DISCLAIMER

All labeling reflected on this website is for informational and promotional purposes only. It is not intended to be used by healthcare professionals or patients for the purpose of prescribing or administering these products. Questions regarding the current content of product labeling should be directed to Akorn's Customer Service department at 800.932.5676.

Myorisan® (isotretinoin capsules, USP) 10 mg, 20 mg, 30 mg, 40 mg

Rx only

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS

Myorisan must not be used by patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking Myorisan in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.

Birth defects which have been documented following Myorisan exposure include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion, and premature births have been reported.

Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted.

If pregnancy does occur during treatment of a patient who is taking Myorisan, Myorisan must be discontinued immediately and the patient should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Special Prescribing Requirements

Because of Myorisan's teratogenicity and to minimize fetal exposure, Myorisan is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called iPLEDGE®. Myorisan must only be prescribed by prescribers who are registered and activated with the iPLEDGE Program. Myorisan must only be dispensed by a pharmacy registered and activated with iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE (see **PRECAUTIONS**).

Table 1 Monthly Required iPLEDGE Interactions

	Patients Who Can Become Pregnant	Patients Who Cannot Become Pregnant
PRESCRIBER		
Confirms patient counseling	X	X
Enters the 2 contraception forms chosen by the patient	X	
Enters pregnancy test results	X	
PATIENT		
Answers educational questions before every prescription	X	
Enters 2 forms of contraception	X	
PHARMACIST		
Contacts system to get an authorization	X	X

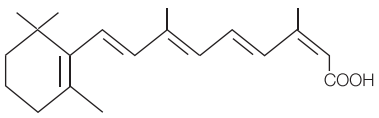
DESCRIPTION

Isotretinoin, a retinoid, is available as Myorisan in 10-mg, 20-mg, 30-mg and 40-mg soft gelatin capsules for oral administration. Each capsule contains yellow wax, butylated hydroxyanisole, edetate disodium, hydrogenated vegetable oil, tocopherol, and soybean oil. Gelatin capsules contain gelatin, glycerin and non-crystallizing sorbitol solution, with the following dye systems: 10 mg — ferric oxide (yellow) and titanium dioxide; 20 mg — titanium dioxide; 30 mg — titanium dioxide and ferric oxide (red); 40 mg — FD&C Yellow No. 6 and titanium dioxide.

The edible imprinting ink for all the capsules contains: shellac glaze, dehydrated alcohol, isopropyl alcohol, iron oxide black, N-butyl alcohol, propylene glycol, and ammonium hydroxide.

Meets USP Dissolution Test 6.

Chemically, isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and retinol (vitamin A). It is a yellow to orange crystalline powder with a molecular weight of 300.44. The structural formula is:



CLINICAL PHARMACOLOGY

Isotretinoin is a retinoid, which when administered in pharmacologic dosages of 0.5 to 1 mg/kg/day (see **DOSAGE AND ADMINISTRATION**), inhibits sebaceous gland function and keratinization. The exact mechanism of action of isotretinoin is unknown.

Nodular Acne

Clinical improvement in nodular acne patients occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is temporary and is related to the dose and duration of treatment with Myorisan, and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.[1]

Pharmacokinetics

Absorption

Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when given with a high-fat meal. In a crossover study, 74 healthy adult subjects received a single 80 mg oral dose (2 x 40 mg capsules) of Myorisan under fasted and fed conditions. Both peak plasma concentration (C_{max}) and the total exposure (AUC) of isotretinoin were more than doubled following a standardized high-fat meal when compared with Myorisan given under fasted conditions (see **Table 2**). The observed elimination half-life was unchanged. This lack of change in half-life suggests that food increases the bioavailability of isotretinoin without altering its disposition. The time to peak concentration (T_{max}) was also increased with food and may be related to a longer absorption phase. Therefore, Myorisan capsules should always be taken with food (see **DOSAGE AND ADMINISTRATION**). Clinical studies have shown that there is no difference in the pharmacokinetics of isotretinoin between patients with nodular acne and healthy subjects with normal skin.

Table 2 Pharmacokinetic Parameters of Isotretinoin Mean (%CV), N=74

Myorisan 2x40 mg Capsules	$AUC_{0-\infty}$ (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Fed*	10,004 (22%)	862 (22%)	5.3 (77%)	21 (39%)
Fasted	3,703 (46%)	301 (63%)	3.2 (56%)	21 (30%)

*Eating a standardized high-fat meal.

Distribution

Isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin.

Metabolism

Following oral administration of isotretinoin, at least three metabolites have been identified in human plasma: 4-*oxo*-isotretinoin, retinoic acid (tretinoin), and 4-*oxo*-retinoic acid (4-*oxo*-tretinoin). Retinoic acid and 13-*cis*-retinoic acid are geometric isomers and show reversible interconversion. The administration of one isomer will give rise to the other. Isotretinoin is also irreversibly oxidized to 4-*oxo*-isotretinoin, which forms its geometric isomer 4-*oxo*-tretinoin.

After a single 80 mg oral dose of Myorisan to 74 healthy adult subjects, concurrent administration of food increased the extent of formation of all metabolites in plasma when compared to the extent of formation under fasted conditions.

All of these metabolites possess retinoid activity that is in some *in vitro* models more than that of the parent isotretinoin. However, the clinical significance of these models is unknown. After multiple oral dose administration of isotretinoin to adult cystic acne patients (≥18 years), the exposure of patients to 4-oxo-isotretinoin at steady-state under fasted and fed conditions was approximately 3.4 times higher than that of isotretinoin.

In vitro studies indicate that the primary P450 isoforms involved in isotretinoin metabolism are 2C8, 2C9, 3A4, and 2B6. Isotretinoin and its metabolites are further metabolized into conjugates, which are then excreted in urine and feces.

Elimination

Following oral administration of an 80 mg dose of ^{14}C-isotretinoin as a liquid suspension, ^{14}C-activity in blood declined with a half-life of 90 hours. The metabolites of isotretinoin and any conjugates are ultimately excreted in the feces and urine in relatively equal amounts (total of 65% to 83%). After a single 80 mg oral dose of Myorisan to 74 healthy adult subjects under fed conditions, the mean ±SD elimination half-lives ($t_{1/2}$) of isotretinoin and 4-*oxo*-isotretinoin were 21 ± 8.2 hours and 24 ± 5.3 hours, respectively. After both single and multiple doses, the observed accumulation ratios of isotretinoin ranged from 0.9 to 5.43 in patients with cystic acne.

Special Patient Populations

Pediatric Patients

The pharmacokinetics of isotretinoin were evaluated after single and multiple doses in 38 pediatric patients (12 to 15 years) and 19 adult patients (≥18 years) who received Myorisan for the treatment of severe recalcitrant nodular acne. In both age groups, 4-*oxo*-isotretinoin was the major metabolite; tretinoin and 4-*oxo*-tretinoin were also observed. The dose-normalized pharmacokinetic parameters for isotretinoin following single and multiple doses are summarized in **Table 3** for pediatric patients. There were no statistically significant differences in the pharmacokinetics of isotretinoin between pediatric and adult patients.

Table 3 Pharmacokinetic Parameters of Isotretinoin Following Single and Multiple Dose Administration in Pediatric Patients, 12 to 15 Years of Age Mean (± SD), N=38*

Parameter	Isotretinoin (Single Dose)	Isotretinoin (Steady-State)
C_{max} (ng/mL)	573.25 (278.79)	731.98 (361.86)
$AUC_{(0-12)}$ (ng·hr/mL)	3033.37 (1394.17)	5082 (2184.23)
$AUC_{(0-24)}$ (ng·hr/mL)	6003.81 (2885.67)	–
T_{max} (hr) †	6 (1-24.6)	4 (0-12)
Css_{min} (ng/mL)	–	352.32 (184.44)
$T_{1/2}$ (hr)	–	15.69 (5.12)
CL/F (L/hr)	–	17.96 (6.27)

* The single and multiple dose data in this table were obtained following a nonstandardized meal that is not comparable to the high-fat meal that was used in the study in **Table 2**.

† Median (range)

In pediatric patients (12 to 15 years), the mean ± SD elimination half-lives ($t_{1/2}$) 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 for pediatric patients.

INDICATIONS AND USAGE

Severe Recalcitrant Nodular Acne

Myorisan is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition,[2] means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, Myorisan should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, Myorisan is indicated only for those patients who are not pregnant, because Myorisan can cause severe birth defects (see **Boxed CONTRAINDICATIONS AND WARNINGS**).

A single course of therapy for 15 to 20 weeks has been shown to result in complete and prolonged remission of disease in many patients.[1,3,4] 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 Myorisan. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth (see **WARNINGS: Skeletal: Bone Mineral Density, Hyperostosis, Premature Epiphyseal Closure**).

CONTRAINDICATIONS

Pregnancy: Category X. See Boxed CONTRAINDICATIONS AND WARNINGS.

Allergic Reactions

Myorisan is contraindicated in patients who are hypersensitive to this medication or to any of its components (see **PRECAUTIONS: Hypersensitivity**).

WARNINGS

Psychiatric Disorders

Myorisan may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. No mechanism of action has been established for these events (see ADVERSE REACTIONS: Psychiatric). Prescribers should read the brochure, *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin*. Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need. Therefore, prior to initiation of Myorisan therapy, patients and family members should be asked about any history of psychiatric disorder, and at each visit during therapy patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary. Signs and symptoms of depression, as described in the brochure ("Recognizing Psychiatric Disorders in Adolescents and Young Adults"), include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment. Patients should stop Myorisan and the patient or a family member should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression, without waiting until the next visit. Discontinuation of Myorisan therapy may be insufficient; further evaluation may be necessary. While such monitoring may be helpful, it may not detect all patients at risk. Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether Myorisan therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of Myorisan therapy.

Pseudotumor Cerebri

Myorisan use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines. Concomitant treatment with tetracyclines should therefore be avoided. Early signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, they should be told to discontinue Myorisan immediately and be referred to a neurologist for further diagnosis and care (see ADVERSE REACTIONS: Neurological).

Serious Skin Reactions

There have been post-marketing reports of erythema multiforme and severe skin reactions [eg, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)] associated with isotretinoin use. These events may be serious and result in death, life-threatening events, hospitalization, or disability. Patients should be monitored closely for severe skin reactions, and discontinuation of Myorisan should be considered if warranted.

Pancreatitis

Acute pancreatitis has been reported in patients with either elevated or normal serum triglyceride levels. **In rare instances, fatal hemorrhagic pancreatitis has been reported.** Myorisan should be stopped if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur.

Lipids

Elevations of serum triglycerides in excess of 800 mg/dL have been reported in patients treated with Myorisan. Marked elevations of serum triglycerides were reported in approximately 25% of patients receiving Myorisan in clinical trials. In addition, approximately 15% developed a decrease in high-density lipoproteins and about 7% showed an increase in cholesterol levels. In clinical trials, the effects on triglycerides, HDL, and cholesterol were reversible upon cessation of Myorisan therapy. Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in dose while continuing Myorisan.[5]

Blood lipid determinations should be performed before Myorisan is given and then at intervals until the lipid response to Myorisan is established, which usually occurs within 4 weeks. Especially careful consideration must be given to risk/benefit for patients who may be at high risk during Myorisan therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If Myorisan therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended (see **PRECAUTIONS: Laboratory Tests**).

The cardiovascular consequences of hypertriglyceridemia associated with Myorisan are unknown. *Animal Studies:* In rats given 8 or 32 mg/kg/day of isotretinoin (1.3 to 5.3 times the recommended clinical dose of 1 mg/kg/day after normalization for total body surface area) for 18 months or longer, the incidences of focal calcification, fibrosis and inflammation of the myocardium, calcification of coronary, pulmonary and mesenteric arteries, and metastatic calcification of the gastric mucosa were greater than in control rats of similar age. Focal endocardial and myocardial calcifications associated with calcification of the coronary arteries were observed in two dogs after approximately 6 to 7 months of treatment with isotretinoin at a dosage of 60 to 120 mg/kg/day (30 to 60 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area).

Hearing Impairment

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

Hepatotoxicity

Clinical hepatitis considered to be possibly or probably related to Myorisan therapy has been reported. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials, some of which normalized with dosage reduction or continued administration of the drug. If normalization does not readily occur or if hepatitis is suspected during treatment with Myorisan, the drug should be discontinued and the etiology further investigated.

Inflammatory Bowel Disease

Myorisan has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. In some instances, symptoms have been reported to persist after Myorisan treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue Myorisan immediately (see **ADVERSE REACTIONS: Gastrointestinal**).

Skeletal

Bone Mineral Density

Effects of multiple courses of Myorisan 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 Myorisan 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 eight of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in five patients at the lumbar spine, while the other three 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 five of eight patients (62.5%).

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

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

Hyperostosis

A high prevalence of skeletal hyperostosis was noted in clinical trials for disorders of keratinization with a mean dose of 2.24 mg/kg/day. Additionally, skeletal hyperostosis was noted in six of eight patients in a prospective study of disorders of keratinization.[6] Minimal skeletal hyperostosis and calcification of ligaments and tendons have also been observed by x-ray in prospective studies of nodular acne patients treated with a single course of therapy at recommended doses. The skeletal effects of multiple Myorisan treatment courses for acne are unknown.

In a clinical study of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, hyperostosis was not observed after 16 to 20 weeks of treatment with approximately 1 mg/kg/day of Myorisan given in two divided doses. Hyperostosis may require a longer time frame to appear. The clinical course and significance remain unknown.

Premature Epiphyseal Closure

There are spontaneous reports of premature epiphyseal closure in acne patients receiving recommended doses of Myorisan. The effect of multiple courses of Myorisan on epiphyseal closure is unknown.

Vision Impairment
Visual problems should be carefully monitored. All Myorisan patients experiencing visual difficulties should discontinue Myorisan treatment and have an ophthalmological examination (see **ADVERSE REACTIONS: Special Senses**).

Corneal Opacities
Corneal opacities have occurred in patients receiving Myorisan for acne and more frequently when higher drug dosages were used in patients with disorders of keratinization. The corneal opacities that have been observed in clinical trial patients treated with Myorisan have either completely resolved or were resolving at follow-up 6 to 7 weeks after discontinuation of the drug (see **ADVERSE REACTIONS: Special Senses**).

Decreased Night Vision
Decreased night vision has been reported during Myorisan therapy and in some instances the event has persisted after therapy was discontinued. 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 any vehicle at night.

PRECAUTIONS
Myorisan must only be prescribed by prescribers who are registered and activated with the iPLEDGE Program. Myorisan must only be dispensed by a pharmacy registered and activated with iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE. Registered and activated pharmacies must receive Myorisan only from wholesalers registered with iPLEDGE.

iPLEDGE Program requirements for wholesalers, prescribers, and pharmacists are described below:

Wholesalers:
For the purpose of the iPLEDGE Program, the term wholesaler refers to wholesaler, distributor, and/or chain pharmacy distributor. To distribute Myorisan, wholesalers must be registered with iPLEDGE, and agree to meet all iPLEDGE requirements for wholesale distribution of isotretinoin products. Wholesalers must register with iPLEDGE by signing and returning the iPLEDGE wholesaler agreement that affirms they will comply with all iPLEDGE requirements for distribution of isotretinoin. These include:

- Registering prior to distributing isotretinoin and re-registering annually thereafter
- Distributing only FDA approved isotretinoin product
- Only shipping isotretinoin to
  - wholesalers registered in the iPLEDGE Program with prior written consent from the manufacturer or
  - pharmacies licensed in the US and registered and activated in the iPLEDGE Program
- Notifying the isotretinoin manufacturer (or delegate) of any non-registered and/or non-activated pharmacy or unregistered wholesaler that attempts to order isotretinoin
- Complying with inspection of wholesaler records for verification of compliance with the iPLEDGE Program by the isotretinoin manufacturer (or delegate)
- Returning to the manufacturer (or delegate) any undistributed product if the wholesaler is deactivated by the iPLEDGE Program or if the wholesaler chooses to not re-register annually.

Prescribers:
To prescribe isotretinoin, the prescriber must be registered and activated with the pregnancy risk management program iPLEDGE. Prescribers can register by signing and returning the completed registration form. Prescribers can only activate their registration by affirming that they meet requirements and will comply with all iPLEDGE requirements by attesting to the following points:

- I know the risk and severity of fetal injury/birth defects from isotretinoin.
- I know the risk factors for unplanned pregnancy and the effective measures for avoidance of unplanned pregnancy.
- I have the expertise to provide the patient with detailed pregnancy prevention counseling, or I will refer the patient to an expert for such counseling, reimbursed by the manufacturer.
- I will comply with the iPLEDGE Program requirements described in the booklets entitled *Guide To Best Practices for the iPLEDGE Program and The iPLEDGE Program Prescriber Contraception Counseling Guide*.
- Before beginning treatment of patients who can become pregnant with isotretinoin, and on a monthly basis, the patient will be counseled to avoid pregnancy by using two forms of contraception simultaneously and continuously for at least one month prior to initiation of isotretinoin treatment, during isotretinoin treatment and for one month after discontinuing isotretinoin treatment, unless the patient commits to continuous abstinence, not having any sexual contact with a partner that could result in pregnancy.
- I will not prescribe isotretinoin to any patients who can become pregnant until verifying the patient has a negative screening pregnancy test and monthly negative CLIA-certified (Clinical Laboratory Improvement Amendment) pregnancy tests. Patients should have a pregnancy test at the completion of the entire course of isotretinoin and another pregnancy test one month later.
- I will report any pregnancy case that I become aware of while the patient who can become pregnant is on isotretinoin or 1 month after the last dose to the pregnancy registry.

To prescribe isotretinoin, the prescriber must access the iPLEDGE system via the internet (www.ipledgeprogram.com) or telephone (1-866-495-0654) to:

1) Register each patient in the iPLEDGE Program.
2) Confirm monthly that each patient has received counseling and education.
3) For *patients who can become pregnant:*

- Enter patient's two chosen forms of contraception each month.
- Enter monthly result from CLIA-certified laboratory conducted pregnancy test.

Isotretinoin must only be prescribed to patients who are known not to be pregnant as confirmed by a negative CLIA-certified laboratory conducted pregnancy test.

Isotretinoin must only be dispensed by a pharmacy registered and activated with the pregnancy risk management program iPLEDGE and only when the registered patient meets all the requirements of the iPLEDGE Program. Meeting the requirements for a patient who can become pregnant signifies the patient:

- Has been counseled and has signed a Patient Information/Informed Consent About Birth Defects (for patients who can get pregnant) form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin. The patient must sign the informed consent form before starting treatment and patient counseling must also be done at that time and on a monthly basis thereafter.
- Has had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial isotretinoin prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for isotretinoin. The second pregnancy test (a confirmation test) must be done in a CLIA-certified laboratory. The interval between the two tests should be at least 19 days.
  - For patients with regular menstrual cycles, the second pregnancy test should be done during the first 5 days of the menstrual period immediately preceding the beginning of isotretinoin therapy and after the patient has used two forms of contraception for one month.
  - For patients with amenorrhea, irregular cycles, or using a contraceptive form that precludes withdrawal bleeding, the second pregnancy test must be done immediately preceding the beginning of isotretinoin therapy and after the patient has used two forms of contraception for one month.
- Has had a negative result from a urine or serum pregnancy test in a CLIA-certified laboratory before receiving each subsequent course of isotretinoin. A pregnancy test must be repeated every month, in a CLIA-certified laboratory, prior to the patient who can become pregnant receiving each prescription.
- Has selected and has committed to use two forms of effective contraception simultaneously, at least one of which must be a primary form, unless the patient commits to continuous abstinence not having any sexual contact with a partner that could result in pregnancy, or the patient has undergone a hysterectomy or bilateral oophorectomy, or has been medically confirmed to be post-menopausal. Patients must use two forms of effective contraception for at least one month prior to initiation of isotretinoin therapy, during isotretinoin therapy, and for one month after discontinuing isotretinoin therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis.

If the patient has unprotected sexual contact with a partner that could result in pregnancy at any time one month before, during, or one month after therapy, the patient must:

1. Stop taking Myorisan immediately, if on therapy
2. Have a pregnancy test at least 19 days after the last act of unprotected sexual contact with a partner that could result in pregnancy.
3. Start using two forms of effective contraception simultaneously again for one month before resuming Myorisan therapy
4. Have a second pregnancy test after using two forms of effective contraception for one month as described above depending on whether the partner has regular menses or not.

Effective forms of contraception include both primary and secondary forms of contraception:

Primary forms
- tubal sterilization
- male vasectomy
- intrauterine device
- hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring)

Secondary forms
Barrier:
- male latex condom with or without spermicide
- diaphragm with spermicide
- cervical cap with spermicide

Other:
- vaginal sponge (contains spermicide)

Any birth control method can fail. There have been reports of pregnancy from patients who can become pregnant who have used oral contraceptives, as well as transdermal patch/injectable/implantable/vaginal hormonal birth control products; these pregnancies occurred while these patients were taking Myorisan. These reports are more frequent for patients who use only a single form of contraception. Therefore, it is critically important that patients who can become pregnant use two effective forms of contraception simultaneously. Patients must receive written warnings about the rates of possible contraception failure (included in patient education kits).

Using two forms of contraception simultaneously substantially reduces the chances that a patient will become pregnant over the risk of pregnancy with either form alone. A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for Myorisan (see **PRECAUTIONS: Drug Interactions**). Although hormonal contraceptives are highly effective, prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.

Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because 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.

If a pregnancy does occur during Myorisan treatment, Myorisan must be discontinued immediately. The patient should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure during or one month after Myorisan therapy must be reported immediately to the FDA via the MedWatch number 1-800-FDA-1088 and also to the iPLEDGE pregnancy registry at 1-866-495-0654 or via the internet (www.ipledgeprogram.com).

All Patients
Isotretinoin is contraindicated in patients who are pregnant. To receive isotretinoin all patients must meet all of the following conditions:

- Must be registered with the iPLEDGE Program by the prescriber
- Must understand that severe birth defects can occur with the use of isotretinoin by patients who can become pregnant
- Must be reliable in understanding and carrying out instructions
- Must sign a Patient Information/Informed Consent (for all patients) form that contains warnings about the potential risks associated with isotretinoin
- Must obtain the prescription within 7 days of the date of specimen collection for the pregnancy test for patients who can become pregnant
- Must obtain the prescription within 30 days of the office visit for patients who cannot become pregnant
- Must not donate blood while on isotretinoin and for one month after treatment has ended
- Must not share isotretinoin with anyone, even someone who has similar symptoms

Patients Who Can Become Pregnant
Isotretinoin is contraindicated in patients who are pregnant. In addition to the requirements for all patients described above, patients who can become pregnant must meet the following conditions:

- Must NOT be pregnant or breast-feeding
- Must comply with the required pregnancy testing at a CLIA-certified laboratory
- Must obtain the prescription within 7 days of the date of specimen collection for the pregnancy test
- Must be capable of complying with the mandatory contraceptive measures required for isotretinoin therapy, or commit to continuous abstinence not having any sexual contact with a partner that could result in pregnancy, and understand bechaiors associated with an increased risk of pregnancy
- Must understand that it is the patient who can become pregnant responsibility to avoid pregnancy one month before, during and one month after isotretinoin therapy
- Must have signed an additional Patient Information/Informed Consent About Birth Defects (for patients who can get pregnant) form, before starting isotretinoin, that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin
- Must access the iPLEDGE system via the internet (www.ipledgeprogram.com) or telephone (1-866-495-0654), before starting isotretinoin, on a monthly basis during therapy, and one month after the last dose to answer questions on the program requirements and to enter the patient's two chosen forms of contraception
- Must have been informed of the purpose and importance of providing information to the iPLEDGE Program should the partient become pregnant while taking isotretinoin or within one month of the last dose

Pharmacists:
To dispense isotretinoin, pharmacies must be registered and activated with the pregnancy risk management program iPLEDGE.

The Responsible Site Pharmacist must register the pharmacy by signing and returning the completed registration form. After registration, the Responsible Site Pharmacist can only activate the pharmacy registration by affirming that they meet requirements and will comply with all iPLEDGE requirements by attesting to the following points:

- I know the risk and severity of fetal injury/birth defects from isotretinoin.
- I will train all pharmacists, who participate in the filling and dispensing of isotretinoin prescriptions, on the iPLEDGE Program requirements.
- I will comply and seek to ensure all pharmacists who participate in the filling and dispensing of isotretinoin prescriptions comply with the iPLEDGE Program requirements described in the booklet entitled *Pharmacist Guide*, specifically the "Key Information for Pharmacists" section including the following dispensing information:
  - Prescriptions must be obtained no later than the "Do Not Dispense To After" date, and if not obtained, then the RMA must be reversed in the iPLEDGE Program system and the product returned to inventory.
- I will only obtain Myorisan product from iPLEDGE registered wholesalers.
- I will not sell, buy, borrow, loan or otherwise transfer isotretinoin in any manner to or from another pharmacy.
- I will return to the manufacturer (or delegate) any unused product if the pharmacy is deactivated by the iPLEDGE Program or if the pharmacy chooses not to reactivate annually.
- I will not fill isotretinoin for any party other than a qualified patient.

To dispense isotretinoin, the pharmacist must:

1) be trained by the Responsible Site Pharmacist concerning the iPLEDGE Program requirements.
2) obtain authorization from the iPLEDGE Program via the internet (www.ipledgeprogram.com), telephone (1-866-495-0654) or through electronic telecommunication verification (via submission of an isotretinoin prescription claim) for every isotretinoin prescription. Authorization signifies that the patient has met all program requirements and is qualified to receive Myorisan.
3) write the Risk Management Authorization (RMA) number on the prescription.

Myorisan must only be dispensed:

- in no more than a 30-day supply
- with a Myorisan Medication Guide
- after authorization from the iPLEDGE Program
- prior to the "do not dispense to patient after" date provided by the iPLEDGE system (within 30 days of the office visit for patients who cannot become pregnant and within 7 days of the date of specimen collection for patients who can become pregnant)
- with a new prescription for refills and another authorization from the iPLEDGE Program (No automatic refills are allowed)

A Myorisan Medication Guide must be given to the patient each time Myorisan is dispensed, as required by law. This Myorisan Medication Guide is an important part of the risk management program for the patients.

Myorisan must not be prescribed, dispensed or otherwise obtained through the internet or any other means outside of the iPLEDGE Program. Only FDA-approved Myorisan products must be distributed, prescribed, dispensed, and used. Patients must obtain Myorisan prescriptions only at US licensed pharmacies.

A description of the iPLEDGE Program educational materials available with iPLEDGE is provided below. The main goal of these educational materials is to explain the iPLEDGE Program requirements and to reinforce the educational messages.

1) *Guide to Best Practices for the iPLEDGE Program* includes: isotretinoin teratogenic potential, information on pregnancy testing, and the method to complete a qualified Myorisan prescription.
2) *Prescriber Contraception Counseling Guide* includes: specific information about effective contraception, the limitations of contraceptive methods, behaviors associated with an increased risk of contraceptive failure and pregnancy and the forms to evaluate pregnancy risk.
3) *Pharmacist Guide* includes: isotretinoin teratogenic potential and the method to obtain authorization to dispense an isotretinoin prescription.
4) The iPLEDGE Program is a systematic approach to comprehensive patient education about their responsibilities and includes education for contraception compliance and reinforcement of educational messages. The iPLEDGE Program includes information on the risks and benefits of isotretinoin which is linked to the Medication Guide dispensed by pharmacists with each Myorisan prescription.
5) Patients who cannot become pregnant, and patients who cannot become pregnant are provided with separate booklets. Each booklet contains information on isotretinoin therapy including precautions and warnings, a Patient Information/Informed Consent (for all patients) form, and a toll-free line which provides Myorisan information in two languages.
6) The booklet for patients who cannot become pregnant, *Guide to Isotretinoin for Patients Who Cannot Get Pregnant*, also includes information about male reproduction and a warning not to share isotretinoin with others or to donate blood during Myorisan therapy and for one month following discontinuation of isotretinoin.
7) The booklet for patients who can become pregnant, *Guide to Isotretinoin for Patients Who Can Get Pregnant*, includes a referral program that offers patients free contraception counseling, reimbursed by the manufacturer, by a reproductive specialist; and a second Patient Information/Informed Consent About Birth Defects (for patients who can get pregnant) form concerning birth defects.
8) The booklet, *Birth Control Workbook* includes information on the types of contraceptive forms, the selection and use of appropriate, effective contraception, the rates of possible contraceptive failure and a toll-free contraception counseling line.
9) In addition to the booklets, patient educational materials also include the *iPLEDGE Program Birth Control Information Sheet* and the following videos - "Be Prepared, Be Protected" and "Be Aware: The Risk of Pregnancy While on Isotretinoin" (see **Information for Patients**).

General
Although an effect of Myorisan on bone loss is not established, physicians should use caution when prescribing Myorisan to patients with a genetic predisposition for age-related osteoporosis, a history of childhood osteoporosis conditions, osteomalacia, or other disorders of bone metabolism. This would include patients diagnosed with anorexia nervosa and those who are on chronic drug therapy that causes drug-induced osteoporosis/osteomalacia and/or affects vitamin D metabolism, such as systemic corticosteroids and any anticonvulsant.

Patients may be at increased risk when participating in sports with repetitive impact where the risks of spondylolisthesis with and without pars fractures and hip growth plate injuries in early and late adolescence are known. There are spontaneous reports of fractures and/or delayed healing in patients while on therapy with Myorisan or following cessation of therapy with Myorisan while involved in these activities. While causality to Myorisan has not been established, an effect must not be ruled out.

Information for Patients
See **PRECAUTIONS** and **Boxed CONTRAINDICATIONS AND WARNINGS**.

- Patients must be instructed to read the Medication Guide supplied as required by law when Myorisan is dispensed. The complete text of the Medication Guide is reprinted at the end of this document. For additional information, patients must also be instructed to read the iPLEDGE Program patient educational materials. All patients must sign the Patient Information/Informed Consent (for all patients) form.

- Patients who can become pregnant must be instructed that they must not be pregnant when Myorisan therapy is initiated, and that they should use two forms of effective contraception simultaneously for one month before starting Myorisan, while taking Myorisan, and for one month after Myorisan has been stopped, unless they commit to continuous abstinence not having any sexual contact with a partner that could result in pregnancy. They should also sign a second Patient Information/Informed Consent About Birth Defects (for patients who can get pregnant) form prior to beginning Myorisan therapy. They should be given an opportunity to view the patient video provided by the manufacturer to the prescriber. The video includes information about contraception, the most common reasons that contraception fails, and the importance of using two forms of effective contraception when taking teratogenic drugs and comprehensive information about types of potential birth defects which could occur if a patient who is pregnant takes Myorisan at any time during pregnancy. Patients who can become pregnant should be seen by their prescribers monthly and have a urine or serum pregnancy test, in a CLIA-certified laboratory, performed each month during treatment to confirm negative pregnancy status before another Myorisan prescription is written (see **Boxed CONTRAINDICATIONS AND WARNINGS** and **PRECAUTIONS**).
- Myorisan is found in the semen of male patients taking Myorisan, but the amount delivered to a patient who can become pregnant would be about one million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin induced embryopathy is unknown, 20 years of postmarketing reports include four with isolated defects compatible with features of retinoid exposed fetuses; however two of these reports were incomplete, and two had other possible explanations for the defects observed.
- Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need. Therefore, prior to initiation of Myorisan treatment, patients and family members should be asked about any history of psychiatric disorder, and at each visit during treatment patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary. **Signs and symptoms of depression include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment.** Patients should stop Myorisan and the patient or a family member should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression, without waiting until the next visit. Discontinuation of Myorisan treatment may be insufficient; further evaluation may be necessary. While such monitoring may be helpful, it may not detect all patients at risk. Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether Myorisan therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of Myorisan therapy.
- Patients must be informed that some patients, while taking Myorisan or soon after stopping Myorisan, have become depressed or developed other serious mental problems. Symptoms of depression include sad, "anxious" or empty mood, irritability, acting on dangerous impulses, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating. Some patients taking isotretinoin have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on isotretinoin becoming aggressive or violent. No one knows if Myorisan caused these behaviors or if they would have happened even if the person did not take Myorisan. Some people have had other signs of depression while taking Myorisan.
- Patients must be informed that they must not share Myorisan with anyone else because of the risk of birth defects and other serious adverse events.
- Patients must be informed not to donate blood during therapy and for one month following discontinuation of the drug because the blood might be given to a pregnant patient whose fetus must not be exposed to Myorisan.
- Patients should be reminded to take Myorisan with a meal (see **DOSAGE AND ADMINISTRATION**). To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid.
- Patients should be informed that transient exacerbation (flare) of acne has been seen, generally during the initial period of therapy.
- Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during Myorisan therapy and for at least 6 months thereafter due to the possibility of scarring (see **ADVERSE REACTIONS: Skin and Appendages**).
- Patients should be advised to avoid prolonged exposure to UV rays or sunlight.
- Patients should be informed that they may experience decreased tolerance to contact lenses during and after therapy.
- Patients should be informed that approximately 16% of patients treated with Myorisan in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of the drug. Transient pain in the chest has been reported less frequently. In the clinical trial, these symptoms generally cleared rapidly after discontinuation of Myorisan, but in some cases persisted (see **ADVERSE REACTIONS: Musculoskeletal**). There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity (see **Laboratory Tests: CPK**).
- Pediatric patients and their caregivers should be informed that approximately 29% (104/358) of pediatric patients treated with Myorisan developed back pain. Back pain was severe in 13.5% (14/104) of the cases and occurred at a higher frequency in female patients than male patients. Arthralgias were experienced in 22% (79/358) of pediatric patients. Arthralgias were severe in 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system should be done in patients who present with these symptoms during or after a course of Myorisan. Consideration should be given to discontinuation of Myorisan if any significant abnormality is found.
- Neutropenia and rare cases of agranulocytosis have been reported. Myorisan should be discontinued if clinically significant decreases in white cell counts occur.
- Patients should be advised that severe skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported in post-marketing data. Myorisan should be discontinued if clinically significant skin reactions occur.

Hypersensitivity

Anaphylactic reactions and other allergic reactions have been reported. Cutaneous allergic reactions and serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement (including renal) have been reported. Severe allergic reaction necessitates discontinuation of therapy and appropriate medical management.

Drug Interactions

- *Vitamin A:* Because of the relationship of Myorisan to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.
- *Tetracyclines:* Concomitant treatment with Myorisan and tetracyclines should be avoided because Myorisan use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines.
- *Micro-dosed Progesterone Preparations:* Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) may be an inadequate method of contraception during Myorisan therapy. Although other hormonal contraceptives are highly effective, there have been reports of pregnancy from patients who can become pregnant who have used combined oral contraceptives, as well as transdermal patch/injectable/implantable/vaginal ring hormonal birth control products. These reports are more frequent for patients who can become pregnant who use only a single form of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Myorisan. Therefore, it is critically important for patients who can become pregnant to select and commit to use two forms of effective contraception simultaneously, at least one of which must be a primary form (see **PRECAUTIONS**).
- *Norethindrone/ethinyl estradiol:* In a study of 31 premenopausal female patients with severe recalcitrant nodular acne receiving OrthoNovum® 7/7/7 Tablets as an oral contraceptive agent, Myorisan at the recommended dose of 1 mg/kg/day, did not induce clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Prescribers are advised to consult the package insert of medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.
- *St. John's Wort:* **Myorisan use is associated with depression in some patients** (see **WARNINGS: Psychiatric Disorders** and **ADVERSE REACTIONS: Psychiatric**). Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because 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.
- *Phenytoin:* Myorisan 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 is 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 Myorisan. Therefore, caution should be exercised when using these drugs together.
- *Systemic Corticosteroids:* 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 Myorisan. Therefore, caution should be exercised when using these drugs together.

Laboratory Tests

- *Pregnancy Test:*
  - Patients who can become pregnant must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Myorisan prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Myorisan. The second pregnancy test (a confirmation test) must be done in a CLIA-certified laboratory. The interval between the two tests must be at least 19 days.
  - For patients with regular menstrual cycles, the second pregnancy test must be done during the first 5 days of the menstrual period immediately preceding the beginning of Myorisan therapy and after the patient has used 2 forms of contraception for 1 month.
  - For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, the second pregnancy test must be done immediately preceding the beginning of Myorisan therapy and after the patient has used 2 forms of contraception for 1 month.
  - Each month of therapy, patients must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated each month, in a CLIA-certified laboratory, prior to the patient who can become pregnant receiving each prescription.
- *Lipids:* Pretreatment and follow-up blood lipids should be obtained under fasting conditions. After consumption of alcohol, at least 36 hours should elapse before these determinations are made. It is recommended that these tests be performed at weekly or biweekly intervals

until the lipid response to Myorisan is established. The incidence of hypertriglyceridemia is one patient in four on Myorisan therapy (see **WARNINGS: Lipids**).

- *Liver Function Tests:* Since elevations of liver enzymes have been observed during clinical trials, and hepatitis has been reported, pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to Myorisan has been established (see **WARNINGS: Hepatotoxicity**).
- *Glucose:* Some patients receiving Myorisan have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during Myorisan therapy, although no causal relationship has been established.
- *CPK:* Some patients undergoing vigorous physical activity while on Myorisan therapy have experienced elevated CPK levels; however, the clinical significance is unknown. There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity. In a clinical trial of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, transient elevations in CPK were observed in 12% of patients, including those undergoing strenuous physical activity in association with reported musculoskeletal adverse events such as back pain, arthralgia, limb injury, or muscle sprain. In these patients, approximately half of the CPK elevations returned to normal within 2 weeks and half returned to normal within 4 weeks. No cases of rhabdomyolysis were reported in this trial.

Carcinogenesis, Mutagenesis and Impairment of Fertility
In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day (1.3 to 5.3 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area) for greater than 18 months, there was a dose-related increased incidence of pheochromocytoma relative to controls. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this tumor to the human population is uncertain.

The Ames test was conducted with isotretinoin in two laboratories. The results of the tests in one laboratory were negative while in the second laboratory a weakly positive response (less than 1.6x background) was noted in *S. typhimurium* TA100 when the assay was conducted with metabolic activation. No dose response effect was seen and all other strains were negative. Additionally, other tests designed to assess genotoxicity (Chinese hamster cell assay, mouse micronucleus test, *S. cerevisiae* D7 assay, *in vitro* clastogenesis assay with human-derived lymphocytes, and unscheduled DNA synthesis assay) were all negative.

In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of isotretinoin of 2, 8, or 32 mg/kg/day (0.3, 1.3, or 5.3 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area).

In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area). 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 of 66 men, 30 of whom were patients with nodular acne under treatment with oral isotretinoin, no significant changes were noted in the count or motility of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years) receiving Myorisan therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose.

Pregnancy: Category X. See Boxed CONTRAINDICATIONS AND WARNINGS.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because of the potential for adverse effects, nursing mothers should not receive Myorisan.

Pediatric Use
The use of Myorisan in pediatric patients less than 12 years of age has not been studied. The use of Myorisan for the treatment of severe recalcitrant nodular acne in pediatric patients ages 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists (see **PRECAUTIONS: General**). Use of Myorisan in this age group for severe recalcitrant nodular acne is supported by evidence from a clinical study comparing 103 pediatric patients (13 to 17 years) to 197 adult patients (≥18 years). Results from this study demonstrated that Myorisan, at a dose of 1 mg/kg/day given in two divided doses, was equally effective in treating severe recalcitrant nodular acne in both pediatric and adult patients.

In studies with Myorisan, adverse reactions reported in pediatric patients were similar to those described in adults except for the increased incidence of back pain and arthralgia (both of which were sometimes severe) and myalgia in pediatric patients (see **ADVERSE REACTIONS**).

In an open-label clinical trial (N=217) of a single course of therapy with Myorisan 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 eight of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in five patients at the lumbar spine, while the other three 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 five of eight patients (62.5%).

In a separate open-label extension study of ten patients, ages 13 to 18 years, who started a second course of Myorisan 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25% (see **WARNINGS: Skeletal: Bone Mineral Density**).

Geriatric Use
Clinical studies of isotretinoin did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Although reported clinical experience has not identified differences in responses between elderly and younger patients, effects of aging might be expected to increase some risks associated with isotretinoin therapy (see **WARNINGS** and **PRECAUTIONS**).

ADVERSE REACTIONS

Clinical Trials and Postmarketing Surveillance
The adverse reactions listed below reflect the experience from investigational studies of Myorisan, and the postmarketing experience. The relationship of some of these events to Myorisan therapy is unknown. Many of the side effects and adverse reactions seen in patients receiving Myorisan are similar to those described in patients taking very high doses of vitamin A (dryness of the skin and mucous membranes, eg, of the lips, nasal passage, and eyes).

Dose Relationship
Cheilitis and hypertriglyceridemia are usually dose related. Most adverse reactions reported in clinical trials were reversible when therapy was discontinued; however, some persisted after cessation of therapy (see **WARNINGS** and **ADVERSE REACTIONS**).

Body as a Whole
allergic reactions, including vasculitis, systemic hypersensitivity (see **PRECAUTIONS: Hypersensitivity**), edema, fatigue, lymphadenopathy, weight loss.

Cardiovascular
palpitation, tachycardia, vascular thrombotic disease, stroke.

Endocrine/Metabolic
hypertriglyceridemia (see **WARNINGS: Lipids**), alterations in blood sugar levels (see **PRECAUTIONS: Laboratory Tests**).

Gastrointestinal
inflammatory bowel disease (see **WARNINGS: Inflammatory Bowel Disease**), hepatitis (see **WARNINGS: Hepatotoxicity**), pancreatitis (see **WARNINGS: Lipids**), bleeding and inflammation of the gums, colitis, esophagitis/esophageal ulceration, ileitis, nausea, other nonspecific gastrointestinal symptoms.

Hematologic
allergic reactions (see **PRECAUTIONS: Hypersensitivity**), anemia, thrombocytopenia, neutropenia, rare reports of agranulocytosis (see **PRECAUTIONS: Information for Patients**). See **PRECAUTIONS: Laboratory Tests** for other hematological parameters.

Musculoskeletal
skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, decreases in bone mineral density (see **WARNINGS: Skeletal**), musculoskeletal symptoms (sometimes severe) including back pain, myalgia, and arthralgia (see **PRECAUTIONS: Information for Patients**), transient pain in the chest (see **PRECAUTIONS: Information for Patients**), arthritis, tendonitis, other types of bone abnormalities, elevations of CPK/rare reports of rhabdomyolysis (see **PRECAUTIONS: Laboratory Tests**).

Neurological
pseudotumor cerebri (see **WARNINGS: Pseudotumor Cerebri**), dizziness, drowsiness, headache, insomnia, lethargy, malaise, nervousness, paresthesias, seizures, stroke, syncope, weakness.

Psychiatric
suicidal ideation, suicide attempts, suicide, depression, psychosis, aggression, violent behaviors (see **WARNINGS: Psychiatric Disorders**), emotional instability.

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

Reproductive System
Abnormal menses.

Respiratory
bronchospasms (with or without a history of asthma), respiratory infection, voice alteration.

Skin and Appendages
acne fulminans, alopecia (which in some cases persists), bruising, cheilitis (dry lips), dry mouth, dry nose, dry skin, epistaxis, eruptive xanthomas,[7] erythema multiforme, flushing, fragility of skin, hair abnormalities, hirsutism, hyperpigmentation and hypopigmentation, infections (including disseminated herpes simplex), nail dystrophy, paronychia, peeling of palms and soles, photoallergic/photosensitizing reactions, pruritus, pyogenic granuloma, rash (including facial erythema, seborrhea, and eczema), Stevens-Johnson syndrome, sunburn susceptibility increased, sweating, toxic epidermal necrolysis, urticaria, vasculitis (including Wegener's granulomatosis; see **PRECAUTIONS: Hypersensitivity**), abnormal wound healing (delayed healing or exuberant granulation tissue with crusting; see **PRECAUTIONS: Information for Patients**).

Special Senses

Hearing
hearing impairment (see **WARNINGS: Hearing Impairment**), tinnitus.

Vision
corneal opacities (see **WARNINGS: Corneal Opacities**), decreased night vision which may persist (see **WARNINGS: Decreased Night Vision**), cataracts, color vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic neuritis, photophobia, visual disturbances.

Urinary System
glomerulonephritis (see **PRECAUTIONS: Hypersensitivity**), nonspecific urogenital findings (see **PRECAUTIONS: Laboratory Tests** for other urological parameters).

Laboratory
Elevation of plasma triglycerides (see **WARNINGS: Lipids**), decrease in serum high-density lipoprotein (HDL) levels, elevations of serum cholesterol during treatment.

Increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGTP or LDH (see **WARNINGS: Hepatotoxicity**).

Elevation of fasting blood sugar, elevations of CPK (see **PRECAUTIONS: Laboratory Tests**), hyperuricemia.

Decreases in red blood cell parameters, decreases in white blood cell counts (including severe neutropenia and rare reports of agranulocytosis; see **PRECAUTIONS: Information for Patients**), elevated sedimentation rates, elevated platelet counts, thrombocytopenia.

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

OVERDOSAGE

The oral LD50 of isotretinoin is greater than 4000 mg/kg in rats and mice (>600 times the recommended clinical dose of 1 mg/kg/day after normalization of the rat dose for total body surface area and >300 times the recommended clinical dose of 1 mg/kg/day after normalization of the mouse dose for total body surface area) and is approximately 1960 mg/kg in rabbits (653 times the recommended clinical dose of 1 mg/kg/day after normalization for total body surface area). In humans, overdosage has been associated with vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness, and ataxia. These symptoms quickly resolve without apparent residual effects.

Myorisan causes serious birth defects at any dosage (see **Boxed CONTRAINDICATIONS AND WARNINGS**). Patients who can become pregnant who present with isotretinoin overdose must be evaluated for pregnancy. Patients who are pregnant should receive counseling about the risks to the fetus, as described in the **Boxed CONTRAINDICATIONS AND WARNINGS**. Non-pregnant patients must be warned to avoid pregnancy for at least one month and receive contraceptive counseling as described in **PRECAUTIONS**. Educational materials for such patients can be obtained by calling the manufacturer. 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 one month after the overdose. All patients with isotretinoin overdose should not donate blood for at least one month.

DOSAGE AND ADMINISTRATION

Myorisan should be administered with a meal (see **PRECAUTIONS: Information for Patients**).

The recommended dosage range for Myorisan is 0.5 to 1 mg/kg/day given in two divided doses with food for 15 to 20 weeks. In studies comparing 0.1, 0.5, and 1 mg/kg/day,[8] it was found that all dosages provided initial clearing of disease, but there was a greater need for retreatment with the lower dosages. During treatment, the dose may be adjusted according to response of the disease and/or the appearance of clinical side effects — some of which may be dose related. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 2 mg/kg/day, as tolerated. Failure to take Myorisan with food will significantly decrease absorption. Before upward dose adjustments are made, the patients should be questioned about their compliance with food instructions.

The safety of once daily dosing with Myorisan has not been established. Once daily dosing is **not** recommended.

If the total nodule count has been reduced by more than 70% prior to completing 15 to 20 weeks of treatment, the drug may be discontinued. After a period of 2 months or more off therapy, and if warranted by persistent or recurring severe nodular acne, a second course of therapy may be initiated. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth. Long-term use of Myorisan, even in low doses, has not been studied, and is not recommended. It is important that Myorisan be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of Myorisan on bone loss is unknown (see **WARNINGS: Skeletal: Bone Mineral Density, Hyperostosis, and Premature Epiphyseal closure**).

Contraceptive measures must be followed for any subsequent course of therapy (see **PRECAUTIONS**).

Table 4 Myorisan Dosing by Body Weight (Based on Administration With Food)

Body Weight		Total mg/day		
kilograms	pounds	0.5 mg/kg	1 mg/kg	2 mg/kg*
40	88	20	40	80
50	110	25	50	100
60	132	30	60	120
70	154	35	70	140
80	176	40	80	160
90	198	45	90	180
100	220	50	100	200

*See **DOSAGE AND ADMINISTRATION**: the recommended dosage range is 0.5 to 1 mg/kg/day.

INFORMATION FOR PHARMACISTS

Access the iPLEDGE Program system via the internet (www.ipledgeprogram.com), telephone (1-866-495-0654) or through electronic communication verification (via submission of an isotretinoin prescription claim) to obtain an authorization and the "**do not dispense to patient after**"date. Myorisan must only be dispensed in no more than a 30-day supply.

REFILLS REQUIRE A NEW PRESCRIPTION AND A NEW AUTHORIZATION FROM THE iPLEDGE SYSTEM.

A Myorisan Medication Guide must be given to the patient each time Myorisan is dispensed, as required by law. This Myorisan Medication Guide is an important part of the risk management program for the patient.

HOW SUPPLIED

Soft gelatin capsules, 10 mg (pale yellow), imprinted in black ink with "V10". Boxes of 30 containing 3 Prescription Packs of 10 capsules (NDC 61748-301-13). Boxes of 100 containing 10 Prescription Packs of 10 capsules (NDC 61748-301-11). Soft gelatin capsules, 20 mg (white to slight pink), imprinted in black ink with "V20". Boxes of 30 containing 3 Prescription Packs of 10 capsules (NDC 61748-302-13). Boxes of 100 containing 10 Prescription Packs of 10 capsules (NDC 61748-302-11). Soft gelatin capsules, 30 mg (pink), imprinted in black ink with "V30". Boxes of 30 containing 3 Prescription Packs of 10 capsules (NDC 61748-303-13). Boxes of 100 containing 10 Prescription Packs of 10 capsules (NDC 61748-303-11). Soft gelatin capsules, 40 mg (orange), imprinted in black ink with "V40". Boxes of 30 containing 3 Prescription Packs of 10 capsules (NDC 61748-304-13). Boxes of 100 containing 10 Prescription Packs of 10 capsules (NDC 61748-304-11).

Storage
Store at 20°-25°C (68° to 77°F). [See USP controlled room temperature]. Protect from light.

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