HIGHLIGHTS OF PRESCRIBING

FORMATION These highlights do not include all the needed to use ISOTRETINOIN APSULES safely and effectively. See ful prescribing information for ISOTRETINOIN CAPSULES

ehavior, and aggressive and/or violent

assess for these conditions; stop if these

Intracranial Hypertension (Pseudotumor

Cerebri): Avoid use with concomitant

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and other

Acute Pancreatitis: If occurs, discontinue

Lipid Abnormalities (hypertriglyceridemia

low HDL, and elevation of cholesterol):

Monitor lipid levels at regular intervals

tests prior to and during therapy (5.10,

Inflammatory Bowel Disease: Discontinue

rthralgias, back pain, decreases in bone

mineral density and premature epiphyseal

opacities, decreased night vision: If visual symptoms occur, discontinue and refer

for abdominal pain, rectal bleeding, or severe diarrhea (5.11)

Musculoskeletal Abnormalities

Ocular Abnormalities e.g., corneal

for an ophthalmological exam (5.13)

≥ 5%) are: dry lips, dry skin, back pain

dry eye, arthralgia, epistaxis, headache

creased creatine kinase, cheilitis

nusculoskeletal discomfort, uppe

To report SUSPECTED ADVERSE

medwatch or iPLEDGE at

1-866-495-0654).

REACTIONS, contact Upsher-Sm

nasopharyngitis, chapped lips, dermatitis

espiratory tract infection, reduced visual

Laboratories, LLC at 1-855-899-9180 or

FDA at 1-800-FDA-1088 or www.fda.gov/

--- DRUG INTERACTIONS --

Vitamin A: may cause additive adverse

Tetracyclines: avoid concomitant use

-- USE IN SPECIFIC POPULATIONS ----

Lactation: Breastfeeding not recommended

See Section 17 for PATIENT COUNSELING

Revised: 01/2020

INFORMATION and Medication Guide

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Pregnancy

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stop if hypertriglyceridemia cannot b

refer to specialized care (5.9)

Serious Skin Reactions: Monitor for

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serious skin reactions (5.6)

treatment (5.7

controlled (5.8)

closure (5.12)

conditions occur on therapy (5.4)

viors): Prior to and during therapy

<u>Psychiatric Disorders</u> (depression)

psychosis, suicidal thoughts and

ISOTRETINGIN capsules, for oral use Initial U.S. Approval: 1982

WARNING: EMBRYO-FFTAL TOXICITY CONTRAINDICATED IN PREGNANCY See full prescribing information for

complete boxed warning. lsotretinoin capsules can caus life-threatening birth defects and is ed in pregnancy. is an extremely high risk that severe hirth defects will result if pregnar occurs while taking isotretino cansules 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 a exposed fetus has been affected. (4

5.1, 8.1) Isotretinoin capsules are available called the iPLEDGE REMS. (5.2)

--- INDICATIONS AND USAGE sotretinoin capsules are retinoids indicated for the treatment of severe recalcitrant nodular acne in non-pregnant patients 2 years of age and older with multiple nflammatory nodules with a diameter of 5 mm or greater. Because of significant adverse reactions associated with its use, isotretinoin capsules are reserved for patients with severe nodular acne who are nresponsive to conventional therapy including systemic antibiotics. (1) Limitations of Use:

f a second course of isotretinoin therapy is needed, it is not recommended before a two-month waiting period because the atient's acne may continue to improv following a 15 to 20-week course of

----- DOSAGE AND ADMINISTRATION ---- Recommended dosage for isotretingin capsules is 0.5 to 1 mg/kg/day given in two divided doses without regard to meals for 15 to 20 weeks (2.1) · Adult patients with very severe disease

- (scarring, trunk involvement) may ncrease dosage to 2 mg/kg/day of isotretinoin capsules in divided doses
- Once daily dosing is not recommended.
- · If a dose of isotretinoin capsules is missed just skin that dose. Do not take wo doses of isotretinoin capsules at the same time. (2.1)
- Perform pregnancy tests prior to prescribing, each month during therapy, end of therapy, and one month after

discontinuation. (2.3, 8.3) · Prior to prescribing, perform fasting lipid profile and liver function tests. (2.3)

---- DOSAGE FORMS AND STRENGTHS --Capsules: 40 mg (3)

FULL PRESCRIBING INFORMATION:

CONTENTS* WARNING: EMBRYO-FETAL TOXICITY

USTU besiveA

Кио хя

ISOTRETINOIN CAPSULES

ISOTRETINOIN CAPSULES

Rx only

Revised 0120

APX1149

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2 DOSAGE AND ADMINISTRATION

2.2 Duration of Use 2.3 Laboratory Testing Prior to

3 DOSAGE FORMS AND STRENGTHS

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WARNING: EMBRYO-FETAL TOXICITY – CONTRAINDICATED IN PREGNANC

Isotretinoin capsules 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 capsules 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 expo fetus has been affected. If pregnancy occurs, discontinue isotretinoin capsules immediately and effect the protect ties of beta being. Consection consistenced in the protect of the section of the protect ties. immediately and refer the patient to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling [see Contraindications (4) Warnings and Precautions (5.1), and Use in Specific Populations (8.1)] Because of the risk of embryo-fetal toxicity, isotretingin is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the iPLEDGE REMS [see Warnings and Precautions (5.2)]

1 INDICATIONS AND USAGE

Isotretinoin cansules are indicated for the treatment of severe recalcitrant nodular acne in on-pregnant patients 12 years of age and older with multiple inflammatory nodules with a diameter of 5 mm or greater. Because of significant adverse reactions associated with its use, sotretinoin capsules are reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics.

Limitations of Use a second course of isotretinoin therapy is needed, it is not recommended before a month waiting period because the patient's acne may continue to improve following a 15 to 20-week course of therapy [see Dosage and Administration (2.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage Isotretinoin capsules is 0.5 to 1 mg/kg/day given in two divided doses with or without

meals for 15 to 20 weeks (see Table 1 To decrease the risk of esophageal irritation, instruct patients to swallow the capsules with a

I glass of liquid. During treatment, the dosage may be adjusted according to response of e disease and/or adverse reactions, 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 dosage adjustments up to **2 mg/kg/day for isotretinoin capsules** in divided doses, as

The safety and effectiveness of once daily dosing with isotretinoin capsules has not been established and is not recommended.

If a dose of isotretinoin capsules is missed, just skip that dose. Do not take two doses of sotretinoin capsules at the same time.

CONTRAINDICATIONS	·	Table 1: Isotretinoin Capsules Daily Dosage by Body Weight ¹			
 Pregnancy (4.1, 8.1) 	Body	Total Daily Dosage (mg) ¹			
 Hypersensitivity to this product or any of 	Weight	0.5 mg/kg	1 mg/kg	2 n	
its components (4.2, 5.15)	40 kg	20	40		
WARNINGS AND PRECAUTIONS	50 kg	25	50	·	

i0 kg	25	50	100				
60 kg	30	60	120				
'0 kg	35	70	140				
80 kg	40	80	160				
90 kg	45	90	180				
00 kg	50	100	200				
Administer in two divided doses with or without meals							

2 mg/kg

2.2 Duration of Use A normal course of treatment is 15 to 20 weeks. If the total nodule count has been reduced

by more than 70% prior to completing 15 to 20 weeks of treatment, may discontinue After a period of 2 months or more off therapy, and if warranted by persistent or recu

severe nodular acne, may initiate a second course of isotretinoin capsules in patients who have completed skeletal growth. The use of another course of isotretinoin therapy is not commended before a two-month waiting period because the patient's acne may continue to mprove after a 15 to 20-week course of therapy. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth. Long-term use of isotretinoin capsules, even in low dosages, has not been studied, and is not ecommended. The effect of long-term use of isotretingin capsules on bone loss is unknown

[see Warnings and Precautions (5.12)]. 2.3 Laboratory Testing Prior to Administration

Hearing Impairment: Discontinue and The following laboratory testing **must** be completed prior to isotretinoin use: lepatotoxicity: Monitor liver function

Pregnancy testing: Ensure patient is not pregnant prior to administering isotretinoi capsules [see Contraindications (4) and Use in Specific Populations (8.1, 8.3)] A fasting lipid profile including triglycerides [see Warnings and Precautions (5.8, 5.15)]. Liver function tests [see Warnings and Precautions (5.10, 5.15)].

3 DOSAGE FORMS AND STRENGTHS Isotretinoin capsules, USP 40 mg is available in a pink-brown, oblong, soft gelatin capsule ontaining a yellow/orange opaque viscous liquid, imprinted "575" in blac

4 CONTRAINDICATIONS

4.1 Pregnancy

sotretinoin capsules are contraindicated in pregnancy [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].

4.2 Hypersensitivity

sotretinoin capsules are contraindicated in patients with hypersensitivity to isotretinoin (o (anaphylaxis and other allergic reactions have occurred) [see Warnings and Precautions (5.14)].

5 WARNINGS AND PRECAUTIONS 5.1 Embryo-Fetal Toxicity

Isotretinoin is contraindicated in pregnancy [see Contraindications (4.1)]. Based on human data, isotretinoin can cause fetal harm when administered to a pregnant patient. 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 a exposed fetus has been affected. Major congenital malformations, spontaneous abortion: and premature births have been documented following exposure to isotretinoin during pregnancy [see Use in Specific Populations (8.1)].

f a pregnancy occurs during isotretinoin treatment, discontinue isotretinoin immediately and refer the patient to an obstetrician/gynecologist experienced in reproductive toxicity for urther evaluation and counseling. Any suspected fetal exposure during or 1 month after sotretinoin therapy must be reported immediately to the FDA via the MedWatch telephone number 1-800-FDA-1088, and also to the iPLEDGE pregnancy registry at 1-866-495-0654 or via the internet (www.ipledgeprogram.com).

Patients must be informed not to donate blood during isotretingin therapy and for 1 month following discontinuation because the blood might be given to a pregnant patient whose fetus must not be exposed to isotretinoin. retinoin capsules is available only through a restricted program under a REMS [see

Warnings and Precautions (5.2)1. 5.2 iPLEDGE Program

etinoin capsules are available only through a restricted program under a REMS called the PLEDGE REMS because of the risk of embryo-fetal toxicity *[see Warnings and Precautions (5.1)]*. Notable requirements of the iPLEDGE REMS include the following: · Prescribers must be certified with the program and comply with the following requirements:

. Determine reproductive status of all patients prior to initiating treatment Provide contraception counseling to patients who can get pregnant prior to and during treatment, or refer patients who can get pregnant to an expert for such counseling Provide scheduled pregnancy testing, and verify and document the negative pregnance

test result prior to writing each prescription, for no more than a 30-day supply · Patients who can become pregnant must be enrolled by signing an informed consent form and must comply with the following requirements Comply with the pregnancy testing and contraception requirements *Isee Use in Specific*

Populations (8.3)] Demonstrate comprehension of the safe-use conditions of the program every month

Obtain the prescription within 7 days of the pregnancy test collection Patients who cannot become pregnant must be enrolled by signing an informed consent form and must obtain the prescription within 30 days of the office visit

 Pharmacies that dispense isotretinoin capsules must be certified by being registered and activated in the program, must only dispense to patients who are authorized to receive sotretinoin capsules, and comply with the following requirements:

 Only dispense a maximum of a 30-day supply with a Medication Guide. Do not dispense refills. Dispense only with a new prescription and a new authorization

from the program. Return isotretinoin capsules to inventory if patients do not obtain the prescription by the Do Not Dispense To After" date

Wholesalers and distributors must be registered with the program and must only distribute to certified pharmacies.

Further information, including a list of qualified pharmacies and distributors, is available at www.ipledgeprogram.com or 1-866-495-0654.

zing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers

5.4 Psychiatric Disorders

tinoin may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts suicide, and aggressive and/or violent behaviors [see Adverse Reactions (6)]. **16 HOW SUPPLIED/STORAGE AND** Healthcare providers should be alert to the warning signs of psychiatric disorders to help ensure patients receive the help they need (Prescribers should read the brochure,

17 PATIENT COUNSELING INFORMATION *of isotretinoing)*. Prior to initiation of isotretinoin therapy, patients and family works and isotretinoin best should be asked about any history of psychiatric disorder, and at each visit during therapy patients Sections or subsections omitted from the

full prescribing information are not listed

should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation is necessary. Patients should immediately stop isotretinoin capsules and the patient (or caregiver) should nems should immediately stup isourennom capsules and the patient (or caregiver) should mptly contact their prescriber if the patient develops depression, mod disturbance, ychosis, or aggression. Discontinuation of isotretinoin capsules may be insufficient; further evaluation may be necessary such as a referral to a mental healthcare professional. 5.5 Intracranial Hypertension (Pseudotumor Cerebri)

etinoin use has been associated with cases of intracranial hypertension (pseudotu cerebri), some of which involved concomitant use of tetracyclines. Concomitant treatmen with tetracyclines should therefore he avoided with isotretinoin use. Farly signs and mptoms of intracranial hypertension include papilledema, headache, nausea and vomitir and visual disturbances. Patients with these symptoms should be screened for papi and, if present, they should be told to discontinue isotretinoin capsules immediately referred to a neurologist for further diagnosis and care [see Adverse Reactions (6)]. 5.6 Serious Skin Reactions

There have been post-marketing reports of erythema multiforme and severe skin reactions [e.g., Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)] associated with otretinoin use. These reactions may be serious and result in death, life-threatening events ospitalization, or disability. Patients should be monitored closely for severe skin reactions and isotretinoin capsules should be discontinued if they occur. 5.7 Pancreatitis

Acute pancreatitis has been reported with isotretinoin use in patients with either elevated or Acute participants and been reported with soutention use in patients with entre revated of normal serum triglyceride levels. In a reinstances, fatal hemorrhagic pancreatitis has been reported. If symptoms of pancreatitis occur, discontinue isotretinoin capsules and seek medical attention.

5.8 Lipid Abnormalities

Elevations of serum triglycerides above 800 mg/dL have been reported with isotretinoin use. In clinical trials, marked elevations of serum triglycerides, decreases in high-density lipoproteins (HDL), and increases in cholesterol levels were reported in 25%, 15%, and 7% of patients treated with isotretinoin capsules, respectively. These lipid changes were reversible upon isotretinoin capsule cessation. Some patients have been able to reverse triglyceride elevation by reduction in weight and restriction of dietary fat and alcohol while continuing sotretinoin or through dosage reduction. The cardiovascular consequences of hypertriglyceridemia associated with isotretinoin are unknown.

Easting lipid tests should be performed before isotreting in treatment and then at intervals until the lipid response to isotretinoin is known, which usually occurs within 4 weeks. Careful consideration should be given to risk/benefit of isotretinoin in patients who are at higher risk of hypertriglyceridemia (e.g., patients with diabetes, obesity, increased alcohol intake, lipic subjecting of the second of the second secon cannot be controlled.

5.9 Hearing Impairment

mpaired hearing has been reported in patients taking isotretinoin; in some cases, the hearing npairment has been reported to persist after therapy has been discontinued. Mechanisn and causality for this reaction have not been established. Patients who experience tinnitus or

5.10 Hepatotoxicity nical henatitis has been reported with isotretinoin use. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials with isotretinoin capsules, 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, isotretingin capsules should be discontinued 5.11 Inflammatory Bowel Disease Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis) n patients without a prior history of intestinal disorders. In some instances, symptoms hav

immediately [see Adverse Reactions (6)]. 5.12 Musculoskeletal Abnormalities Bone Mineral Density Changes, Osteoporosis, and Fractures

Intertinoin may have a negative effect on bone mineral density (BMD) in some patients. In a nical trial of isotretinoin and another isotretinoin capsule product, 27/306 (9%) of olescents had BMD declines, defined as $\geq 4\%$ lumbar spine or total hip, or $\geq 5\%$ femoral as during the 20 work teather teather the source of the neck, during the 20-week treatment period. Repeat scans conducted within 2 to 3 months ter the post-treatment scan showed no recovery of BMD. Long-term data at 4 to 11 months nowed that 3 out of 7 patients had total hip and femoral neck BMD below pre-treatment showed that 3 out of 7 patients had total mp and remotal neck blob below pre-nearment baseline, and 2 others did not show the increase in BMD above baseline expected in this adolescent population. Therefore, healthcare providers should use caution when prescribing isotretinoin capsules to patients with a history of childhood osteoporosis conditions steomalacia, 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 ticosteroids and any anticonvulsant [see Use in Specific Populations (8.4)]. re have been spontaneous reports of osteoporosis, osteopenia, fractures and/or delayed

nealing of fractures in patients while on therapy with isotretinoin or following cessation of therapy with isotretinoir Patients in early and late adolescence who participate in sports with repetitive impact may be at an increased risk of spondylolisthesis with and without pars fractures, and hip growth plate injuries have been reported.

Musculoskeletal Abnormalities

Corneal Opacities

Decreased Night Vision

afterwards.

sed night visio

driving or operating any vehicle at night

5.14 Hypersensitivity Reactions

appropriate medical management

Laboratory Monitoring

egnancy Testing

Liver Function Tests

n reported in patients on is

Warnings and Precautions (5.10)1

6 ADVERSE REACTIONS

Dose Relationship

Additional Laboratory Abnormalities

Linid Tests

everoped back pain, back pain was severe in 14% (14/104) of the cases and occurred at a igher frequency in female patients than male patients. Arthralgias were experienced in 22% 79/358) of pediatric patients. Arthralgias were severe in 8% (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 isotretinoin. Consider discontinuing isotretinoin psules if any significant abnormality is found. Effects of multiple courses of isotretinoin on the developing musculoskeletal system ar 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. It is important that isotretinoin capsules be given at the commended dose for no longer than the recommended duration

A high prevalence of skeletal hyperostosis was noted in clinical trials for disorders of in prevalence of schedul hyperbotics was noted in climitar thats for disorders in inzation with a mean dose of 2.24 mg/kg/day of isorterinoin capsules (appro-mes the maximum recommended daily dosage). Additionally, skeletal hyperonoted in 6 of 8 patients in a prospective trial of disorders of keratinization. Minimal skeletal hyperostosis and calcification of ligaments and tendons have also been observed by x-ray in prospective trials of nodular acne patients treated with a single course of therapy at nended doses. The skeletal effects of multiple isotretinoin treatment courses for acne

In a clinical trial of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodula acne, hyperostosis was not observed after 16 to 20 weeks of treatment with approximately mg/kg/day of isotretingin cansules given in two divided doses. Hyperostosis may require a time frame to appear. The clinical course and significance remain unknow Premature Epiphyseal Closure

There are spontaneous literature reports of premature epiphyseal closure in acne patients eceiving recommended doses of isotretinoin capsules. The effect of multiple courses of sotretinoin on epiphyseal closure is unknown. In a 20-week clinical trial that included 289 adolescents on isotretinoin or another isotret capsule product who had hand radiographs taken to assess bone age, a total of 9 (3%) patients had bone age changes that were clinically significant and for which a drug-related effect cannot be excluded 5.13 Ocular Abnormalities

hearing impairment should discontinue isotreting in treatment and be referred for specialized

he parties window a prior instance of interstinal obsorbers. In some instances, symptoms the leen reported to persist after isotretinoin treatment has been stopped. Patients experienci bdominal pain, rectal bleeding or severe diarrhea should discontinue isotretinoin capsule:

proximately 16% of patients treated with isotretinoin capsules in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of isotretinoin. In a trial of pediatric patients treated with isotretinoin capsules, approximately 29% (104/358) ed back pain. Back pain was severe in 14% (14/104) of the cases and occurred at

Visual problems should be carefully monitored. If visual difficulties occur, discontinue etinoin treatment and obtain an ophthalmological examination [see Adverse Reactions (6)].

Corneal opacities have occurred in patients receiving isotretinoin capsules and more requently 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 isotretino apsules have either completely resolved or were resolving at follow-up 6 to 7 weeks after disordiverse of instructions for a driverse particular (61)

discontinuation of isotretinoin [see Adverse Reactions (6)] n has been reported during isotretinoin use 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

Dry eyes have been reported in patients during isotretinoin use. Patients who wear contact lenses may have trouble wearing them while on isotretinoin capsules treatment and

Anaphylactic reactions and other allergic reactions have been reported with isotretinoin use. ous allergic reactions and serious cases of allergic vasculitis, often with purpura is and red patches) of the extremities and extracutaneous involvement (including e been reported. Severe allergic reaction necessitates discontinuation of therapy and

5.15 Laboratory Abnormalities and Laboratory Monitoring for Adverse Reactions

A pregnancy test must be obtained prior to obtaining a prescription, repeated each month, at the end of the entire course of isotretinoin therapy and 1 month after the discontinuation of tinoin capsules [see Use in Specific Ponulations (8.3)]

Pretreatment and follow-up fasting lipid tests should be obtained under fasting conditions After consumption of alcohol, at least 36 hours should elapse before testing is performed. It is recommended that these tests be performed periodically until the lipid response to isotretinoin is known. The incidence of hypertriglyceridemia is 25% in patients treated with isotretinoin capsules [see Warnings and Precautions (5.8)].

As elevations of liver enzymes have been observed during clinical trials, and hepatitis has tests should be performed periodically until the response to isotretinoin is known [see

With isotretinoin use, some patients have experienced problems in the control of their blood

Some patients undergoing vigorous physical activity while taking isotretingin have experienced elevated CPK levels; however, the clinical significance is unknown. There have been rare post-marketing reports of rhabdomyolysis with isotretinoin use, some associated with strenuous physical activity. In a clinical trial of 924 patients, marked elevations in CPK (>350 U/L) were observed in approximately 24% of natients treated with isotretinoin

In another clinical trial of 217 pediatric patients (12 to 17 years old) 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 yolysis were reported in this clinical trial.

The following adverse reactions with isotretinoin or other isotretinoin capsule products are described in more detail in other sections of the labeling:

- Embryo-Fetal Toxicity [see Warnings and Precautions (5.1). Psychiatric Disorders [see Warnings and Precautions (5.4)]
- Intracranial Hypertension (Pseudotumor Cerebri) Isee Warnings and Precautions (5.5)1 Serious Skin Reactions [see Warnings and Precautions (5.6)]
- Pancreatitis [see Warnings and Precautions (5.7)] • Lipid Abnormalities [see Warnings and Precautions (5.8)]

sugar. In addition, new cases of diabetes have been diagnosed during isotretinoin use.

- · Hearing Impairment [see Warnings and Precautions (5.9) Hepatotoxicity [see Warnings and Precautions (5.10)]
- mmatory Bowel Disease [see Warnings and Precautions (5.11)] Musculoskeletal Abnormalities [see Warnings and Precautions (5.12)].
- Ocular Abnormalities [see Warnings and Precautions (5.13)] • Hypersensitivity Reactions [see Warnings and Precautions (5.14)]
- The following adverse reactions associated with the use of isotretinoin capsules were identified in clinical studies or post-marketing reports. Because some of these reactions wer reported voluntarily from a population of uncertain size, it is not always possible to reliably

Cheilitis and hypertriglyceridemia were dose related

estimate their frequency or establish a causal relationship to drug exposure

Body as a Whole

Fatigue, irritability, pain, allergic reactions, systemic hypersensitivity, edema, lymphadenopathy, weight loss Cardiovascular

Vascular thrombotic disease, stroke, palpitation, tachycardia, Endocrine/Metabolism and Nutritional

ased appetite, weight fluctuation, alterations in blood sugar.

/ lips, chapped lips, cheilitis, nausea. constipation. diarrhea. abdominal pain vomiting inflammatory bowel disease, hepatitis, pancreatitis, bleeding and inflammation of the gums, colitis, esophagitis, esophageal ulceration, ileitis.

Hematologic Anemia and decreased RBC parameters, thrombocytopenia, increased platelet counts decreased WBC counts, severe neutropenia, rare reports of agranulocytos

Infections and Infestations Nasopharyngitis, hordeolum, infections (including disseminated herpes simplex and upper respiratory tract infection).

Laboratory Abnormalities

The following lab tests were increased: creatine phosphokinase (CPK) triglycerides alanine ferase (SGPT), aspartate aminotransferase (SGOT), gamma-glutamyItransfer olesterol, low density lipoprotein (LDL), alkaline phosphatase, bilirubin, LDH asting blood glucose, uric acid, and sedimentation rate. However, high density lipoprotein IDL) was decreased. Urine findings included increased white cells, proteinuria, microscopic

Musculoskeletal and Connective Tissue

ecreases in bone mineral density, musculoskeletal symptoms (sometimes severe) including back pain, arthralgia, musculoskeletal pain, neck pain, extremity pain, myalgia, musculoskeletal stiffness [see Warnings and Precautions (5.12)], skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, tendonitis, arthritis, ransient chest pain, and rare reports of rhabdomyolysis.

Neurological adache, syncope, intracranial hypertension (pseudotumor cerebri), dizziness, drowsiness, lethargy, malaise, nervousness, paresthesia, seizures, stroke, weakness.

deation, insomnia, anxiety, depression, irritability, panic attack, anger, euphoria violent behaviors, emotional instability, suicide attempts, suicide, aggression, psychosis and auditory hallucinations. Of the patients reporting depression, some reported that the epression subsided with discontinuation of therapy and recurred with reinstitution of

Reproductive System

Abnormal menses, sexual dysfunction, including erectile dysfunction and decreased libido. Respiratory pistaxis, nasal dryness, bronchospasm (with or without a history of asthma), respiratory infection, voice alteration.

Skin and Subcutaneous Tissue

Dry skin, dermatitis, eczema, rash, contact dermatitis, alopecia, pruritus, sunburn, erythema, acne fulminans, alopecia (which in some cases persisted), bruising, dry nose, eruptive anthomas erythema multiforme flushing skin fragility hair abnormalities hirsutisr Administration and hypopigmentation, naid with rugindy, naid administration, marked and hypopigmentation and hypopigmentation, naid dystrophy, paronychia, peeling of palms and soles, photoallergic/photosensitizing reactions, pruritus, pyogenic granuloma, rash (including facial erythema, seborrhea, and eczema), Stevens-Johnson syndrome, increased sunburn susceptibility, sweating, toxic epidermal necrolysis, urticaria, vasculitis (including ranulomatosis with polyangiitis), abnormal wound healing (delayed healing or exuberant lation tissue with crusting)

Hearing: tinnitus and hearing impairment.

Ocular: dry eyes reduced visual acuity blurred vision eye pruritis eye irritation asthenopia decreased night vision, ocular hyperemia, increased lacrimation, conjunctivitis, corr opacities, decreased night vision which may persist, cataracts, color vision disorder conjunctivitis, eyelid inflammation, keratitis, optic neuritis, photobia, visual disturbances. Renal and Urinary

7 DBUG INTERACTIONS

7.1 Vitamin A

Isotretinoin capsules are closely related to vitamin A. Therefore, the use of both vitamin A and tretinin capsules at the same time may lead to training a method, the use of both warming proteining capsules at the same time may lead to training a leader of the same time reactions. containing Vitamin A to avoid additive toxic effects. 7.2 Tetracyclines

mitant treatment with isotretinoin capsules and tetracyclines should be avoided because isotretinoin use has been associated with a number of cases of intracranial hypertension (pseudotumor cerebri), some of which involved concomitant use of etracyclines [see Warnings and Precautions (5.5)

7.3 Phenvtoin Phenytoin is known to cause osteomalacia. No formal clinical trials have been conducted to assess if there is an interactive effect on bone loss between phenytoin and isotretinoin Therefore, caution should be exercised when using these drugs together.

7.4 Systemic Corticosteroids Systemic corticosteroids are known to cause osteoporosis. No formal clinical trials have been onducted to assess if there is an interactive effect on bone loss with concomitant use of ystemic corticosteroids and isotretinoin. Therefore, caution should be exercised when using

these drugs together. 7.5 Norethindrone and Ethinvl Estradiol

In a trial of 31 premenopausal female patients with severe recalcitrant nodular acne receiving orethindrone and ethinyl estradiol as an oral contraceptive agent, isotretinoin capsules within he recommended dosage, did not induce clinically relevant changes in the pharmacokinetics of ethicyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Although this study did not show any clinically significant interaction between isotretinoin and norethindrone, it is not known if there is an interaction between isotretinoin with other progestins.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in patients exposed to isotretinoin during pregnancy. Report any suspected fetal exposure during or 1 month after isotretinoin therapy immediately to the FDA via the MedWatch telephone number 1-800-FDA-1088 and also to the iPLEDGE pregnancy registry at 1-866-495-0654 or via the internet (www.ipledgeprogram.com). Risk Summary

Isotretinoin is contraindicated during pregnancy because isotretinoin can cause fetal harn when administered to a pregnant patient. There is an increased risk of major congenital nalformations, spontaneous abortions, and premature births following isotretingin exp ecomes pregnant while taking isotretinoin, the patient should be apprised of the patient economic structure and the patient should be apprised of the potential economics of the patient should be apprised of the potential economics and the patient should be apprised of the potential economics and the patient should be apprised of the potential economics and the patient should be apprised of the potential economics and the patient should be apprised of the potential economics and the patient should be apprised of the potential economics and the patient should be apprised of the potential economics and the patient should be apprised of the potential economics and the patient should be apprised of the potential economics and the patient should be apprised of the patient should be a hazard to a fetus. If pregnancy occurs during treatment of a patient who is taking isotretino capsules, isotretinoin capsules must be discontinued immediately and the patient should be ist experienced in reproductive toxicity for furth

Human Data

evaluation and counseling.

Najor congenital malformations that have been documented following isotretinoin exposure include malformations of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. External malformations include: skull; ear cluding anotia, micropinna, small or absent external auditory canals); eye (including icrophthalmia); facial dysmorphia and cleft palate. Internal abnormalities include: CNS ncluding cerebral and cerebellar malformations, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular; thymus gland; parathyroid hormone deficiency. In some cases, death

has occurred as a result of the malformations. Cases of IQ scores less than 85 with or without other abnormalities have been reported in inoin. An increased risk of spontaneous abortion and children exposed in utero to isotretinoin. An increased risk of spontaneous abortion premature births have been reported with isotretinoin exposure during pregnancy.

8.2 Lactation

Risk Summary There are no data on the presence of isotretinoin in either animal or human milk, the effects and the restited infant, protection or normality production. Because of the potential for serious adverse reactions in nursing infants from isotretinoin, advise patients that breastfeeding is not recommended during treatment with isotretinoin, and for at least 8 days after the lot deep of instructions procedure.

last dose of isotretinoin capsules 8.3 Females and Males of Reproductive Potential

All patients who can become pregnant must comply with the iPLEDGE program requirements Isee Warnings and Precautions (5.2)1. Pregnancy Testing

otretinoin capsules must only be prescribed to patients who are known not to be pregnan as confirmed by a negative CLIA-certified laboratory conducted pregnancy test. Patients who as collimned by a negative our vertice and output y concerns program, but a sensitivity of at least 25 mIU/mL before receiving the initial isotretinoin capsules prescription e interval between the two tests must be at least 19 days • The first test (a screening test) is obtained by the prescriber when the decision is made

to prescribe isotretinoin therapy. 2 forms of contraception for 1 month and during the first 5 days of the menstrual period immediately preceding the beginning of isotretinoin therapy (for patients with regular nenstrual cycles) or immediately preceding the beginning of isotretingin therapy (for patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding).

A pregnancy test must be repeated each month, in a CLIA-certified laboratory prior to the atient receiving each prescription. A pregnancy test must also be completed at the end of the entire course of isotretinoin therapy and 1 month after the discontinuation of isotretino

Patients who can become pregnant must use 2 forms of contraception simultaneously, at least 1 of which must be a primary form, for at least 1 month prior to initiation of isotre erapy, during isotretinoin therapy, and for 1 month after discontinuing isotretinoin therap however, 2 forms of contraception are not required if the patient commits to continuous abstinence from not having any sexual contact with a partner which may result in pregnar has undergone a hysterectomy or bilateral oophorectomy, or has been medically confirmed to

be post-menopausal. Micro-dosed progesterone preparations ("minipills" that do not contain

Primary forms

Tubal sterilization

Intrauterine device

Male vasectomy

in estrogen) are an inadequate method of contraception during isotretingin therap Secondary forms • male latex condom with or without spermicid • diaphragm with spermicide

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

Effect on Food

is unknown.

Specific Populations

Drug Interaction Studies

13 NONCLINICAL TOXICOLOGY

tumor to humans is uncertain.

normalization for total body surface area).

were completely atrophic tubules seen.

13.2 Animal Toxicology

14 CLINICAL STUDIES

lodular Lesion

Mean Reduction

Figure 1

Mean Baseline Count

Subjects Achieving

90% Reduction. n (%)

Week 4

16 HOW SUPPLIED/STORAGE AND HANDLING

Box of 30 capsules (3 x 10 Prescription Packs):

[See USP Controlled Room Temperature]. Protect from light.

Storage and Handling

Another isotretinoin capsule product

The pharmacodynamics of isotretinoin are unknown

Absorption Following Isotretinoin Administration

Dosage and Administration (2.1)1.

equal amounts (total of 65% to 83%).

conditions following administration of a single 40 mg dose.

Isotretinoin is a retinoid, which when administered at the recommended dosage *[see Dosage*

duration of treatment with isotretinoin capsules and reflects a reduction in sebaceous gland

size and an inhibition of sehaceous gland differentiation. The exact mechanism of action of

No clinically significant differences in the pharmacokinetics of isotretinoin between patients

The isotretinoin mean T_{max} was 6.4 hours under fed conditions and 2.9 hours under fasting

No clinically significant differences in isotretinoin pharmacokinetics were observed following

stration with a modified high-fat, high-calorie meal (123,2 calories from protein

administration with a normal model in the mean AUC_{D-1} and Carles from factors from protein protein 265.6 calories from carbohydrates, and 468 calories from fact, total calories 857 calories) with reduced vitamin A content. The mean AUC_{D-1} and C_{max} of isotretinoin were 6095 ng*hr/mL and 369 ng/mL, respectively, following administration of a single 40 mg isotretinoin dose

compared to fasting conditions. However, isotretingin may be given with or without meals

The mean elimination half-lives of isotretinoin and its 4-oxo-isotretinoin metabolite were:

Metabolism: Isotretinoin is primarily metabolized by CYP2C8, 2C9, 3A4, and 2B6 in vitro. Isotretinoin and its metabolites are further metabolized into conjugates.

isotretinoin, retinoic acid (tretinoin), and 4-oxo-retinoic acid (4-oxo-tretinoin)) have been

ientified in human plasma. The extent of formation of all metabolites was higher under fed onditions. All of these metabolites possess retinoid activity in vitro. The clinical significance

liquid suspension, the metabolites of isotretinoin were excreted in feces and urine in relatively

Pediatric Patients: No clinically significant differences in the pharmacokinetics of isotretinoin

were observed based on age (12 to 15 years (n=38), and \geq 18 years (n=19)). In both age groups, 4-*oxo*-isotretinoin was the major metabolite; tretinoin and 4-*oxo*-tretinoin were also observed [see Use in Specific Populations (8.4)].

No clinically significant differences in the pharmacokinetics of phenytoin (CYP2C9 substrate) were observed when used concomitantly with isotretinoin.

In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day

If that and the matrix of the second rates of

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

atively high level of spontaneous pheochromocytomas occurring in the male Fische

344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this

The Ames test was conducted with isotretinoin in two laboratories. The results of the tests in

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

parturition were observed at oral dosages of isotretinoin of 2, 8, or 32 mg/kg/day (0.3, 1.3 5.3 times the recommended clinical isotretinoin dosage of 1 mg/kg/day, respectively, after

In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately

a) weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the recommended clinical isotretinoin dosage of 1 mg/kg/day, respectively, after normalization for total body surface area). In general, there was microscopic evidence for appreciable depression of

In rats given 8 or 32 mg/kg/day of isotretinoin (1.3 or 5.3 times the recommended clinical

myocardium, aclification of coronary, pulmonary and mesanteric 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 arterie

were observed in two doos 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 isotretinoin dosage of 1 mg/kg/day, respectively, after normalization for total body surface area).

The effectiveness of isotretinoin for the treatment of severe recalcitrant nodular acne i

of 925 subjects were randomized 1.1 to receive isotretinoin or another isot

patients 12 years of age and older has been established and is based on a double-blind

randomized, parallel group trial (Study 1) in subjects with severe recalcitrant nodular acne

White, 4% Black, 6% Asian, and 3% Other. Enrolled subjects had a weight of 40 to 110 kg

and had at least 10 nodular lesions on the face and/or trunk. Subjects were treated with an

Change from baseline to Week 20 in total nodular lesion count and proportion of subject

course of isotretinoin and another isotretinoin capsule product therapy for 15 to 20 weeks has been shown to result in complete and prolonged remission of acne in many patients.

presented in Table 3. Total nodular lesion counts by visit are presented in Figure 1. A single

Table 3: Efficacy Results in Subjects with Severe Recalcitrant Nodular Acne at Week 20

(Study 1)

Isotretinoin

N-464

18.4

-15.68

324 (70%)

Recalcitrant Nodular Acne by Visit in Study 1

Week 8

Cinar SL, Kartal D, Aksoy H, et al. Long-term effect of systemic isotretinoin on female fertility. Cutan Ocul Toxicol. 2017; 36(2):132–134.

Isotretinoin capsules, USP 40 mg is supplied as pink-brown, oblong, soft gelatin capsule,

containing a yellow/orange opaque viscous liquid, imprinted "575" in black ink. They are

Store at 20° to 25°C (68° to 77°F), excursion permitted between 15° to 30°C (59° to 86°F)

: Total Nodular (Facial and Truncal) Lesion Count in Subjects with Severe

with at least a 90% reduction in total nodular lesion count from baseline to Week 20 are

initial does of 0.5 mg/kg/day in two divided does for the first 4 weeks, followed by 1 mg/kg/day in two divided does for the following 16 weeks.

who received isotretinoin or another isotretinoin capsule product under fed conditions. A total

ct. Study subjects ranged from 12 to 54 years of age (including 397 pediatric subjects 17 years old); 60% were male, 40% were female; and the racial groups included 87%

spermatogenesis, but some sperm were observed in all testes examined, and in no instance

isotretinoin dosage of 1 mg/kg/day, respectively, after normalization for total body surface area) for 18 months or longer, the incidences of focal calcification, fibrosis and inflammation of the

oin of 2, 8, or 32 mg/kg/day (0.3, 1.3, or

Isotretinoin Capsule

17.7

-15.62

344 (75%)

e o e Isotretinoin*

Week 16

NDC 0245-0575-01

Week 12

Analysis Visit

human-derived lymphocytes, and unscheduled DNA synthesis assay) were all negative.

In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or

Following oral administration of isotretinoin capsules, at least three metabolites (4-oxe

• 18 hours and 38 hours, respectively, after a single oral isotretinoin 40 mg dose.

under fed conditions; which were approximately 50% and 26% higher, respectively,

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

Excretion: Following oral administration of an 80 mg dose of radiolabeled-is

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

with nodular acne and healthy subjects without acne were reported in published literature

pin in the treatment of severe recalcitrant nodular acne is unknow

s a relinition, which when a dimension and the recommended usage (see tration (2, 1)), inhibits sebaceous gland function and keratinization. Clinica in nodular acne patients occurs in association with a reduction in sebur

. The decrease in sebum secretion is temporary and is related to the dose and

· cervical cap with spermicide Hormonal (combination oral contraceptives, vaginal systems

ginal inserts, transdermal Vaginal sponge (contains spermicide) stems, injections, or implants)

Any birth control method can fail. There have been reports of pregnancy from patients who have used combination oral contracentives, as well as contracentive vaginal systems, vaginal isotretinoin. These reports are more frequent for patients who use only a single taking isotretinoin. These reports are more frequent for patients who use only a single method of contraception. Therefore, it is critically important that patients who can become pregnant use 2 methods of contraception simultaneously.

A clinical drug interaction study did not show any clinically significant interaction between noin and norethindrone and ethinyl estradiol: however, it is not known if there is an action between isotretinoin with other progestins [see Drug Interactions (7.5)] cribers are advised to consult the prescribing information of any medication a concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.

Patients who can become pregnant should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because of a possible interaction with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly aft 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 the nationt has unprotected sexual contact with a partner that could result in pregnancy at

iny time 1 month before, during, or 1 month after therapy, the patient must a. Stop taking isotretinoin immediately, if on therapy b. Have a pregnancy test at least 19 days after the last act of unprotected sexual contact

- with a partner that could result in pregnancy c. Start using 2 forms of contraception simultaneously again for 1 month before resuming
- isotretinoin therapy d. Have a second pregnancy test after using 2 forms of contraception for 1 month.

nean total ovarian volume, the total antral follicle count and mean anti-Mullerian hormone lecreased at the end of the treatment (sixth month). However, the values returned to normal at the 18th month (12 months after the end of treatment). There were no statistically ficant changes in terms of follicle-stimulating hormone and luteinizing hormone both at significant charges in terms of nonce-stimulary forming and neurally forming the results the end of the treatment and 12 months after the end of treatment. Although the results suggest that possible deteriorative effects of isotretinoin on ovarian reserve may be reversible, the study has important methodological limitations, including a small sample size, lack of a control group, and lack of generalizability

Sperm Study In trials of 66 men, 30 of whom were patients with nodular acne under treatment with ora 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 isotretinoin therapy for odular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm lity, morphology or seminal plasma fructose 8.4 Pediatric Use

The safety and effectiveness of isotretinoin for the treatment of severe recalcitrant nodular cne have been established in pediatric subjects ages 12 to 17 years. Use of isotretinoir this age group for this indication is supported by evidence from a clinical trial (Study 1) that compared the use isotretinoin to another isotretinoin capsule product in 397 pediatric subjects (12 to 17 years) [see Clinical Studies (14)] and pharmacokinetic data in pediatric subjects [see Clinical Pharmacology (12.3)]. The safety and effectiveness of isotretinoin in pediatric patients less than 12 years of age have

not been established. Adverse Reactions in Pediatric Subjects

trials with isotretinoin capsules, adverse reactions reported in pediatric subjects aged 12 to 7 years old 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 subjects. In a trial of pediatric subjects aged 12 to 17 years old treated with isotretinoi capsules, approximately 29% (104/358) developed back pain. Back pain was severe in 14% (14/104) of the cases and occurred at a higher frequency in female subjects than male subjects Arthralgias were experienced in 22% (79/358) of pediatric subjects including severe arthralgias in *all of control* of obtine the subjects and the subjects including severe arthralgias in *all of control* of obtine the subjects and the subjects including severe arthralgias and the subjects subjects arthralgias the subjects including severe arthralgias and the subjects subjects arthralgias the subjects including severe arthralgias arthralgias back of obtine the subjects arthralgias arthralgias are subjects and arthralgias arthralgias back of the subject subjects are subjects arthralgias arthralgias back of the subject arthralgias arthralgias back of the subject subject arthralgias arthralgias back of the subject arthralgias arthralgias back of the subject subject arthralgias arthralgias back of the subjec in 8% (6/79) of subjects. Appropriate evaluation of the musculoskeletal system should be don in adolescents who present with these symptoms during or after a course of isotretinoin Consider discontinuing isotretinoin capsules if any significant abnormality is found

Effects on Bone Mineral Density in Pediatric Subjects The effect on bone mineral density (BMD) of a 20-week course of therapy with isotretinoin o nother isotretingin capsule product was evaluated in a double-blind, randomized clinical tri involving 396 adolescents with severe recalcitrant nodular acne (mean age 15.4 years old, range 12 to 17 years old, 80% males). Given that there were no statistically significant fferences between the two isotretinoin capsule groups following 20 weeks of treatment, the esults are presented for the pooled treatment groups. The mean changes in BMD from aseline for the overall trial population were 1.8% for lumbar spine, -0.1% for total hip and 0.3% for femoral neck Mean BMD 2-scores declined from baseline at each of these sites (-0.053, -0.109 and -0.104 respectively). Out of 306 adolescents, 27 (9%) had clinically significant BMD declines defined as ≥4% lumbar spine or total hip, or ≥5% femoral neck, luding 2 subjects for lumbar spine, 17 for total hip and 20 for femoral neck. Repea DXA scans within 2 to 3 months after the post treatment scan showed no recovery of BME rm follow-up at 4 to 11 months showed that 3 out of 7 subjects had total hip and neck BMD below pre-treatment baseline, and 2 others did not show the increase i BMD above baseline expected in this adolescent population. The significance of these

changes in regard to long-term bone health and future fracture risk is unknown [see ings and Precautions (5.12)] In an open-label clinical trial (N=217) of a single course of therapy with isotretinoin ca

r adolescents with severe rècalcitránt nodular acne, BMD at several skeletal sites were no significantly decreased (lumbar spine change >-4% and total hip change >-5%) or were creased in the majority of subjects. One patient had a decrease in lumbar spine BMD >4% ased on unadjusted data. Sixteen (8%) subjects had decreases in lumbar spine BMD >4% dal dlh eo ther subjects (92%) did not have significant decreases in turnal spine bind 24 n dal dlh eo ther subjects (92%) did not have significant decreases or had increases (adjust r body mass index). Nine subjects (5%) had a decrease in total hip BMD >5% based on inadjusted data. Twenty-one (11%) subjects had decreases in total hip BMD >5%, and all the other subjects (89%) did not have significant decreases or had increases (adjusted for body nass index). Follow-up trials performed in 8 of the subjects with decreased BMD for up to the other 3 subjects had lumbar spine BMD measurements below baseline values. BMD remained below baseline (range -1.6% to -7.6%) in 5 of 8 subjects (63%). In a separate open-label extension trial of 10 subjects including those ages 13 to 17 years,

who started a second course of isotretinoin capsules 4 months after the first course, two subjects showed a decrease in mean lumbar spine BMD up to 3.3%. piphyseal Closure

There are reports of premature epiphyseal closure in acne natients who used isotretinoin at nere are reports on premative physical observe in acres patients wind used isotretion at ecommended doses. The effect of multiple courses of isotretinoin on epiphysical closure is inknown. In a 20-week clinical trial that included 289 adolescents who had hand radiographs aken to assess bone age, a total of 9 subjects had bone age changes that were clinical significant and for which an isotretinoin-related effect cannot be excluded [see Warnings and Precautions (5.12)1.

8.5 Geriatric Use

Clinical studies of isotretinoin did not include sufficient numbers of geriatric subjects (subjects aged 65 years of age and older) to determine whether they respond differently from younger adults. Although reported clinical experience has not identified differences in responses between geriatric and younger adults, effects of aging may increase some risks associated with an isotretinoin therapy.

10 OVERDOSAGE

11 DESCRIPTION

In humans, isotretinoin overdosage has been associated with vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness, and ataxia. These symptoms quickly resolved without apparent residual effects. Patients who can become pregnant who present with an isotretinoin overdosage should be evaluated for pregnancy. Because an overdosage would be expected to result in higher levels

of isotretinoin in semen than found during a normal treatment course, male patients treated

with isotretinoin should use a condom, or avoid reproductive sexual activity with a patient

Isotretinoin capsules, USP contain 40 mg of isotretinoin (a retinoid) in soft gelatin capsul

for oral administration. In addition to the active ingredient, isotretinoin USP, each capsule

hydrogenated vegetable oil Type I, hydrogenated vegetable oil Type II, soybean oil, vitamin E and yellow wax. The gelatin capsules contain glycerin, iron oxide (red and yellow),

ically, isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and re

(vitamin A). It is a vellow to orange crystalline powder with a molecular weight of 300.44. It is

COOH

practically insoluble in water, soluble in chloroform and sparingly soluble in alcohol and in

contains the following inactive ingredients: butylated hydroxyanisole, disodium edeta

All patients with isotretinoin overdose should not donate blood for at least 1 month.

who is or might become pregnant, for 1 month after the overdose

rosoferric oxide, sorbitol and titanium dioxide.

isopropyl alcohol. The structural formula is

Meets USP Dissolution Test 6

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

iPLEDGE

Lactation

Psychiatric Disorders

cautions (5.6)

Precautions (5.11)].

Ocular Abnormalities

Rhabdomyolysis

Precautions (5.14)

Lipid Abnormalities

nform patients:

of therapy

Manufactured for

DOUG13

APX1149

Made in New Zealand

Isotretinoin (

patients that:

Inflammatory Bowel Disease

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

nere is an extremely high risk of severe high defects when isotreting is used in pregnancy *see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].* Instruct patien who can become pregnant that they must not be pregnant during or up to one month after isotretinoin therapy. Instruct patients to not donate blood during isotretinoin therapy and for 1 month following discontinuation to avoid blood donation to a pregnant patien

Isotretinoin capsules are available only through a restricted program called iPLEDGE *[see* Warnings and Precautions (5.2)]. Inform patients who can become pregnant of the following ptable requirements. These patients must: Sign an informed consent form to be enrolled in the program

· Comply with the pregnancy testing and contraception requirements [see Use in Specific oulations (8.3)] Demonstrate comprehension of the safe-use conditions of the program every month

Obtain the prescription within 7 days of the pregnancy test collection form patients who cannot become pregnant of the following notable requirements. These tients must sign an informed consent form to enroll in the program and they must obtain the prescription within 30 days of the office visit.

Isotretinoin is available only from certified pharmacies participating in the program Therefore, provide patients with the telephone number and website for information on how to obtain isotretinoin [see Warnings and Precautions (5.2)].

Because of the potential for serious adverse reactions in nursing infants from isotretinoir advise patients that breastfeeding is not recommended during treatment with isotretinoin capsules, and for at least 8 days after the last dose of isotretinoin capsules [see Use in Specific Populations (8.2)1.

Instruct patients and/or their caregivers/families that isotretinoin may cause depression chosis, suicidal ideation, suicide attempts, and aggressive or violent behavior. Instruct tients to read the *Recognizing Psychiatric Disorders in Adolescents and Young Adults* ochure prior to taking isotretinoin capsules. Instruct patients to stop isotretinoin capsul and to contact a healthcare provider if they develop any of these signs or symptoms [see Warnings and Precautions (5.4)].

Important Administration Instructions To decrease the risk of esophageal irritation, instruct patients to swallow the capsules with a full glass of liquid [see Dosage and Administration (2.1)]. Intracranial Hypertension (Pseudotumor Cerebri)

se patients that intracranial hypertension (pseudotumor cerebri) has occurred with etinoin use including concomitant use with tetracyclines. Thus, advise patients to avoid incomitant use with tetracyclines and to discontinue isotretinoin capsules immediately in hey have symptoms of intracranial hypertension (see Warnings and Precautions (5.5)) Serious Skin Reactions

Advise patients that severe skin reactions (Stevens-Johnson syndrome and toxic epidermal crolysis) have been reported in patients treated with isotretinoin and to discontinu tinoin capsules if clinically significant skin reactions occur [see Warnings and

Advise patients that inflammatory bowel disease (including regional ileitis) have occurred with otretinoin use including those without a prior history of IBD and if they experience IBD mptoms, they should discontinue isotretinoin capsules immediately [see Warnings and

Musculoskeletal Abnormalities

• There have been reports of osteoporosis and fractures and that isotretinoin may have a negative effect on bone mineral density [see Warnings and Precautions (5.12)] Isotretinoin use has been associated with musculoskeletal abnormalities (e.g., arthralgia, back pain) [see Warnings and Precautions (5.12)].

Inform adolescents and their families that isotretinoin use in adolescents who participated in ports with repetitive impact increase their risk of spondylolisthesis or hip growth plat ijuries [see Warnings and Precautions (5.12)].

Inform pediatric patients and their caregivers that pediatric patients treated with isotretinoir capsules developed back pain including severe back pain, and arthralgias including severe arthralgias *[see Use in Specific Populations (8.4)]*.

Inform patients that they may experience dry eyes, corneal opacities, and decreased night vision and contact lens wearers may experience decreased tolerance to contact lenses during and after therapy [see Warnings and Precautions (5.13)].

form patients there have been rare post-marketing reports of rhabdomyolysis in patients eated with isotretinoin capsules, some associated with strenuous physical activity [see Warnings and Precautions (5.15)]. Hypersensitivity Reactions

Given that anaphylactic reactions and other allergic reactions have been reported in patients ated with isotretinoin capsules, instruct the patient to discontinue isotretinoin capsules ntact their healthcare provider if they have a severe allergic reaction [see Warnings and

truct patients that hypertriglyceridemia, decreased HDL, and increased cholesterol levels re reported in patients treated with isotretinoin capsules [see Warnings and Precautions Additional Instructions

 To not share isotretinoin capsules with anyone else because of the risk of birth defects and other serious adverse reactions That transient exacerbation (flare) of acne has been seen, generally during the initial period

That wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during isotretinoin therapy and for at least 6 months thereafter due to the

possibility of scarring. To avoid prolonged exposure to UV rays or sunlight.

UPSHER-SMITH LABORATORIES, LLC Maple Grove, MN 55369

Revised 0120

ME	DICA			GUIDE	
eye"	soe	tret'	İ	noyn) Capsules,	USP

Read the Medication Guide that comes with otretinoin capsules before you start taking it and each time you get a prescription. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about isotretinoin capsules? Isotretinoin capsules can harm your unborn baby, including birth defects (deformed babies) loss of a baby before birth (miscarriage), death of the baby, and early (premature) births. Patients who are pregnant or who plan to become pregnant must not take isotretinoin capsules. Patients must not get pregnant:

• for 1 month before starting isotretinoin capsules • during treatment with isotretinoin capsules • for 1 month after stopping isotretinoin capsules If you get pregnant during treatment with

isotretinoin capsules, stop taking it right away and call your healthcare provider. Healthcare providers and patients should report all cases of pregnancy during treatment or 1 month after stopping treatment to:

• FDA MedWatch at 1-800-FDA-1088, and the iPLEDGE Pregnancy Registry at 1-866-495-0654 or www.ipledgeprogram.com

Because isotretinoin capsules can cause birth **defects**, isotretinoin capsules are only for patients who can understand and agree to carry out all of the instructions in the iPLEDGE Program.

Serious mental health problems, including: • depression

- **psychosis** (seeing or hearing things that are not
- **suicide.** Some patients taking isotretinoin capsules have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. Some people have ended their own lives.

Stop taking isotretinoin capsules and call your healthcare provider right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:

- start to feel sad or have crying spells
- lose interest in activities you once enjoyed
- sleep too much or have trouble sleeping
- become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
- have a change in your appetite or body weight • have trouble concentrating
- withdraw from your friends or family
- feel like you have no energy
- have feelings of worthlessness or guilt
- start having thoughts about hurting yourself or taking your own life (suicidal thoughts)
- start acting on dangerous impulses
- start seeing or hearing things that are not real

Your healthcare provider may tell you to see a mental healthcare professional if you had any of these symptoms.

What are isotretinoin capsules?

Isotretinoin capsules are prescription medicines used in patients 12 years of age and older, who are not pregnant, for the treatment of severe acne (nodular acne) that cannot be cleared up by any other acne treatments, including antibiotics. Isotretinoin capsules can cause serious side effects (see "What

is the most important information I should know about isotretinoin capsules?").

- Isotretinoin capsules can only be: • prescribed by healthcare providers that are registered in the iPLEDGE Program
- dispensed by a pharmacy that is registered with the iPLEDGE Program
- given to patients who are registered in the iPLEDGE Program and agree to do everything required in the program.

It is not known if isotretinoin capsules are safe and effective in children less than 12 years of age.

Do not take isotretinoin capsules if you:

- are pregnant, plan to become pregnant, or become pregnant during isotretinoin capsules **treatment.** Isotretinoin capsules cause severe birth defects. See "What is the most important information I should know about isotretinoin capsules?"
- are allergic to isotretinoin, vitamin A, or any of the ingredients in isotretinoin capsules. See the end of this Medication Guide for a complete list of ingredients in isotretinoin capsules.

Before taking isotretinoin capsules, tell your healthcare provider if you or a family member has any of the following health conditions:

- mental health problems
- asthma
- liver problems
- diabetes
- heart disease
- increase blood fat levels (cholesterol and triglycerides) bone loss (osteoporosis), weak bones or any other
- bone problems an eating problem called anorexia nervosa (where
- people eat too little) food or medicine allergies, including aspirin or
- tartrazine

Tell your healthcare provider if you are pregnant or breastfeeding. Do not breastfeed during treatment or for at least 8 days after the last dose of isotretinoin capsules.

Tell your healthcare provider about all of the medicines you take including prescription and over-the-counter medicines, vitamins and herbal supplements, including St. John's Wort. isotretinoin capsules and certain other medicines can affect each other, sometimes causing serious side effects.

Do not take the following medicines during treatment with isotretinoin capsules:

- vitamin A supplements
- tetracycline antibiotics

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist. Do not take any new medicine without talking with your healthcare provider.

How should I take isotretinoin capsules?

You must take isotretinoin capsules exactly as prescribed. You must also follow all the instructions of the iPLEDGE Program. Before prescribing isotretinoin capsules, your healthcare provider will:

- explain the iPLEDGE Program to you • have you sign the Patient Information/Informed
- Consent form (for all patients). Patients who can get pregnant must also sign another consent
- give you a pregnancy test to make sure you are not pregnant before you start isotretinoin capsules. You will receive 2 pregnancy tests at least 19 days apart.

You will not be prescribed isotretinoin capsules if you cannot agree to or follow all the instructions of the iPLEDGE Program.

- You will get no more than a 30-day supply of isotretinoin capsules at a time. This is to make sure you are following the isotretinoin capsules iPLEDGE Program.
- The amount of isotretinoin capsules you take has been specially chosen for you. It is based on your body weight and may change during treatment.
- Take isotretinoin capsules 2 times a day with or without meals, unless your healthcare provider tells you otherwise. Swallow your isotretinoin capsules whole with a full glass of liquid. Do not chew or suck on the capsule. Isotretinoin capsules can hurt the tube that connects your mouth to your stomach (esophagus) if not swallowed whole.
- Your healthcare provider will tell you how long you will receive treatment with isotretinoin capsules. Your acne may continue to improve after treatment.
- If you miss a dose, just skip that dose. Do **not** take two doses at the same time.
- If you take too much isotretinoin capsules, call your healthcare provider or poison control center right away.
- Your acne may get worse when you first start taking isotretinoin capsules. This should last only a short while. Talk with your healthcare provider if this is a concern for you.
- You must return to your healthcare provider as directed to make sure you don't have signs of serious side effects. Your healthcare provider may do blood tests to check for serious side effects from isotretinoin capsules and may stop treatment if you get certain side effects.
- Patients who can get pregnant will get a pregnancy test each month, after you finish your course of treatment, and 1 month after you stop treatment with isotretinoin capsules.
- Patients who can get pregnant must use two separate forms of birth control at the same time for at least 1 month before, during treatment, and for 1 month after treatment with isotretinoin capsules. You must access the iPLEDGE Program system to answer questions about the program requirements and to enter your two chosen forms of birth control. To access the iPLEDGE Program system, go to www.ipledgeprogram.com or call 1-866-495-0654.

Talk about birth control options with your healthcare provider or go for a free visit to talk about birth control with another healthcare provider or family planning expert. Your healthcare provider can arrange this **free** visit, which will be paid for by the company that makes isotretinoin capsules.

If you have sex at any time without using two forms of birth control 1 month before, during, or 1 month after treatment, get pregnant, or miss your expected period, stop taking isotretinoin capsules and call your healthcare provider right away.

What should I avoid while taking isotretinoin capsules?

- Do not give blood during treatment with isotretinoin capsules and for one month after stopping isotretinoin capsules. If someone who is pregnant gets your donated blood, their baby may be exposed to isotretinoin and may be born with birth defects.
- Do not take other medicines or herbal products with isotretinoin capsules unless you talk to

your healthcare provider. See "**Before taking** isotretinoin capsules".

- Do not drive at night until you know if isotretinoin capsules have affected your vision. Isotretinoin capsules may decrease your ability to see in the dark.
- Do not have cosmetic procedures to smooth your skin, including waxing, dermabrasion, or laser procedures, during treatment with isotretinoin capsules and for at least 6 months after you **stop.** Isotretinoin capsules can increase your chance of scarring from these procedures. Check with your healthcare provider for advice about when you can have cosmetic procedures.
- Avoid sunlight and ultraviolet lights as much as possible. Tanning machines use ultraviolet lights. Isotretinoin capsules may make your skin more sensitive to light.
- Do not share isotretinoin capsules with other **people**. Isotretinoin capsules can cause birth defects and other serious health problems.

What are the possible side effects of isotretinoin capsules?

Isotretinoin capsules can cause serious side

- effects, including:
- See "What is the most important information I should know about isotretinoin capsules?" increased pressure in the brain (intracranial **hypertension**). Isotretinoin capsules can increase the pressure in your brain. This can lead to permanent loss of eyesight, and in rare cases, death. Stop taking isotretinoin capsules and call your healthcare provider right away if you get any
- of these signs of increased brain pressure: bad headache
- blurred vision
- dizziness
- nausea or vomiting
- seizures (convulsions)
- stroke
- serious skin problems. Skin rash can occur in patients taking isotretinoin capsules. Sometimes rash can be serious and may lead to death. Stop using isotretinoin capsules and call your healthcare provider right away if you get:
- conjunctivitis (red or inflamed eyes, like "pink eye")
- rash with a fever
- blisters on legs, arms or face • sores in your mouth, throat, nose or eyes
- peeling of your skin inflammation of your pancreas (pancreatitis) can happen in patients who take isotretinoin capsules and can lead to death. Call your healthcare provider right away if you have any of the following symptoms of pancreatitis:
- severe upper stomach (abdomen) pain
- swelling of your stomach
- nausea and vomiting ° fever
- increased blood fat (lipid) levels. Isotretinoin capsules can raise blood fat levels (cholesterol and triglycerides). Your healthcare provider will do blood tests to check your lipids before and during treatment. These problems usually go away when isotretinoin capsules treatment is finished.
- hearing problems. Stop using isotretinoin capsules and call your healthcare provider if your hearing gets worse or if you have ringing in your ears. Your hearing loss may be permanent.
- liver problems, including hepatitis. Your healthcare provider will do tests to check your liver before and during treatment with isotretinoin capsules. Call your healthcare provider if you get:
- ° vellowing of your skin or the whites of your eyes
- pain on the right side of your stomach area (abdomen)
- dark urine

diarrhea

rectal bleeding

• bleeding or bruising more easily than normal

inflammation of your digestive tract (inflammatory bowel disease). Stop taking isotretinoin capsules and call your healthcare

• trouble swallowing or painful swallowing

bone and muscle problems. Bone problems

may lead to fractures). Tell your healthcare

include bone pain, softening or thinning (which

provider if you get:

• new or worsening heartburn

• severe stomach, chest or bowel pain nausea or vomiting

provider if you plan hard physical activity during treatment with isotretinoin capsules. Tell your healthcare provider if you get:

 joint pain or muscle pain • broken bone. Tell all healthcare providers that you take isotretinoin capsules if you break a bone.

Stop isotretinoin capsules and call your healthcare provider right away if you have muscle weakness. Muscle weakness with or without pain can be a sign of serious muscle

back pain

damage.

bruises on your legs.

capsules include:

dry lips

dry skin

• back pain

dry eyes

• joint pain

nose bleeds

headache

skin reactions

muscle problems

the reach of children.

dioxide.

DOUG13

APX1149

Manufactured for

Maple Grove, MN 55369

Made in New Zealand

Isotretinoin capsules may stop long bone growth in teenagers who are still growing.

vision problems. Stop taking isotretinoin capsules and call your healthcare provider right away if you have any vision changes. isotretinoin capsules may affect your ability to see in the dark. This usually goes away after you stop taking isotretinoin capsules, but it may be permanent. Some patients get dry eyes during treatment. If you wear contact lenses, you may have trouble wearing them during and after you stop treatment with isotretinoin capsules.

serious allergic reactions. Stop taking isotretinoin capsules and get emergency medical help right away if you get hives, a swollen face or mouth, or have trouble breathing. Stop taking isotretinoin capsules and call your healthcare provider if you get a fever, rash, or red patches or

blood sugar problems, including diabetes. Tell your healthcare provider if you are very thirsty or urinate more than usual.

The most common side effects of isotretinoin

 upper respiratory tract infection (common cold) chapped lips or swelling of the lips

 eye problems, including decreased vision These are not all of the possible side effects of isotretinoin capsules. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or Upsher-Smith Laboratories, LLC at 1-855-899-9180.

How should I store isotretinoin capsules? Store isotretinoin capsules at room temperature. 68°F to 77°F (20°C to 25°C). Protect from light.

Keep isotretinoin capsules and all medicines out of

General Information about the safe and effective use of isotretinoin capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use isotretinoin capsules for a condition for which it was not prescribed. Do not give isotretinoin capsules to other people, even if they have the same nploms lhal you nave. Il may harm lhem. You can ask your healthcare provider or pharmacist for information about isotretinoin capsules that is written for health professionals. You can also call iPLEDGE Program at 1-866-495-0654 or visit www.ipledgeprogram.com.

What are the ingredients in isotretinoin capsules? Active ingredient: isotretinoin **Inactive ingredients:** butylated hydroxyanisole,

disodium edetate, hydrogenated vegetable oil Type I, hydrogenated vegetable oil Type II, soybean oil, vitamin E and yellow wax. The gelatin capsules contain the following: glycerin, iron oxide (red and yellow), ferrosoferric oxide, sorbitol and titanium

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For Medication Guides, please visit www.upsher-smith.com or call 1-888-650-3789.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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