects associated with the use of isotretinoin are dose related. The side effects are generally reversible after altering the dose or discontinuation of treatment, however some may persist after treatment has stopped. The following symptoms are the most frequently reported undesirable effects with isotretinoin: dryness of the skin, dryness of the mucosae e.g. of the lips (cheilitis), the nasal mucosa (epistaxis) and the eyes (conjunctivitis).

### Tabulated list of adverse reactions

The adverse reactions are listed below by MedDRA system organ class (SOC) and categories of frequency. Within each frequency grouping and SOC, adverse reactions are presented in order of decreasing seriousness.

**Table 1 Tabulated list of adverse reactions in patients treated with isotretinoin**

| **System Organ Class** | **Frequency** | | |
|---|---|---|---|
| | **Frequent** | **Less Frequent** | **Not known*** |

| | | | |
|---|---|---|---|
| Infections and infestations | | Gram positive (mucocutaneous) bacterial infection | |
| Blood and lymphatic system disorders | Thrombocytopenia, anaemia, thrombocytosis, red blood cell sedimentation rate increased Neutropenia | Lymphadenopathy | |
| Immune system disorders | | Anaphylactic reactions, hypersensitivity, allergic skin reaction | |
| Metabolism and nutrition disorders | | Diabetes mellitus, hyperuricaemia | |
| Psychiatric disorders | | Depression, depression aggravated, aggressive tendencies, anxiety, mood alterations, | |

| | | | |
|---|---|---|---|
| | | suicide, suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour | |
| Nervous system disorders | Headache | Benign intracranial hypertension, convulsions, drowsiness, dizziness | |
| Eye disorders | Blepharitis, conjunctivitis, dry eye, eye irritation | Papilloedema (as sign of benign intracranial hypertensin), cataract, colour blindness (colour vision deficiencies), contact lens intolerance, corneal opacity, decreased night vision, keratitis, photophobia, | |

| | | | |
|---|---|---|---|
| | | visual disturbances, blurred vision. | |
| Ear and labyrinth disorders | | Hearing impaired | |
| Vascular disorders | | Vasculitis (for example Wegener's granulomatosis, allergic vasculitis) | |
| Respiratory, thoracic and mediastinal disorders | Nasopharyngitis, epistaxis, nasal dryness | Bronchospasm (particularly in patients with asthma), hoarseness | |
| Gastrointestinal disorders | | Inflammatory bowel disease, colitis, ileitis, pancreatitis, gastrointestinal haemorrhage, haemorrhagic diarrhoea, | |

| | | | |
|---|---|---|---|
| | | nausea, dry throat (see section 4.4) | |
| Hepatobiliary disorders | Transaminase increased (see section 4.4) | Hepatitis | |
| Skin and subcutaneous tissue disorders | Pruritus, rash erythematous, dermatitis, cheilitis, dry skin, localised exfoliation, skin fragility (risk of frictional trauma) | Alopecia, acne fulminans, acne aggravated (acne flare), erythema (facial), exanthema, hair disorders, hirsutism, nail dystrophy, paronychia, photosensitivity reaction, pyogenic granuloma, skin hyperpigmentation, sweating increased | Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis |
| Musculoskeletal and connective tissue disorders | Arthralgia, myalgia, back pain (particularly in | Arthritis, calcinosis (calcification of ligaments and tendons), | Rhabdomyolysis |

| | | | |
|---|---|---|---|
| | children and adolescent patients) | epiphyses premature fusion, exostosis, (hyperostosis), reduced bone density, tendonitis | |
| Renal and urinary disorders | | Glomerulonephritis | |
| Reproductive system and breast disorders | | | Sexual dysfunction including erectile dysfunction and decreased libido, gynaecomastia, vulvovaginal dryness |
| General disorders and administration site conditions | | Granulation tissue (increased formation of), malaise | |
| Investigations | Blood triglycerides increased, high density lipoprotein decreased | Blood creatine phosphokinase increased | |

| | | | |
|---|---|---|---|
| | Blood cholesterol increased, blood glucose increased, haematuria, proteinuria | | |

* cannot be estimated from the available data

**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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: **https://www.sahpra.org.za/Publications/Index/8**

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

### 4.9 Overdose

Isotretinoin is a derivative of vitamin A. Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Manifestations of acute vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with isotretinoin would probably be similar. These symptoms would be expected to be reversible. Further treatment is supportive and symptomatic.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and Class: A 13.4.2 – Dermatological preparations – other.

Pharmacotherapeutic group: Retinoid for treatment of acne

ATC Code: D10BA01

### Mechanism of action

Isotretinoin is a stereoisomer of all-*trans* retinoic acid (tretinoin). The exact mechanism of action of isotretinoin has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous gland activity and a histologically demonstrated reduction in the size of the sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.

### Clinical efficacy and safety

Hyper cornification of the epithelial lining of the pilosebaceous unit leads to shedding of corneocytes into the duct and blockage by keratin and excess

sebum. This is followed by formation of a come done and, eventually, inflammatory lesions. Isotretinoin inhibits proliferation of sebocytes and appears to act in acne by re-setting the orderly program of differentiation. Sebum is a major substrate for the growth of Propionibacterium acnes so that reduced sebum production inhibits bacterial colonisation of the duct.

**5.2 Pharmacokinetic properties**

Time-related blood concentrations can be predicted from single-dose data on the basis of linear pharmacokinetics. This property also provides some evidence that the activity of hepatic medicine metabolising enzymes is not induced by isotretinoin.

**Absorption**

Oral absorption of isotretinoin is optimal when taken with food or milk. After oral administration of 80 mg, peak blood concentrations ranged from 167 ng/mL to 459 ng/mL (means 256 ng/mL) and were achieved in 1 - 6 hours (mean 3,2 hours) in healthy volunteers, while in acne patients peak concentrations ranged from 98 ng/mL to 535 ng/mL (mean 262 ng/mL), and occurred at 2 to 4 hours after administration (mean 2,9 hours). The mean ± SD minimum steady-state blood concentration of isotretinoin was 160 ± 19 ng/mL. The terminal elimination half-life was consistent with that observed in healthy subjects.

**Distribution**

Isotretinoin is 99,9 % bound to plasma proteins, primarily albumin. Steady state blood concentrations ($C_{min.ss}$) of isotretinoin in patients with severe acne treated with 40 mg two times a day ranged from 20 - 200 ng/mL: the

concentration of 4-oxo-isotretinoin in these patients were 2 - times higher than the isotretinoin concentrations.

**Biotransformation**

After oral administration of isotretinoin, three major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin, (all-*trans* retinoic acid), and 4-oxo-tretinoin. These metabolites have shown biological activity in several *in vitro* tests. 4-oxo-isotretinoin has been shown in a clinical study to be a significant contributor to the activity of isotretinoin (reduction in sebum excretion rate despite no effect on plasma levels of isotretinoin and tretinoin). Other minor metabolites include glucuronide conjugates. The major metabolite is 4-oxo-isotretinoin with plasma concentrations at steady state, that are 2,5 times higher than those of the parent compound.

Isotretinoin and tretinoin (all-*trans* retinoic acid) are reversibly metabolised (= interconverted), and the metabolism of tretinoin is therefore linked with that of isotretinoin. It has been estimated that 20 - 0 % of an isotretinoin dose is metabolised by isomerisation.
Enterohepatic circulation may play a significant role in the pharmacokinetics of isotretinoin in man.

*In vitro* metabolism studies have demonstrated that several CYP enzymes are involved in the metabolism of isotretinoin to 4-oxo-isotretinoin and tretinoin. No single isoform appears to have a predominant role. Isotretinoin and its metabolites do not significantly affect CYP activity.

**Elimination**

After oral administration of radiolabelled isotretinoin approximately equal fractions of the dose were recovered in urine and faeces. Following oral administration of isotretinoin, the terminal elimination half-life of unchanged medicine in patients with acne has a mean value of 19 hours. The terminal elimination half-life of 4-oxo-isotretinoin is longer, with a mean value of 29 hours.

Isotretinoin is a physiological retinoid and endogenous retinoid concentrations are reached within approximately two weeks following the end of isotretinoin therapy.

**Hepatic impairment**

Since isotretinoin is contraindicated in patients with hepatic impairment, limited information on the kinetics of isotretinoin is available in this patient population.

**Renal impairment**

Renal failure does not significantly reduce the plasma clearance of isotretinoin or 4-oxo-isotretinoin. Patients with severe renal failure being treated with oral isotretinoin should be started at a lower dose. The dose can be gradually increased as tolerated.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content:

Sorbitane oleate

Soya-bean oil refined

Stearoyl macrogolglycerides

Cap:

Gelatin

Indigocarmine (E132)

Red iron oxide (E172)

Titanium dioxide (E171)

Yellow iron oxide (E172)

Body:

Gelatin

Titanium dioxide (E171)

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

Store at or below 25 °C

Store in the original package in order to protect from light and moisture.

**6.5 Nature and contents of container**

**SUPATANE 8 mg & 16 mg** capsules are packaged in thermosealed blisters

that consist in two parts:

- a white PVC foil (thickness: 250 µm),
- an aluminium foil (thickness: 20 µm).

Packed in blisters containing 7, 14, 10 capsules.

Blisters are packed in boxes containing 28, 30, 56, 60 capsules.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements for disposal.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

**8. REGISTRATION NUMBERS**

SUPATANE 8 mg hard gelatin capsule: 51/13.4.2/0006

SUPATANE 16 mg hard gelatin capsule: 51/13.4.2/0007

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

23 August 2022

**10. DATE OF REVISION OF THE TEXT**