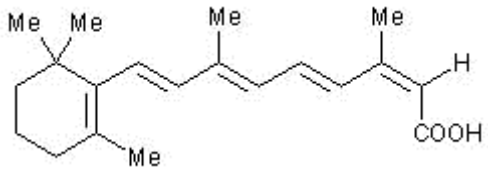
CHEMMART ISOTRETINOIN CAPSULES

NAME OF MEDICINE

Chemmart Isotretinoin (isotretinoin) «M_10mg_PI_ref» 20 mg soft gelatin capsules.

Chemically, isotretinoin is (2*Z*, 4*E*, 6*E*, 8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid (also known as 13-cis-retinoic acid).

Structurally it is represented as:



Isotretinoin is related to both retinoic acid and retinol (vitamin A).

Molecular Formula: $C_{20}H_{28}0_2$

Molecular Weight: 300.44

CAS Registry Number: 4759-48-2

DESCRIPTION

Isotretinoin is a yellow–orange to orange crystalline powder that is practically insoluble in water, soluble in methylene chloride, sparingly soluble in ether and slightly soluble in alcohol. It is sensitive to air, heat and light, especially in solution.

PHARMACOLOGY

Pharmacodynamics

Isotretinoin is a retinoid that inhibits sebaceous gland function and keratinisation. The exact mechanism of action of isotretinoin is unknown.

Clinical improvement in cystic acne patients occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is reversible and the extent is related to the dose and duration of treatment with isotretinoin and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.

Pharmacokinetics

Absorption

There is considerable inter-individual variation in the bioavailability of oral isotretinoin. After oral administration of 80 mg isotretinoin (2 x 40 mg capsules) given in the fasting state, peak plasma concentrations ranged from 167 to 459 nanogram/mL and mean time to peak was 3.2 hours in healthy volunteers, while in acne patients peak concentrations ranged from 98 to 535 nanogram/mL (mean 262 nanogram/mL) with a mean time to peak of 2.9 hours.

The bioavailability of isotretinoin capsules taken with food is 1½ to 2 times greater than when taken in a fasting state.

Distribution

Tissue Distribution in Animals:

Tissue distribution of ^{14}C-isotretinoin in rats revealed high concentrations of radioactivity in many tissues after 15 minutes, with a maximum in 1 hour and declining to non-detectable levels by 24 hours in most

tissues. After seven days, however, low levels of radioactivity were detected in the liver, ureter, adrenal, ovary and lacrimal gland.

The drug is 99.9% bound in human plasma almost exclusively to albumin.

Metabolism

The major identified metabolite in blood and urine is 4-oxo-isotretinoin. Tretinoin and 4-oxo-tretinoin were also observed. After two 40 mg capsules of isotretinoin, maximum concentrations of the metabolite of 87 to 399 nanogram/mL occurred at 6 to 20 hours. The blood concentration of the major metabolite generally exceeded that of isotretinoin after 6 hours.

The mean ± SD minimum steady state blood concentrations of isotretinoin were 160 ± 19 nanogram/mL in ten patients receiving 40 mg twice daily. After single and multiple doses, the mean ratio of areas under the curves of isotretinoin to 4-oxo-isotretinoin is 3 to 3.5.

Excretion

The terminal elimination half-life of isotretinoin ranged from 10 to 20 hours in volunteers and patients. Following an 80 mg liquid suspension oral dose of ^{14}C-isotretinoin, ^{14}C activity in blood declined with a half-life of 90 hours. Relatively equal amounts of radioactivity were recovered in the urine and faeces with 65 to 83% of the dose recovered. The apparent half-life for elimination of the 4-oxo-metabolite ranged from 11 to 50 hours with a mean of 29 hours. This metabolite is subject to recycling in the enterohepatic circulation.

INDICATIONS

Isotretinoin is indicated for the treatment of severe cystic acne. 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 eight weeks after completion of the first course, since experience has shown that patients may continue to improve while off the drug.

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

CONTRAINDICATIONS

Use in Pregnancy (Category X)

Isotretinoin must not be used by females who are pregnant or who may possibly become pregnant while undergoing treatment.

Major human fetal abnormalities related to isotretinoin administration have been reported, including hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent external auditory canals), eye abnormalities (including microphthalmia), cardiovascular abnormalities, (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), facial dysmorphia, cleft palate, thymus gland abnormality, parathyroid gland abnormalities and cerebellar malformation/abnormalities. There is also an increased incidence of spontaneous abortion.

Women of childbearing potential should not be given isotretinoin until pregnancy is excluded. It is strongly recommended that a pregnancy test be performed within two weeks prior to isotretinoin therapy. Isotretinoin therapy should start on the second or third day of the next normal menstrual period. An effective form of contraception should be used for at least one month before and also throughout isotretinoin therapy.

It is recommended that contraception be continued for one month following discontinuation of isotretinoin therapy. Females should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy.

Use in Lactation

Isotretinoin is contraindicated in patients who are breast-feeding (see **PRECAUTIONS,** Use in Lactation).

Isotretinoin is contraindicated in patients with severely impaired liver function and in patients with chronic abnormally elevated blood lipid values.

Isotretinoin is also contraindicated in people who are hypersensitive to the drug or any of the other excipients listed at the start of this document or to other retinoids. Isotretinoin contains soya oil and partially hydrogenated soya oil, therefore isotretinoin is contraindicated in patients allergic to soya.

Isotretinoin is contraindicated in patients who have pre-existing hypervitaminosis A.

Rare cases of benign intracranial hypertension have been reported after isotretinoin and after tetracyclines. Concomitant treatment with tetracyclines is therefore contraindicated (see also **PRECAUTIONS**, Interactions with Other Medicines).

PRECAUTIONS

Information for Patients
Women of childbearing potential should be warned that the drug causes birth defects. They should be instructed that they must not be pregnant when isotretinoin therapy is initiated, and that they should use an effective form of contraception while taking isotretinoin and for one month after isotretinoin has been stopped (see **CONTRAINDICATIONS**).

Patients should be informed that transient exacerbation of acne has been seen, generally during the initial period of therapy. This subsides with continued treatment, usually within 7-10 days, and usually does not require dose adjustments.

Because of the relationship of isotretinoin to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.

Donation of blood by patients during and within one month of cessation of isotretinoin treatment to women of childbearing potential should be avoided.

Wax epilation should be avoided in patients on Isotretinoin and for a period of 5-6 months after treatment because of the risk of epidermal stripping, scarring or dermatitis.

Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on iIsotretinoin and for a period of 5-6 months after the end of treatment because of the risk of hypertrophic scarring in atypical areas and more rarely hyper- or hypo-pigmentation in treated areas.

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

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

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.

Pseudotumour Cerebri
Isotretinoin use has been associated with a number of cases of pseudotumour cerebri (benign intracranial hypertension), some of which involved the concomitant use of tetracylines. Early signs and symptoms of pseudotumour cerebri include papilloedema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilloedema and, if present, they should be told to discontinue isotretinoin immediately and be referred to a neurologist for further diagnosis and care.

Visual Abnormalities
Corneal opacities have occurred in patients receiving isotretinoin for acne and more frequently when higher drug dosages were used in patients with disorders of keratinisation. All isotretinoin patients experiencing visual difficulties should discontinue the drug and have an ophthalmological examination.

A number of cases of decreased night vision have occurred during isotretinoin therapy. As the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night.

Dry eyes, corneal opacities, conjunctivitis, blepharitis, intolerance to contact lenses, 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 application of tear replacement therapy. Due to the possible occurrence of keratitis, patients with dry eyes should be monitored. Patients experiencing visual difficulties should be referred for an ophthalmological examination and withdrawal of isotretinoin considered.

Hearing Impairment

Impaired hearing at certain frequencies has been reported in patients taking isotretinoin; in come cases, the hearing impairment has been reported to persist after therapy has been discontinued. Mechanism(s) and causality for this event have not bee established. Patients who experience tinnitus or hearing impairment should discontinue isotretinoin treatment and be referred for specialized care for futher evaluation (see **ADVERSE EFFECTS: Special Senses**).

Biochemical Abnormalities

Transient and reversible rises in alanine and aspartate aminotransferases enzymes (ALT and AST) have been reported. Liver function tests, especially AST and blood lipids, should be measured before therapy and at monthly intervals during therapy and at the end of treatment. When transaminase levels exceed the normal levels, reduction of dose or discontinuation of treatment may be necessary.

Isotretinoin causes elevation of serum triglycerides and cholesterol as well as a decrease in high-density lipoprotein (HDL), which appear to be related to duration of treatment and are reversible on cessation of treatment. The degree of elevation may also be dose dependent, although this has not been conclusively established.

At doses of greater than 1 mg/kg/day, approximately one in four patients has been found to develop elevated triglycerides while taking isotretinoin. At lower doses triglyceride levels elevated above the normal range are uncommon. Some patients have been able to reverse triglyceride elevations by weight reduction and restriction of dietary fat and alcohol while continuing to take isotretinoin. Serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment.

Acute pancreatitis, which is potentially fatal, sometimes associated with serum triglycerides levels > 8 g/L, has been reported. Hence isotretinoin should be discontinued if uncontrolled hypertriglyceridaemia or symptoms of pancreatitis occur.

Predisposing factors such as a family history of lipid disorders, obesity, alcohol abuse, diabetes and smoking should be assessed. Serum lipid levels (fasting) should be determined one month prior to therapy and again after about four weeks of therapy and subsequently at three month intervals unless more frequent monitoring is clinically indicated. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during isotretinoin therapy.

Some patients have been able to reverse triglyceride elevations by weight reduction and restriction of dietary fat and alcohol while continuing to take isotretinoin. Serum lipid values usually return to normal on reduction of dose or discontinuation of treatment.

Predisposing factors such as a family history of lipid metabolism disorders, obesity, alcoholism, diabetes and smoking should be assessed. In high risk patients (with diabetes, obesity, alcoholism or lipid metabolism disorder) undergoing treatment with isotretinoin, more frequent checks of serum values for lipids and/or blood glucose may be necessary.

Skeletal

Bone Mineral Density

Effects of multiple courses of isotretinoin on the developing musculoskeletal system are unknown. There is some evidence that long-term, high dose, or multiple courses of therapy with isotretinoin have more of an effect than a single course of therapy on the musculoskeletal system. In an open-label clinical trial (N=217) of a single course of therapy with isotretinoin for severe recalcitrant nodular acne, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change >-4% and total hip change >-5%) or were increased in the majority of patients. One patient

had a decrease in lumbar spine bone mineral density >4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density >4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range −1.6% to −7.6%) in 5 of 8 patients (62.5%).

In a separate open-label extension study of 10 patients, ages 13-18 years, who started a second course of Accutane 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25% (see **PRECAUTIONS: Use in Children**).

Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures have been seen in the isotretinoin population. While causality to isotretinoin has not been established, an effect cannot be ruled out. Longer term effects have not been studied. It is important that isotretinoin be given at the recommended doses for no longer than the recommended duration.

Hyperostosis
Myalgia, arthralgia and increased serum creatine phosphokinase may occur and may be associated with reduced tolerance to vigorous exercise (see **ADVERSE EFFECTS**).

In clinical trials of disorders of keratinisation with a mean dose of 2.24 mg/kg/day, a high prevalence of skeletal hyperostosis was noted. Bone changes including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments have occurred after administration of high doses for long periods 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.

Minimal skeletal hyperostosis has also been observed by X-rays in prospective studies of cystic acne patients treated with a single course of therapy at recommended doses.

Due to the possible occurrence of these bone changes, a careful evaluation of the risk/benefit ratio should be carried out in every patient and isotretinoin administration should be restricted to severe cases.

Hepatobiliary Disorders
Several cases of clinical hepatitis have been noted which are considered to be possibly or probably related to isotretinoin therapy. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials, some of which normalised with dosage reduction or continued administration of the drug. If normalisation does not readily occur or if hepatitis is suspected during treatment with isotretinoin, the drug should be discontinued and the etiology further investigated.

Psychiatric Disorders
Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychosis and, rarely, suicide, suicidal ideation and suicide attempts and suicide have been reported with isotretinoin. 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. Although no mechanism of action for these events has been established, discontinuation of therapy may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Inflammatory Bowel Disease
Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing abdominal pain, rectal bleeding or severe (hemorrhagic) diarrhoea should discontinue isotretinoin immediately.

Anaphylactic Reactions
These have been reported rarely and only 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.

Renal Impairment
Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, isotretinoin should be started at a lower dose in patients with severe renal insufficiency and afterwards dose adjusted according to tolerance.

Exercise Tolerance
Myalgia and arthralgia may occur and be associated with reduced tolerance to vigorous exercise (see **ADVERSE REACTIONS**). Isolated instances of raised CPK levels have been reported in patients receiving isotretinoin, particularly those undergoing vigorous physical activity.

Effects on Ability to Drive or Operate Machinery
A number of decreased night vision has occurred during isotretinoin therapy and in rare instances has persisted after discontinuation of therapy. As the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night.

Drowsiness, dizziness and visual disturbances have been reported very rarely. 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.

Carcinogenesis / Mutagenesis / Impairment of Fertility
In Fischer, 344 rats given isotretinoin at dosages of 32 or 8 mg/kg/day for greater than 18 months, there was dose related increased incidence of phaeochromocytoma. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage. There is doubt as to the validity of this animal model as a predictor of tumorigenicity in humans, as the Fischer rat is genetically predisposed to the Multiple Endocrine Neoplasia Syndrome which includes spontaneous occurrence of phaeochromocytoma. In these studies there was also a dose related decrease in the incidence of liver adenomata, liver angiomata and leukaemia.

Isotretinoin was negative in tests for gene mutation (histidine reversion in *S. typhimurium*), chromosomal damage *in vitro* (chinese hamster lung cell and *S. cervisiae* D7 assays) and in *vivo* (mouse micronucleus test), and unscheduled DNA synthesis *in vitro* (rat hepatocytes)

In the reproductive studies in rats (2, 8 or 32 mg/kg/day; two generation), no adverse effects were noted on gonadal function, fertility, gestation or neonatal viability, although the average weight in the high dose group was slightly reduced.

In dogs, testicular atrophy was noted after treatment with isotretinoin for approximately 30 weeks at dosages of 60 or 20 mg/kg/day. In general, there was microscopic evidence for appreciable depression of spermatogenesis, but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen. In studies in 66 human males, 30 of whom were patients with cystic acne, no significant changes were noted in the count or motility of spermatozoa in the ejaculate.

Use in Pregnancy (Category X)
Isotretinoin is a known human teratogen and should not under any circumstances be administered during pregnancy (see **CONTRAINDICATIONS**).

Isotretinoin should only be prescribed by physicians who are experienced in the use of systemic retinoids and understand the risk of teratogenicity.

Isotretinoin is teratogenic in rats and rabbits although sensitivity differs. In the rat, doses up to 50 mg/kg/day were not teratogenic but 150 mg/kg/day were teratogenic. At lower doses in the rat perinatal and post-natal studies (5, 15, 32 mg/kg/day) increased pup mortality was noted in all treatment groups. This was attributed to a dose-related reduction in maternal food intake. Body weight development of pups was significantly impaired in high dose groups.

In the rabbit, a dose of 10 mg/kg/day caused abortions in 9 out of 13 animals and teratogenicity and embryotoxicity were observed in the remaining 4 litters.

Use in Lactation
As isotretinoin is highly lipophilic, the passage of the drug in human milk is very likely. Because of the potential for adverse effects, breastfeeding mothers should not receive isotretinoin.

Use in Children
The approved therapeutic indication does not involve use in children and safety in pre-pubertal children has not been established (see also **PRECAUTIONS,** Hyperostosis).

Interactions with Other Medicines
As a rule concomitant therapy is not indicated but non-irritant topical preparations may be used if required.

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

Concurrent treatment with vitamin A must be avoided, as symptoms of hypervitaminosis A may be intensified (see **ADVERSE EFFECTS**).

Cases of pseudotumour cerebri and/or papilloedema have been reported in association with the use of isotretinoin. Four out of ten of these patients had retinal haemorrhages. Symptoms appeared after 21 days to 6 months therapy with 40 to 120 mg daily. Concomitant tetracycline or minocycline was administered in 5 out of 10 cases – both of these drugs have been implicated in causing intracranial hypertension. Concomitant therapy with tetracyclines is contraindicated (see **CONTRAINDICATIONS**).

Since acne is an androgen-dependent disease, contraceptives containing an androgen progestational substance, such as one derived from 19-nortestosterone (norsteroid), particulary in the presence of gynaeco-endocrinological problems, should be avoided.

The effect of microdosed progesterone preparations may be diminished by interaction with isotretinoin. Therefore, microdosed progesterone preparations or “minipills” should not be used.

In a study of 31 premenopausal female patients with severe recalcitrant nodular acne, isotretinoin at the recommended dose of 1 mg/kg/day , did not induce clinically relevant changes in the pharmacokinetics of ethinyl oestradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Prescribers are advised to consult the Product Information of the medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.

Isotretinoin is associated with depression in some patients (see **PRECAUTIONS, Psychiatric Disorders and ADVERSE EFFECTS,** Psychiatric and Central Nervous System Disorders). Patients should be prospectively cautioned not to self-medicate with the herbal supplements St John’s Wortbecause a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St John’s Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St John’s Wort.

Isotretinoin has not been shown to alter the pharmacokinetics of phenytoin in a study in seven healthy volunteers. These results are consistent with the *in vitro* finding that neither isotretinoin nor its metabolites induce or inhibit the activity of the CYP 2C9 human hepatic P450 enzyme. Phenytoin I known to cause osteomalacia. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between phenytoin and isotretinoin. Therefore, caution should be exercised when using these drugs together.

Systemic corticosteroids are known to cause osteoporosis. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between systemic corticosteroids and isotretinoin. Therefore, caution should be exercised when using these drugs together.

Effects on Laboratory Tests
Elevation of lipid (triglycerides and cholesterol) levels occurs with isotretinoin therapy. These are usually mild in doses less than 1 mg/kg/day and elevations above the normal range are unusual at 0.5 mg/kg/day. At doses above 1 mg/kg/day, elevation (above normal range) occurs in 25% of patients.

These changes are seen more frequently in patients where a family history of lipid disorders, or obesity, alcohol abuse, diabetes mellitus or smoking is present. The changes are dose related and may be controlled by dietary means (including alcohol restriction) or dosage reduction (see also **PRECAUTIONS,** Biochemical Abnormalities).

Elevated ESR values occur in about 40% of patients treated with isotretinoin.

A rise in aspartate aminotransferase (AST) levels may occur, especially with higher doses of isotretinoin. Although the changes have usually been within the normal range, and may return to baseline levels despite continued treatment, significant increases have occurred in a few cases, necessitating dosage reduction or discontinuation of isotretinoin.

Certain patients receiving isotretinoin have experienced problems in the control of their blood sugar. Therefore, known or suspected diabetics should have frequent blood sugar determinations performed during isotretinoin therapy. New cases of diabetes have been diagnosed.

A small number of patients have shown proteinuria, microscopic or gross haematuria and elevated CPK.

ADVERSE EFFECTS

Dose Relationship and Duration

Most adverse effects appear to be dose related with the more pronounced effects occurring at doses above 1 mg/kg/day. The adverse effects may recede during continued therapy and the mucocutaneous effects were reversible with dosage reduction or discontinuation of therapy. Exacerbation of the cystic acne may occur during the initial stages of therapy.

Many of the adverse effects seen in patients receiving isotretinoin are similar to those described in patients taking very high doses of vitamin A.

Post-Marketing Experience

Symptoms Associated with Hypervitaminosis A

The most common side effects are mucocutaneous. The most frequently reported effects are dryness of the skin, in particular peeling of the palms and soles, dryness of the mucosa e.g. lips (cheilitis which occurs in over 90% of patients), the nasal mucosa (epistaxis is seen in up to 30% of patients), nasopharyngitis, the pharynx (hoarseness) and eyes (conjunctivitis, reversible corneal opacities and intolerance to contact lenses).

Skin and Appendages Disorders

Exanthema, pruritis, facial erythema/dermatitis, dry skin, localized exfoliation, sweating, pyogenic granuloma, paronychia, nail dystrophy, abnormal wound healing (delayed healing or increased formation of granulation tissue with crusting, persistent hair thinning, reversible alopecia (which in some cases persists), bruising, dry mouth, epistaxis, eruptive xanthomas, flushing, infections (including disseminated herpes simplex), peeling of palms and soles, rash (including seborrhea, and eczema), sunburn susceptibility increased, urticaria, acne fulminans, hirsutism, hyperpigmentation and hypopigmentation, photosensitivity, photoallergic reactions, skin fragility. Acne flare occurs at start of treatment and persists for several weeks.

Musculoskeletal System Disorders

Myalgia (muscle pain) with or without elevated serum CPK values (see **PRECAUTIONS)**, arthralgia (joint pain), hyperostosis, exostosis, arthritis, calcification of ligaments and tendons and other bone changes, reduced bone density, musculoskeletal symptoms (sometimes severe) including back pain, epiphyses, premature fusion, tendinitis, transient pain in the chest, arthritis, elevations of CPK/rare reports of rhabdomyolysis.

Psychiatric and Central Nervous System Disorders

Behavioural disorders, depression, depression aggravated, suicide attempt, suicidal ideation, suicide, (see **PRECAUTIONS**), psychosis, violent behavious, emotional instability, aggressive tendencies, anxiety, mood alterations, headache, increased intracranial pressure (pseudotumour cerebri), and seizures.

Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy.

Sensory Disorders

Visual disturbances, photophobia, decreased night vision (which may persist), colour vision disturbances, lenticular cataracts, keratitis, blurred vision, blepharitis, conjunctivitis, dry eyes, contact lens intolerance, corneal opacities, eyelid inflammation, optic neuritis, eye irritation, papilledema as a sign of benign intracranial hypertension, impaired hearing at certain frequencies.

Gastrointestinal System Disorders

Nausea, severe diarrhea, bleeding and inflammation of the gums, oesophagitis/oesophageal ulceration, (haemorrhagic), dry throat, pancreatitis, inflammatory bowel disease such as colitis, ileitis and haemorrhage have been reported to occur. Patients on isotretinoin, especially those with high triglyceride levels, are at risk of developing pancreatitis. Fatal pancreatitis has been rarely reported (see **PRECAUTIONS**).

Liver and Biliary System Disorders

Transitory and reversible increases in liver transaminases, some cases of hepatitis.

Respiratory System Disorders

Bronchospasm (with or without a history of asthma), respiratory infection, voice alteration has been rarely reported; sometimes in patients with a pre-history of asthma.

Disorders of the Blood

Decrease in white blood cell count, neutropenia, disorders of red blood cell parameters (such as decrease in red blood cell count and haematocrit), elevation of sedimentation rate increase or decrease in platelet count (thrombocytopenia), anemia, thrombocytosis, neutropenia,, rare reports of agranulocytosis.

Cardiovascular Disorders

Palpitation, tachycardia, vascular thrombotic disease, stroke.

Laboratory Findings

Increase in serum triglyceride and cholesterol levels, decrease in HDL, hyperuricemia. Rare cases of elevated blood glucose have been reported, and new cases of diabetes have been diagnosed (see **PRECAUTIONS**).

Increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGTP or LDH. Elevations of fasting blood sugar, elevations of CPL (see **PRECAUTIONS: Biochemical Abnormalities**), hyperuricaemia.

White cells in the urine, proteinuria, microscopic or gross haematuria.

Resistance Mechanism Disorders

Local or systemic infections due to Gram-positive microorganisms (*Staphylococcus aureus*).

Miscellaneous Reactions

Decreases in haematocrit, lymphadeonpathy, haematuria, and proteinuria, vasculitis (for example Wegener's granulomatosis, allergic vasculitis), allergic responses, systemic hypersensitivity,fatigue, oedema, weight loss, insomnia, lethargy, malaise, nervousness, paraesthesia, syncope, weakness, nonspecific urogenital findings, abnormal menses, anaphylactic reactions, diabetes mellitus, hyperuricaemia, hoarseness, convulsions, drowsiness, dizziness, and glomerulonephritis.

DOSAGE AND ADMINISTRATION

The therapeutic response to isotretinoin is dose related and varies between patients. This necessitates individual adjustment of dosage according to the response of the condition and the patient's tolerance of the drug. In most cases complete or near complete suppression of acne is achieved with a 16 week course of treatment.

Initial Treatment
All patients should initially receive doses up to 0.5 mg/kg bodyweight daily for a period of two to four weeks, when their responsiveness to the drug will usually be apparent. It should be noted that the transient exacerbation of acne is occasionally seen during this initial period. Satisfactory initial responses have been reported from 0.05 mg/kg/day. Relapse rates on the lower doses are higher (a second course may be required in about two-thirds of patients on 0.1 mg/kg/day for 16 weeks), but there is decreased incidence and severity of adverse reactions at lower doses.

The daily dosage should be taken with food in the nearest number of whole capsules, either as a single dose or in two divided doses during the day, whichever is more convenient.

Doses up to 1 mg/kg/day may be used in patients refractory to initial treatment at lower doses.

The above daily dosages of isotretinoin should be continued for 16 weeks to complete the course of treatment.

After a period of two months off therapy, and if warranted by persistent severe cystic acne, a second course of therapy may be initiated.

OVERDOSAGE

Isotretinoin is a derivative of vitamin A. Although acute toxicity of isotretinoin is low, signs of hypervitaminosis could appear in cases of accidental overdose. Clinically, overdose has been associated with transient headache, (severe), nausea or vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness, drowsiness, irritability, pruritus and ataxia. All symptoms quickly resolved without apparent residual effects.

The oral LD_{50} of isotretinoin is greater than 4000 mg/kg in rats and mice and approximately 1960 mg/kg in rabbits.

Isotretinoin causes serious birth defects at any dosage (see CONTRAINDICATIONS and PRECAUTIONS). Female patients of childbearing potential who present with isotretinoin overdose must be evaluated for pregnancy. Patients who are pregnant should receive conoseling about the risks to the foetus. Non-pregnant patients must be warned to avoid pregnancy for at least one month and receive contraceptive counseling. Because an overdose would be expected to result in higher levels of isotretinoin in semen than found during a normal treatment course, male patients should use a condom, or avoid reproductive sexual activity with a female patient who is or might become pregnant, for 1 month after the overdose. All patients with isotretinoin overdose should not donate blood for at least one month.

Contact the Poisons Information Centre on 13 11 26 (Australia) advice on the management of overdosage,

PRESENTATION AND STORAGE CONDITIONS

Chemmart Isotretinoin 20 mg capsules are maroon coloured oval soft gelatin capsules containing a yellow/orange viscous liquid. AUST R 91351.

Chemmart Isotretinoin 20 mg capsules are available in blister packs of 60 capsules.

Chemmart Isotretinoin capsules contain isotretinoin, soya oil, dl-alpha-tocopherol, disodium edetate, butylated hydroxyanisole, soya oil–(partly) hydrogenated, beeswax–yellow and vegetable oil–hydrogenated.

The capsule shell contains gelatine, glycerol, sorbitol solution 70% (non-crystallising), Brilliant Scarlet 4R CI16255, indigo carmine CI73015, titanium dioxide and water-purified.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
ABN 52 096 916 148
66 Waterloo Road
North Ryde NSW 2113
Australia

DISTRIBUTOR

Symbion Pharmacy Services Pty Ltd
ABN 25 000 875 034
48-58 Overseas Drive
Noble Park North VIC 3174
Australia

Chemmart is a registered trade mark of Symbion Pharmacy Services Pty Ltd.

POISONS SCHEDULE OF THE MEDICINE
S4 – Prescription Only Medicine

Date of TGA approval : 28 November 2002

Date of most recent amendment :15 December 2008