Pharmacode Barcode placement must be 75 mm from the Top Right hand edge, reading from Top to Bottom.

UNILAB

Isotretinoin
Oratane®

5 mg, 10 mg & 20 mg Soft-Gelatin Capsule

Anti-Acne Preparation

Rx

FORMULATION
Each Soft-Gelatin capsule contains:
Isotretinoin...5 mg, 10 mg, or 20 mg

PRODUCT DESCRIPTION
Isotretinoin (Oratane®) 5 mg Soft-Gelatin Capsule: Oval, faint pinkish/cream to cream-colored soft gelatin capsule containing yellow or orange, opaque, viscous liquid
Isotretinoin (Oratane®)10 mg Soft-Gelatin Capsule: Oval, light violet soft gelatin capsule containing yellow or orange, opaque, viscous liquid
Isotretinoin (Oratane®) 20 mg Soft-Gelatin Capsule: Oval, maroon soft gelatin capsule containing yellow or orange, opaque, viscous liquid

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
Isotretinoin is a retinoid and the synthetic stereoisomer of all-trans retinoic acid (tretinoin). Its exact mechanism of action is not yet fully elucidated, but it has been established that the clinical improvement observed in severe acne is associated with the suppression of sebaceous gland activity and a histologically demonstrated reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation. In addition, the decrease in sebum secretion is temporary and its extent is related to the dose and duration of isotretinoin treatment. Isotretinoin also exhibits anti-keratinizing and anti-inflammatory effect.

PHARMACOKINETICS
The absorption of orally administered isotretinoin within the therapeutic range is variable and dose-linear. Following the oral administration of 80 mg (two doses of 40 mg capsules), the peak plasma concentrations (C_{max}) ranged from 167 to 459 ng/mL (mean: 256 ng/mL), with a mean time of peak (t_{max}) of 3.2 hours in healthy volunteers, the C_{max} in acne patients ranged from 98 to 535 ng/mL (mean: 262 ng/mL), with a mean t_{max} of 2.9 hours. The absolute bioavailability of isotretinoin has not been determined, but extrapolation from animal studies would suggest a fairly low and variable systemic bioavailability. Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when it is administered with a high-fat meal. Both the C_{max} and the area under the concentration-time curve (AUC) were more than doubled following a standardized high-fat meal when compared with the administration of isotretinoin under fasting conditions. The t_{max} was also increased with food and may be related to a longer absorption phase. There are no differences in the pharmacokinetics of isotretinoin between subjects with normal skin and patients with nodular acne.

Isotretinoin is more than 99.9% bound to plasma protein, almost exclusively to albumin. Thus, the free and the pharmacologically active fraction of isotretinoin is <0.1% over a wide range of therapeutic concentrations. Its volume of distribution in humans has not been determined, and there is limited information available on the distribution of isotretinoin into tissue and body fluids. Isotretinoin concentrations in the epidermis are only half of those in serum. Plasma concentrations of isotretinoin are about 1.7 times those of whole blood due to the poor penetration of the drug into red blood cells. Endogenous retinoid concentrations are attained within approximately 2 weeks after the end of isotretinoin therapy.

Following the oral administration of isotretinoin, at least three major metabolites have been identified in plasma: 4-oxo-isotretinoin (the major metabolite), tretinoin, and 4-oxo-tretinoin. The extent of formation of all metabolites was higher in fed conditions. Isotretinoin and tretinoin are geometric isomers and demonstrate reversible interconversion. Isotretinoin is also irreversibly oxidized to 4-oxo-isotretinoin, which forms its geometric isomer, 4-oxo-tretinoin. Minor metabolites, including glucuronide conjugates, have been detected. It has been shown in several *in vitro* models that these metabolites have retinoid activity, but the clinical significance of these models is unknown. In addition, 4-oxo-isotretinoin has been shown in a clinical study to be a significant contributor to the reduction in sebum excretion rate despite having no effect on plasma levels of isotretinoin and tretinoin. Approximately 20% to 30% of an isotretinoin dose is metabolized by isomerization.

In vitro metabolism studies have demonstrated that several CYP enzymes are involved in the metabolism of isotretinoin to 4-oxo-isotretinoin and tretinoin. Six hours after dosing, the blood concentrations of 4-oxo-isotretinoin generally exceeded that of isotretinoin, and, the plasma concentrations of 4-oxo-isotretinoin at steady state are 2.5 times higher than those of the parent compound. Isotretinoin and its metabolites undergo enterohepatic recycling.

The metabolites of isotretinoin and its conjugates are excreted in urine and feces in relatively equal amounts (total of 65% to 83% of the dose recovered). The mean terminal elimination half-lives of the unchanged drug and of 4-oxo-isotretinoin are 19 and 29 hours, respectively. The observed accumulation ratios of isotretinoin following both single and multiple doses in patients with cystic acne ranged from 0.9 to 5.43.

Special Populations
Children: In a study involving patients 12 to 15 years old with severe recalcitrant nodular acne, the mean ± standard deviation (SD) elimination half-lives of isotretinoin and 4-oxo-isotretinoin were 15.7±5.1 hours and 23.1±5.7 hours, respectively.
The accumulation ratios of isotretinoin ranged from 0.46 to 3.65 in these pediatric patients. There were no statistically significant differences in the pharmacokinetics of isotretinoin between pediatric and adult patients.

Renal Impairment: Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Renal failure does not significantly reduce the plasma clearance of isotretinoin or 4-oxo-isotretinoin.

Hepatic Impairment: There are limited information of the pharmacokinetics of isotretinoin in patients with hepatic impairment.

INDICATIONS
For the treatment of severe forms of nodulo-cystic acne which are resistant to therapy, particularly cystic acne and acne conglobata, especially when the lesions involve the trunk.

DOSAGE AND MODE OF ADMINISTRATION
Isotretinoin should only be prescribed by physicians who are experienced in the use of systemic retinoids, preferably dermatologists, and understand the risk of teratogenicity if isotretinoin is used during pregnancy.

Patient response to isotretinoin is dose-related and varies from case to case. This necessitates adapting the dosage to individual needs according to severity of the clinical picture and side effects. With a dosage of between 0.1 and 1 mg/kg daily over 12 to 16 weeks, it is generally possible to achieve a considerable improvement or complete healing. The daily dose is taken with meals; low doses once daily and higher amounts as a single dose or in several doses spread over the day.

Initial Treatment
As a rule, therapy is started with 0.5 mg/kg daily and maintained for 2 to 4 weeks until the patient's response is clear. Transient exacerbation (or flare) may occur during the first few weeks of therapy.

A cumulative dose of 120 mg/kg per treatment has been documented to increase remission rates and prevent relapse. The duration of therapy of patients therefore varies as a function of the individual daily dose. Complete remission of the acne is often achieved by a therapy course of 16 to 24 weeks. In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequence of longer therapy duration.

Follow-up Treatment (Maintenance Dose)
In patients who respond well to isotretinoin, treatment should be continued with a dosage of 0.5 mg/kg daily. With patients who show signs of intolerance during the initial therapy, the daily dosage should be reduced to 0.1 to 0.2 mg/kg. Where response to the initial dosage is slight, and in particularly severe cases, the daily dosage may be increased to 1 mg/kg provided the medicine is well tolerated.

The maintenance dose is administered for a period of 12 weeks after which the first stage of therapy is generally terminated. After discontinuation of treatment, often a further improvement is observed which may last from a few weeks to several months. There should, therefore, be an interval of at least 8 weeks before restarting treatment. In the event of recurrence of the acne, treatment should be resumed on the above lines, bearing in mind that recurrences may respond to a lower dosage.

Concurrent Adjuvant Treatment
Isotretinoin is not indicated as adjuvant treatment with antimicrobials. It is advisable to discontinue antimicrobials before beginning treatment with isotretinoin. Concomitant radiation (ultraviolet) therapy and exposure to sunlight should also be avoided. Concomitant topical therapy of a mild nature may, however, be carried out.

Special Populations
Children: The efficacy and safety of isotretinoin use is not established in children<12 years of age.

Renal Impairment: If appropriate, treatment should be started at a lower dose (e.g., 10 mg/day) and afterwards, individually adjusted according to tolerability.

CONTRAINDICATIONS
- Hypersensitivity to isotretinoin or to any other component in the product
- Pregnancy or breastfeeding
- Women of childbearing potential who may become pregnant during isotretinoin treatment or unless pregnancy is excluded (see Warnings and Precautions)
- Hepatic and renal insufficiency
- Excessively elevated blood lipid values
- Hypervitaminosis A
- Concomitant use with tetracyclines (see Interactions with Other Medicaments)

WARNINGS AND PRECAUTIONS

EMBRYOFETAL TOXICITY – CONTRAINDICATED IN PREGNANCY, AND THE NEUROLOGIC/PSYCHIATRIC EFFECTS OF ISOTRETINOIN

Isotretinoin can cause severe life-threatening birth defects and is contraindicated in pregnancy. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking any amount of isotretinoin even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining prenatally whether an exposed fetus has been affected.
If pregnancy occurs, discontinue isotretinoin immediately and refer the patient to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling (see Warnings and Precautions).

Some patients treated with isotretinoin have become depressed and some attempted or committed suicide. Although a causal relationship has not been established, all patients should be screened and monitored for signs of depression before and during therapy. Physicians should determine whether the patient may be depressed or has a history of depression including a family history of major depression before starting therapy with isotretinoin. If symptoms of depression develop or worsen during treatment with isotretinoin, the drug should be discontinued promptly and the patient referred for appropriate psychiatric treatment as necessary. However, discontinuation of isotretinoin may not alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary (see ***Warnings and Precautions***).

Isotretinoin use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines. Early symptoms of pseudotumor cerebri include headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, the drug should be discontinued immediately and the patient referred to a neurologist for diagnosis and care. Concomitant treatment with tetracyclines should be avoided.

Isotretinoin should only be prescribed by physicians who are experienced in the use of systemic retinoids, preferably dermatologists, and understand the risk of teratogenicity if isotretinoin is used during pregnancy.

Embryofetal Toxicity
Isotretinoin is contraindicated in pregnancy, as it can cause fetal harm when administered to a pregnant patient. There is an extremely high risk that the intake of any dose of isotretinoin during pregnancy, even for short periods of time, will result to severe birth defects. Potentially any fetus exposed to isotretinoin during pregnancy can be affected. There are no accurate means to determine prenatally whether an exposed fetus has been affected. Major congenital malformations, spontaneous abortions, and premature births have been documented following isotretinoin exposure during pregnancy (see ***Statement of Usage for High Risk Groups***).

Prescribers should inform their patients of the serious risks to the fetus associated with the use of isotretinoin use during pregnancy. Female patients of childbearing potential should not be treated with isotretinoin until pregnancy is excluded. Two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL must be obtained before initiating isotretinoin treatment. The first pregnancy test (a screening test) is to be conducted at initial assessment when the patient is qualified for isotretinoin therapy by the physician, while the second pregnancy test serves as a confirmation test. The interval between these two pregnancy tests should be at least 19 days. Patients with regular menstrual cycles should have their second pregnancy test done during the first 5 days of the menstrual period and within 7 days of the clinic visit, immediately preceding the beginning of isotretinoin therapy and after the patient has used two forms of contraception for 1 month before initiating therapy. Isotretinoin treatment should be started on the second or third day of the next normal menstrual period after this negative pregnancy test. Patients with amenorrhea, irregular cycles, or using a contraceptive method that prevents withdrawal bleeding should have their second pregnancy test done within 7 days after clinic visit, immediately before starting isotretinoin therapy, and after the patient has used two forms of contraception for 1 month.

Pregnancy should be avoided during isotretinoin therapy. Patients may use two forms of effective contraception 1 month before starting treatment, during treatment, and until 1 month after discontinuation. To reinforce the necessity of avoiding pregnancy, all female patients of childbearing potential treated with isotretinoin therapy should have regular monthly pregnancy test during treatment and 1 month after discontinuation. Prescriptions should be written for no more than a 30-day treatment period, and the pregnancy test results should be presented to rule out pregnancy prior to refilling the prescription. Two forms of contraception may not be required if the patient commits to continuous abstinence from not having any sexual contact with a partner which may result in pregnancy, has undergone a hysterectomy or bilateral oophorectomy, or has been medically confirmed to be post-menopausal.

Psychiatric Disorders
Isotretinoin may cause depression, psychosis, anxiety, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. A causal relationship of these adverse effects with isotretinoin use has not been established. Signs and symptoms of depression include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, irritability, difficulty concentrating, fatigue, changes in sleep pattern, change in weight or appetite, acting on dangerous impulses, restlessness, irritability, fatigue, and persistent physical symptoms unresponsive to treatment.

All patients should be screened for signs of depression before and during therapy. Prior to treatment initiation, the physician should determine whether the patient may be depressed or has a history of depression, including a family history of major depression. Isotretinoin should be given with caution in patients with a history of depression or psychiatric disorder.

Patients should be monitored for the manifestations of depression or psychiatric disorders. The patient should also be assessed for symptoms of depression, mood disturbance, psychosis, or aggression every clinic visit to determine if further evaluation may be necessary. Awareness by family or friends may be useful in identifying the mental health deterioration of the patient. If a patient reports mental health problems or a family history of psychiatric disorders, such reports should be discussed with the patient and/or family members. The physician should consider if the benefits of isotretinoin treatment outweigh the risk to these patients. A referral to a mental health professional may be necessary. Isotretinoin treatment should be discontinued, without waiting for the next clinic visit, if the patient develops or has worsened symptoms of depression, mood disturbance, psychosis, or aggression. In addition, the patient or caregivers should contact the prescriber promptly, as treatment discontinuation may not be sufficient to alleviate symptoms and further psychiatric or psychological evaluation may be necessary.

Dermatological Reactions
Acute exacerbation of acne occasionally occurs during the initial period of the treatment, but subsides with continued treatment. Dose adjustments are usually not necessary.
In addition, patients with severe nodular acne should be informed that an occasional exaggerated healing response, manifested by exuberant granulation tissue with crusting, may occur during isotretinoin treatment.

Exposure to intense sunlight or to UV rays, especially for prolonged period, should be avoided during isotretinoin use. A sun-protection product with high protection factor at least SPF 15 should be used if necessary.

Skin resurfacing procedures (such as aggressive chemical dermabrasion and cutaneous laser treatment) should be avoided during isotretinoin use and for 5 to 6 months after the end of the treatment due to the risk of hypertrophic scarring in atypical areas and more rarely, post-inflammatory hyperpigmentation or hypopigmentation in treated areas. Wax epilation should be avoided during isotretinoin use and for at least 6 months after treatment to prevent the risk of epidermal stripping, scarring, or dermatitis. The use of topical keratolytic or exfoliative anti-acne agents should be avoided (see ***Interactions with Other Medicaments***).

Since isotretinoin may cause dryness of the skin and lips, the use of lip balm and skin moisturizing ointment or cream from the start of the treatment is recommended.

Serious Skin Reactions
There have been rare reports of erythema multiforme and severe skin reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) associated with isotretinoin use during postmarketing experience. Some of these cases may be serious and may result to disfiguration, life-threatening events, hospitalization, disability, or death.

Patients treated with isotretinoin should be closely monitored for severe skin reaction. As these may be difficult to distinguish from other skin condition that may occur, physicians should inform their patients of the signs and symptoms of these severe skin reactions. Discontinue isotretinoin use if severe skin reaction is suspected, or if patients developed any of the following skin reactions: rash (especially if associated with fever and/or malaise), conjunctivitis, blisters on legs, arms, or face; and/or sores in mouth, throat, nose, or eyes; peeling of skin, or other serious skin reactions.

Pancreatitis
Acute pancreatitis has been reported with patients with either normal or elevated serum triglyceride levels. Cases of fatal hemorrhagic pancreatitis have occurred in rare instances. Patients should be advised to discontinue isotretinoin therapy if symptoms of pancreatitis occur and to seek medical attention immediately.

Metabolic Effects
Lipid Metabolism
Isotretinoin use is associated with elevations of serum triglycerides and cholesterol, as well as reductions in high-density lipoprotein (HDL), which appear to be related to the duration of treatment. The degree of elevation may also be dose-dependent, but this has not been fully established. Elevation of serum triglycerides >800 mg/dL or 9 mmol/L have been associated with acute pancreatitis, which is known to be potentially fatal. The cardiovascular consequences of hypertriglyceridemia are not fully understood, but it may increase the risk status of the patient. In addition, the short- and long-term effects of isotretinoin-induced changes in serum lipid concentrations with the usual course of treatment are not known, however these should be considered as potentially serious if long-term treatment is planned.

Serum lipid levels under fasting condition should be determined 1 month before treatment, 4 weeks after starting treatment (when the lipid response to isotretinoin is usually established), and subsequently at 3-month intervals. Careful consideration should be given to the risk and benefit of treatment in high risk patients (e.g., patients with diabetes, obesity, increased alcohol intake, smoking, lipid metabolism disorder, or family history of lipid metabolism disorder); more frequent monitoring may be necessary in these patients. Triglyceride, HDL, and cholesterol levels usually return to normal upon dose reduction or treatment reduction. Increased triglyceride levels have been reversible by weight reduction and restriction of dietary fat and alcohol while continuing isotretinoin therapy. Treatment should be discontinued if uncontrolled hypertriglyceridemia occurs.

Blood Glucose Management
Patients with diabetes mellitus or a family history of diabetes had difficulties in controlling their blood glucose levels during isotretinoin use. New cases of diabetes mellitus have also been diagnosed during therapy; however, no causal relationship with the drug has been established. Patients should have their blood glucose levels checked periodically during treatment; more frequent checks of blood glucose levels may be necessary in patients at high risk (e.g., patients with diabetes, obesity, alcoholism, lipid metabolism disorder).

Hepatotoxicity
Cases of clinical hepatitis, which are considered to be possibly or probably related to isotretinoin treatment, have been reported. In clinical trials, mild to moderate elevations of liver enzymes have been observed in approximately 15% of patients receiving isotretinoin, some of which were transient and have resolved despite continued treatment or following dose reductions.

Liver function tests should be monitored before treatment, 1 month after starting therapy, and at least every 3 months thereafter, unless more frequent monitoring is clinically indicated. Consider dose reduction in the event of persistent clinically relevant elevation of transaminase levels. Discontinue treatment if normalization of liver enzymes levels does not readily occur or if hepatitis is suspected, and further investigations on the etiology of these effects should be performed.

Auditory Effects
Impaired hearing has been reported in patients treated with isotretinoin. Hearing impairment can be unilateral or bilateral, and symptoms include tinnitus, impaired hearing at certain frequencies, and deafness. In some patients, hearing impairment has been reported to persist even after treatment discontinuation. The mechanism of this adverse event and a causal relationship to the drug have not been established. Patients who developed tinnitus or hearing impairment should discontinue isotretinoin use and should be referred for specialized care for urgent formal audiology assessment.

Inflammatory Bowel Disease
Isotretinoin has been temporally associated with inflammatory bowel disease (including regional ileitis, colitis, and hemorrhage), even in patients without prior history of intestinal disorders. In some cases, symptoms have been reported to persist even after discontinuing the treatment. Isotretinoin should be used with caution in patients with history or family history of inflammatory bowel disease or symptoms suggestive of the condition. Discontinue isotretinoin use if abdominal pain, rectal bleeding, or severe (hemorrhagic) diarrhea have occurred.

Size: 510 x 210 mm

Musculoskeletal and Connective Tissue Disorders
Adverse musculoskeletal adverse effects (e.g., myalgia, arthralgia) have been reported in patients treated with isotretinoin. Most of these cases have been mild to moderate in severity but have occasionally required drug discontinuation. Increased serum creatine phosphokinase values have also occurred in patients on isotretinoin therapy, especially in those undertaking vigorous physical activity. In some cases, this may progress to serious cases of rhabdomyolysis, often leading to hospitalization and some with fatal outcome. Patients should abstain from vigorous exercise during isotretinoin use.

Isotretinoin may have a negative effect on bone density in some patients. In addition, there have been spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fracture; the causal relationship of these effects with isotretinoin has not been established. Minimal skeletal hyperostosis and calcification of tendons have been observed by x-rays in studies involving cystic acne patients treated with a single course of therapy at recommended doses. Administration of very high doses of isotretinoin for several years for the treatment of disorders of keratinization have also resulted to bone changes, including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments; the dose levels, duration of treatment, and total cumulative dose in these patients generally far exceeded those indicated for the treatment of acne.

Participation in sports with repetitive impact may increase the risk of the patient, particularly in activities where the risks of spondylolisthesis with and without pars fractures and hip growth plate injuries in early and late adolescents are known. There are spontaneous reports of fractures and/or delayed healing during isotretinoin treatment or following discontinuation of therapy in patients involved in these activities.

Due to possible risk of bone changes, the risk/benefit ratio should be carefully assessed in every patient, and isotretinoin treatment should be restricted to patients with severe cases of acne. Isotretinoin should be used with caution in patients with history of childhood osteoporosis conditions, osteomalacia, or other disorders of bone metabolism, including those with anorexia nervosa or those on chronic drug treatment that would induce osteoporosis, osteomalacia, and/or affect vitamin D metabolism (see ***Interactions with Other Medicaments***). Since there is some evidence that long-term, high-dose, multiple courses of isotretinoin therapy have more effect on the musculoskeletal system than a single dose of therapy, isotretinoin should only be given at the recommended doses for the recommended duration of treatment. Patients presenting with symptoms of musculoskeletal disorders during or after isotretinoin treatment should be evaluated appropriately. Consider discontinuation of treatment if any significant abnormality is found.

Ocular Abnormalities
Corneal opacities have occurred in patients on isotretinoin therapy for acne and more frequently in patients treated with higher dosages for disorders of keratinization. In addition, decreased night vision has been reported during isotretinoin therapy, which has persisted in some cases even after treatment was discontinued. Vision impairment, including photophobia or blurred vision, may also develop.

Dry eyes, keratitis, blepharitis, and conjunctivitis have been reported to occur in some patients, and cases were usually resolve after discontinuing the treatment. Patients on isotretinoin treatment, especially those with dry eyes, should be monitored for the development of keratitis. Visual problems should be carefully monitored. If visual difficulties occur, patients should discontinue isotretinoin treatment and undergo an ophthalmological examination. Lubricating eye ointment or tear replacement therapy may be applied to manage dry eyes. Patients who wear contact lenses should be advised that they may experience intolerance to contact lenses, which may necessitate wearing eyeglasses while on isotretinoin treatment. Since the onset of decreased night vision was sudden in some patients, patients are advised of this potential problem and be advised to be cautious when driving or operating any vehicle at night.

Hematological Effects
Neutropenia and rare cases of agranulocytosis have been reported during isotretinoin use. For the early detection of leukopenia, neutropenia, thrombocytopenia, and anemia, complete blood count with differential count should be performed before starting treatment, at first month of treatment, then as clinically indicated. Isotretinoin treatment should be discontinued if there are clinically significant reductions in white blood cell counts.

Hypersensitivity Reactions
There have been reports of anaphylactic reactions with isotretinoin; these reactions were more serious after prior exposure to topical retinoids. Cutaneous allergic reactions and serious cases of allergic vasculitis, often with purpura of the extremities and extracutaneous involvement (including renal), have been reported. In cases of severe allergic reactions, therapy should be discontinued and appropriate medical management should be provided. Careful monitoring of patients is also recommended.

Precautions on Blood Donation
It is recommended that blood donation for transfusion purposes be deferred during therapy and for 1 month after discontinuation of treatment with isotretinoin. Theoretically, blood from such donors could present a small risk to the fetus if transfused to a pregnant mother during the first trimester of pregnancy.

Effects on Dental Health
Isotretinoin-induced dryness of the mouth may increase the occurrence of dental diseases, including tooth decay, gum disease, and fungus infections. Patients should have regular dental appointments during therapy, and the use of sugarless candy or saliva substitute may be recommended to reduce the risk of dental problems.

Effects on ability to drive and use machines
Some of the adverse events associated with isotretinoin may affect the ability to drive and use machines (e.g., somnolence, dizziness, visual disturbance). Patients should be advised that they should not drive, operate machinery, or be involved in any other activities where these effects could put either themselves or others at risk. In addition, the onset of decreased night vision was sudden in some patients, and has persisted even after discontinuation of treatment. Patients should be warned of the potential occurrence of this adverse event and to be cautious when driving or operating any vehicle at night.

INTERACTIONS WITH OTHER MEDICAMENTS

- ***Alcohol:*** Excessive alcohol intake may increase triglyceride levels in patients on isotretinoin therapy. Alcohol intake should be avoided or limited in these patients.
- ***Microdosed progesterone preparations ("minipills" that do not contain an estrogen):*** These drugs may be an inadequate method of contraception as its effect may be diminished by an interaction with isotretinoin. Microdosed progesterone preparations are not suitable for use during isotretinoin therapy.
- ***Norethindrone/ethinyl estradiol:*** Isotretinoin administered at the recommended dose of 1 mg/kg/day did not result to clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone, and luteinizing hormone. However, an interaction decreasing the effectiveness of hormonal contraceptives has not been entirely ruled out for isotretinoin.
- ***Phenytoin:*** Phenytoin use is known to cause osteomalacia. There have been no clinical studies conducted to evaluate whether there is an interactive effect on bone loss between isotretinoin and phenytoin. Caution should be exercised when these drugs are concurrently administered.
- ***St. John's wort:*** Depression has occurred in some patients receiving isotretinoin. Isotretinoin may interact with hormonal contraceptives, resulting to breakthrough bleeding and pregnancies. Patients should be cautioned not to self-medicate with St. John's wort, an herbal supplement used for depression, due to its possible interaction with hormonal contraceptives.
- ***Systemic corticosteroids:*** Systemic corticosteroids are known to cause osteoporosis. Clinical studies assessing the possible interactive effect on bone less between systemic corticosteroids and isotretinoin have not been conducted. Systemic corticosteroids should be coadministered with caution in patients receiving isotretinoin.
- ***Tetracyclines***: Benign intracranial hypertension (pseudomotor cerebri) and/or papilloedema have been reported rarely after use of isotretinoin. Some of the cases involved concomitant use with tetracyclines (see Warnings and Precautions). Thus, the concomitant use of isotretinoin with tetracyclines is contraindicated.
- ***Topical keratolytic or exfoliative anti-acne agents:*** The use of isotretinoin with topical keratolytic or exfoliative anti-acne agents may increase local skin irritation. Concurrent use of these drugs is not recommended.
- ***Vitamin A:*** Patients currently on isotretinoin therapy should be advised against taking supplements containing vitamin A or its derivatives to avoid the potential of additive adverse effects and the risk of developing hypervitaminosis A.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: ***Pregnancy Category X.***
Isotretinoin is highly teratogenic and must not be given to women who are pregnant. Major congenital malformations, spontaneous abortions, and premature births have been documented following isotretinoin exposure during pregnancy. Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; and cleft palate. Documented internal abnormalities include: central nervous system abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects); thymus gland abnormality; and parathyroid hormone deficiency. Death has occurred with some cases of these abnormalities. Cases of IQ scores less than 85 with or without other abnormalities have also been reported.

Discontinue isotretinoin immediately if pregnancy occurs during treatment. The patient should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling. The risk of severe and serious malformations of the fetus remains even if pregnancy occurs following treatment discontinuations, as the risk persists until 1 month following the end of treatment.

Lactation
It is not known whether isotretinoin is excreted in human milk. Isotretinoin is highly lipophilic, thus its passage in human milk is highly probable. Due to the potential effects of the drug to the breastfed infant, isotretinoin is contraindicated in breastfeeding women.

Children
The efficacy and safety of isotretinoin in children <12 years old has not been established, thus its use in this population is not recommended. The use of isotretinoin in children 12 to 17 years old should be carefully considered, especially in patients who have known metabolic or structural bone disease. Isotretinoin may also be associated with growth retardation in prepubertal children. Increased incidence of back pain and arthralgia was observed in patients 12 to 17 years old; some of the cases were reported to be severe. Back pain occurred more frequently in female than in male patients. Appropriate evaluation of the musculoskeletal system should be performed in patients who have experienced these symptoms during or after treatment with isotretinoin. Discontinuation of treatment should be considered if any significant abnormality has occurred.

Long-term isotretinoin treatment in children <13 years should be avoided due to the risk of premature epiphyseal closure.

Elderly
Clinical studies did not include sufficient number of elderly subjects to determine whether they responded differently from younger subjects. In clinical experience, there are no observed differences in the response of younger subjects to elderly subjects. However, effects of aging might be expected to increase some risks associated with isotretinoin treatment.

Hepatic Impairment
The use of isotretinoin is contraindicated in patients with hepatic insufficiency.

Renal Impairment
Dose adjustment are necessary for patients with renal impairment (see ***Dosage and Mode of Administration***). The use of isotretinoin is contraindicated in patients with renal insufficiency.

UNDESIRABLE EFFECTS

The most commonly reported adverse effects associated with isotretinoin are dryness of the skin and of mucous membranes e.g., of the lips (cheilitis), of the nasal mucosa (epistaxis), of the pharyngeal mucosa (hoarseness), and of the eyes (conjunctivitis, corneal opacity, contact lens intolerance).

Infections and infestations: Disseminated herpes simplex, gram positive (mucocutaneous) bacterial infection, hordeolum, infection, paronychia, respiratory tract infection, skin infection
Neoplasms benign, malignant and unspecified (including cysts and polyps): Pyoderma gangrenosum, pyogenic granuloma
Blood and lymphatic system disorders: Agranulocytosis, anemia, eosinophilic pleural effusion, lymphadenopathy, neutropenia, thrombocytopenia, thrombocytosis
Immune system disorders: Allergic dermatitis, anaphylactic reaction, bronchospasm, erythema nodosum, hypersensitivity, photoallergy reaction, photosensitivity reaction, ulcerative keratitis, urticaria
Metabolism and nutrition disorders: Anorexia, decreased appetite, diabetes mellitus, edema, hypercalcemia, hypertriglyceridemia, hyperuricemia, increased appetite, thirst, weight change, weight fluctuation, weight loss, xanthoma
Psychiatric disorders: Abnormal behavior, affect lability, aggravated depression, aggression, anger, anxiety, apathy, auditory hallucinations, behavior disorder, depressed mood, depression, disturbance in attention, euphoria, feeling guilty, feeling of worthlessness, helplessness, hopelessness, impulse control disorder, insomnia, mood altered, nervousness, panic attack, psychotic disorder, sleep disorder, suicide attempt, suicidal ideation
Nervous system disorders: Abnormal dreams, benign intracranial hypertension, cerebrovascular accident, convulsion, diplopia, dizziness, Guillain-Barre syndrome, headache, idiopathic intracranial hypertension, intracranial pressure increased, paresthesia, restlessness, seizure, somnolence, tunnel vision
Eye disorders: Asthenopia, blepharitis, blurred vision, cataract, color blindness, conjunctival hemorrhage, dry eyes, eye irritation, eye pruritus, keratitis, lacrimation increased, myopia, night blindness, ocular discomfort, ocular hyperemia, optic neuritis, papilledema, photophobia, retinal hemorrhage, tear osmolarity increased, transient blindness, visual acuity reduced, visual impairment
Ear and labyrinth disorders: Hypoacusis, tinnitus
Cardiac disorders: Arrhythmia, atrial tachycardia, bundle branch block right, cardiac myositis, chest pain, myocardial infarction, palpitation, tachycardia
Vascular disorders: Epistaxis, flushing, granulomatosis with polyangiitis (Wegener's granulomatosis), hemorrhage, hypersensitivity vasculitis, syncope, thrombosis, vasculitis
Respiratory, thoracic, and mediastinal disorders: Asthma aggravated, dysphonia, nasal dryness, nasopharyngitis, pneumothorax, pulmonary embolism, pulmonary fibrosis, pulmonary granuloma, upper respiratory tract infection, wheezing
Gastrointestinal disorders: Abdominal pain, acute pancreatitis, ageusia, chapped lips, colitis, constipation, Crohn's disease, diarrhea, dry mouth, dry throat, esophagitis, esophageal ulceration, gastrointestinal disorder, gastrointestinal hemorrhage, gingival bleeding, gingival swelling, hemorrhagic colitis, hemorrhagic diarrhea, hemorrhagic pancreatitis, ileitis, inflammatory bowel disease, nausea, pancreatitis, rectal hemorrhage, ulcerative colitis, vomiting
Hepatic and hepatobiliary disorders: Hepatic steatosis, hepatitis, hepatotoxicity
Skin and subcutaneous tissue disorders: Acne aggravated, acne fulminans, alopecia, contact dermatitis, dermatitis, eczema, erythema, erythema multiforme, erythematous rash, excessive granulation tissue, facial erythema, generalized exfoliative dermatitis, hair disorder, hair texture abnormal, hirsutism, melasma, nail dystrophy, onycholysis, photosensitivity reaction, pruritus, purpura, pyogenic granuloma, rash, seborrhea, skin exfoliation, skin fragility, skin hyperpigmentation, skin hypopigmentation, Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders: Arthralgia, arthritis, back pain, bone abnormalities, bone hypertrophy, epiphyses premature fusion, exostosis, joint effusion, muscle injury, musculoskeletal pain, musculoskeletal stiffness, myalgia, myositis, neck pain, osteopenia, osteoporosis, pain in extremity, rhabdomyolysis, tendonitis
Renal and urinary disorders: Glomerulonephritis, hematuria, hypercalciuria, leukocyturia, myoglobinuria, proteinuria, urogenital disorder
Reproductive system and breast disorders: Decreased libido, ejaculation failure, erectile dysfunction, gynecomastia, menstrual disorder, sexual dysfunction, vulvovaginal dryness
General disorders and administration site conditions: Asthenia, calcinosis, fatigue, hyperhidrosis, impaired healing, irritability, lethargy, malaise, pain, suicide, xerosis
Investigations: Abnormal blood glucose level, liver function; decreased bone density, hematocrit, hemoglobin, high density lipoprotein, platelet count, red blood cell count, red blood cell parameters, reticulocyte count, white blood cell count; increased alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, bilirubin, blood cholesterol, blood creatine phosphokinase, blood glucose, blood triglycerides, erythrocyte sedimentation rate, fasting blood glucose, gamma-glutamyltransferase, lactate dehydrogenase, low density lipoprotein, platelet counts, red blood cell count, reticulocyte count, serum cholesterol, serum high density lipoprotein, serum triglycerides, serum very low density lipoprotein, total cholesterol, transaminase, uric acid; red blood cell urine positive; white blood cell urine positive
Injury, poisoning and procedural complications: Contusion, fracture, ligament sprain, limb injury, sunburn

OVERDOSE AND TREATMENT
The acute toxicity of isotretinoin is low. Signs and symptoms of acute isotretinoin overdose include headache, vomiting, facial flushing, cheilosis, abdominal pain, dizziness, and ataxia. Since isotretinoin is a derivative of vitamin A, signs of hypervitaminosis A (e.g., severe headache, nausea or vomiting, drowsiness, irritability, and pruritus) may appear in cases of overdose. Symptoms of overdose are expected to be reversible and are reported to resolve promptly without apparent residual effects and usually without treatment.

General supportive measures should be provided. Evacuation of stomach contents should be considered during the first few hours of acute isotretinoin overdose. In addition, patients should be closely monitored for signs of increased intracranial pressure.

Isotretinoin can cause teratogenic effects at any dosage. Thus, the following precautions should be performed in all female patients of childbearing potential who have taken an overdose of isotretinoin:

- At the time of overdose, pregnancy test results must be obtained. Blood sample should be collected for the determination of isotretinoin and metabolite concentrations.
- A complete menstrual cycle following the overdose, a second pregnancy test must be performed, and a second blood sample should be collected for the determination of isotretinoin and metabolite concentrations.
- Non-pregnant patients must be advised to avoid pregnancy for at least one complete menstrual cycle after the overdose and for a longer period, if necessary, until physiological plasma concentration of isotretinoin and its major metabolites are attained. Since an overdose would be expected to result in higher isotretinoin levels in semen than found during a normal treatment course, male patients should avoid reproductive sexual activity with a female patient who is or might become pregnant for 1 month after the overdose.
- Patients who have a positive pregnancy test results at the time of overdose, one complete menstrual cycle following overdose, or while isotretinoin or metabolite blood concentrations are measurable, should be fully informed on the serious risk to the fetus due to isotretinoin exposure.

All patients who had isotretinoin overdoses should be advised not to donate blood for at least 1 month.

STORAGE CONDITIONS
Store below 30°C.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Isotretinoin (Oratane®) 5 mg Soft-Gelatin Capsule: PVC / PVDC - Alu Blister pack x 10's (Box of 30's)
Isotretinoin (Oratane®)10 mg Soft-Gelatin Capsule: PVC / PVDC - Alu Blister pack x 15's (Box of 30's)
Isotretinoin (Oratane®) 20 mg Soft-Gelatin Capsule: PVC / PVDC - Alu Blister pack x 15's (Box of 30's)

Date of First Authorization: February 1, 2019
Date of Revision: November 2020
Isotretinoin (Oratane®) 5 mg Soft-Gelatin Capsule: DR-XY46471
Isotretinoin (Oratane®)10 mg Soft-Gelatin Capsule: DR-XY46470
Isotretinoin (Oratane®) 20 mg Soft-Gelatin Capsule: DR-XY46469

Manufactured by: Swiss Caps AG
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Trusted Quality Healthcare

Size: 510 x 210 mm

DATE CREATED : Oct. 13, 2020
DATE REVISED: Oct. 27, 2020
Nov. 10, 2020
Nov. 16, 2020
Nov. 20, 2020
Dec. 4, 2020
Dec. 9, 2020
by gsvillegas