

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ABSORICA safely and effectively. See full prescribing information for ABSORICA.

ABSORICA® (isotretinoin) capsules, for oral use
Initial U.S. Approval: 1982

WARNING: CAUSES BIRTH DEFECTS

See full prescribing information for complete boxed warning.

Pregnancy Category X.

- ABSORICA must not be used by female patients who are or may become pregnant (5, 8.1, 8.6).
- There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking ABSORICA in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected (5.1, 8.1).
- There are no accurate means of determining whether an exposed fetus has been affected (5.1, 8.1).
- ABSORICA is available only through a restricted program called the iPLEDGE program. Prescribers, patients, pharmacies, and distributors must enroll in the program (5.2).

INDICATIONS AND USAGE

ABSORICA is a retinoid indicated for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older (1).

Limitations of Use

ABSORICA may only be administered to patients enrolled in the iPLEDGE program (1, 5.2).

DOSAGE AND ADMINISTRATION

- Recommended dosage of 0.5 to 1 mg/kg/day given in two divided doses without regards to meals for 15 to 20 weeks (2.1).
- Once daily dosing is **not** recommended (2.1).
- Perform pregnancy tests prior to prescribing, each month during therapy, end of therapy, and one month after discontinuation (2.4, 8.6).
- Prior to prescribing, perform fasting lipid profile and liver function tests (2.4).
- ABSORICA is not substitutable with other forms of isotretinoin (12.3).

DOSAGE FORMS AND STRENGTHS

Capsules: 10 mg, 20 mg, 25 mg, 30 mg, 35 mg and 40 mg (3)

CONTRAINDICATIONS

- Pregnancy (4.1, 8.1)
- Hypersensitivity to this product or any of its components (4.2, 5.14)

WARNINGS AND PRECAUTIONS

- Unacceptable Contraception: Micro-dosed progesterone preparations are not an acceptable method of contraception during ABSORICA therapy (5.3)
- Psychiatric Disorders: Depression, psychosis, suicidal thoughts and behavior, and aggressive and/or violent behaviors (5.4)
- Pseudotumor cerebri, some cases with concomitant tetracyclines (5.5)
- Serious skin reactions: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (5.6)
- Acute pancreatitis, rarely fatal hemorrhagic pancreatitis, in patients with either elevated or normal serum triglyceride levels (5.7)
- Lipid Abnormalities: Triglyceridemia low HDL and elevation of cholesterol. Monitor lipid levels at regular intervals (5.8, 5.15)
- Hearing Impairment (5.9)
- Hepatotoxicity: Monitor liver function tests at regular intervals (5.10, 5.15)
- Inflammatory Bowel Disease (5.11)
- Skeletal Abnormalities: Arthralgias, back pain, decreases in bone mineral density and premature epiphyseal closure (5.12)
- Ocular Abnormalities: corneal opacities, decreased night vision (5.13)
- Glucose and CPK Abnormalities (5.15)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 5\%$) are: lip dry, dry skin, back pain, dry eye, arthralgia, epistaxis, headache, nasopharyngitis, chapped lips, dermatitis, blood creatine kinase increased, cheilitis, musculoskeletal discomfort, upper respiratory tract infection, visual acuity reduced (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Ranbaxy, Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch or iPLEDGE at (1-866-495-0654).

DRUG INTERACTIONS

- Vitamin A: may cause additive adverse reactions (7.1)
- Tetracyclines: avoid concomitant use (7.2)
- St. John's Wort: may interfere with oral contraceptives (7.4)

See Section 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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FULL PRESCRIBING INFORMATION

WARNING: CAUSES BIRTH DEFECTS

Pregnancy Category X.

- **ABSORICA must not be used by female patients who are or may become pregnant** [see *Warnings and Precautions (5)* and *Use in Specific Populations (8.1, 8.6)*].
- **There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking ABSORICA in any amount, even for short periods of time** [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)*].
- **Potentially any fetus exposed during pregnancy can be affected** [see *Use in Specific Populations (8.1)*].
- **There are no accurate means of determining whether an exposed fetus has been affected** [see *Warning and Precautions (5.1)* and *Use in Specific Populations (8.1)*].
- **Birth defects which have been documented following isotretinoin 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** [see *Use in Specific Populations (8.1)*].
- **Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia; facial dysmorphism; 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 abnormalities previously noted** [see *Use in Specific Populations (8.1)*].
- **If pregnancy does occur during the treatment of a female patient who is taking ABSORICA, ABSORICA must be discontinued immediately and she should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling** [see *Use in Specific Populations (8.1)*].

Special Prescribing Requirements

- **Because of the risk of teratogenicity and to minimize fetal exposure, ABSORICA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called iPLEDGE™. Under the ABSORICA REMS, prescribers, patients, pharmacies, and distributors must enroll and be registered in the program** [see *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

ABSORICA is a retinoid indicated for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. “Severe,” by definition, means “many” as opposed to “few or several” nodules. Because of significant adverse reactions associated with its use, ABSORICA should be reserved for patients with multiple severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, ABSORICA is indicated only for those female patients who are not pregnant, because ABSORICA can cause severe birth defects [see *Contraindications (4.1)*].

Limitations of Use

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. 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 with isotretinoin has shown that patients may continue to improve following treatment with isotretinoin. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth [see *Warnings and Precautions (5.12)*].

As a part of the iPLEDGE program, ABSORICA may only be administered to patients enrolled in the program [see *Warnings and Precautions (5.2)*].

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe ABSORICA must be certified in the iPLEDGE program and must comply with the required monitoring to ensure safe use of ABSORICA [see *Warnings and Precautions (5.2)*].

The required laboratory testing must be completed prior to dosing ABSORICA [see *Dosage and Administration (2.4)*].

Pregnancy Testing, and Contraceptive measures must be followed prior to dosing ABSORICA [see *Use in Specific Populations (8.6)*].

2.1 Recommended Dosage

The recommended dosage range for ABSORICA is 0.5 to 1 mg/kg/day given in two divided doses without regard to meals for 15 to 20 weeks (see Table 1). To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid [see *Patient Counseling Information (17)*].

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

Table 1: ABSORICA Dosing by Body Weight (Based on Administration With or Without Food)

Body Weight		Total Daily (mg)		
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

2.2 Dosage Range

In trials comparing 0.1, 0.5, and 1 mg/kg/day, 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.

2.3 Duration of Use

A normal course of treatment is 15 – 20 weeks. 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 ABSORICA, even in low doses, has not been studied, and is not recommended. It is important that ABSORICA be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of ABSORICA on bone loss is unknown [see *Warnings and Precautions (5.12)*].

2.4 Laboratory Testing

Pregnancy Testing

[See *Use in Specific Populations (8.6)*]

Lipid Profile

Perform a fasting lipid profile including triglycerides prior to use of ABSORICA [see *Warnings and Precautions (5.8, 5.15)*].

Liver Function Test

Perform liver function tests prior to use of ABSORICA [see *Warnings and Precautions (5.10, 5.15)*].

3 DOSAGE FORMS AND STRENGTHS

ABSORICA is available in 10 mg, 20 mg, 25 mg, 30 mg, 35 mg and 40 mg capsules.

- **10 mg:** Dark yellow, opaque, capsule imprinted with black ink “G 240” on cap and “10” on the body
- **20 mg:** Red, opaque, capsule imprinted with black ink “G 241” on cap and “20” on the body

- **25 mg:** Green, opaque, capsule imprinted with white ink “G 342” on cap and “25” on the body
- **30 mg:** Brown, opaque, capsule imprinted with white ink “G 242” on cap and “30” on the body
- **35 mg:** Dark blue, opaque, capsule imprinted with white ink “G 343” on cap and “35” on the body
- **40 mg:** Brown and red, capsule imprinted with white ink “G 325” on cap and “40” on the body

4 CONTRAINDICATIONS

4.1 Pregnancy

ABSORICA can cause fetal harm when administered to a pregnant woman. Major congenital malformations, spontaneous abortions, and premature births have been documented following pregnancy exposure to isotretinoin in any amount and even for short periods of time. ABSORICA is contraindicated in females who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient should be apprised of the potential hazard to the fetus [see *Use in Specific Populations* (8.1)].

4.2 Hypersensitivity

Hypersensitivity to this product (or Vitamin A, given the chemical similarity to isotretinoin) or to any of its components [see *Warnings and Precautions* (5.14)].

5 WARNINGS AND PRECAUTIONS

ABSORICA must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking ABSORICA in any amount, even for short periods of time.

5.1 Embryofetal Toxicity

Teratogenicity

Major congenital malformations, spontaneous abortions, and premature births have been documented following pregnancy exposure to isotretinoin [see *Use in Specific Populations* (8.1)]. Females of childbearing potential must comply with the pregnancy testing and contraception requirements described in the iPLEDGE program [see *Warnings and Precautions* (5.2) and *Use in Specific Populations* (8.6)]. There are no accurate means of determining whether an exposed fetus has been affected.

No Blood Donation

Patients must be informed not to donate blood during isotretinoin therapy and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to isotretinoin.

5.2 iPLEDGE Program

Because of the risk of teratogenicity and to minimize fetal exposure, ABSORICA is available only through a restricted program under a REMS called iPLEDGE. Under the ABSORICA REMS, prescribers, patients, pharmacies, and distributors must enroll and be registered in the program. ABSORICA must not be prescribed, dispensed or otherwise obtained through the internet or any other means outside of the iPLEDGE program. Only FDA-approved isotretinoin products must be distributed, prescribed, dispensed, and used.

Required components of the iPLEDGE Program are:

- ABSORICA must only be prescribed by prescribers who are registered and activated with the iPLEDGE program and agree to comply with the REMS requirements described in the booklets entitled *The Guide to Best Practices for the iPLEDGE Program*, *The iPLEDGE Program Prescriber Contraception Counseling Guide*, and *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin*.
- Male patients and Female patients not of childbearing potential: To obtain ABSORICA, these patients must understand the risks and benefits of ABSORICA, comply with the REMS requirements described in the booklet entitled *The iPLEDGE Program Guide to Isotretinoin for Male Patients and Female Patients Who Cannot Get Pregnant*, and sign a Patient Information/Informed Consent form.
- Female patients of childbearing potential: ABSORICA is contraindicated in female patients who are or may become pregnant [see *Contraindications* (4.1)].
- Female patients of childbearing potential who are not pregnant must understand the risks and benefits, comply with the REMS requirements

described in the booklet entitled *The iPLEDGE Program Guide to Isotretinoin for Female Patients Who Can Get Pregnant and The iPLEDGE Program Birth Control Workbook* (including the pregnancy testing and contraception requirements [see *Use in Specific Populations* (8.6) and *Patient Counseling Information* (17)]), and sign a Patient Information/Informed Consent form and Patient Information/Informed Consent About Birth Defects form. Additionally, the patient must answer questions about the iPLEDGE program and pregnancy prevention monthly.

- Pharmacies that dispense ABSORICA must be registered and activated with iPLEDGE, must only dispense to patients who are authorized to receive ABSORICA, and agree to comply with the REMS requirements described in the booklet entitled *The Pharmacist Guide for the iPLEDGE Program*.
- Female patients of childbearing potential must fill and pick up the prescription within 7 days of the specimen collection for the pregnancy test; male patients and female patients not of childbearing potential must fill and pick up the prescription within 30 days of the office visit.
- ABSORICA must only be dispensed in no more than a 30-day supply with a Medication Guide. Refills require a new prescription and a new authorization from the iPLEDGE system.
- Wholesalers and distributors that distribute ABSORICA must be registered with iPLEDGE and agree to comply with the REMS requirements.

If a pregnancy does occur during ABSORICA treatment, ABSORICA 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 1 month after ABSORICA 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).

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

5.3 Unacceptable Contraception

Micro-dosed Progesterone Preparations

Micro-dosed progesterone preparations (“minipills” that do not contain an estrogen) are an inadequate method of contraception during ABSORICA therapy.

5.4 Psychiatric Disorders

Isotretinoin 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 reactions [see *Adverse Reactions* (6.1)]. 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 ABSORICA 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 ABSORICA 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 ABSORICA 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 ABSORICA therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of ABSORICA therapy.

5.5 Pseudotumor Cerebri

Isotretinoin use has been associated with 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 ABSORICA immediately and be referred to a neurologist for further diagnosis and care [see *Adverse Reactions* (6.1)].

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 isotretinoin use. These reactions 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 ABSORICA should be considered if warranted.

5.7 Pancreatitis

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

5.8 Lipid Abnormalities

Elevations of serum triglycerides in excess of 800 mg/dL have been reported in patients treated with isotretinoin. Marked elevations of serum triglycerides were reported in approximately 25% of patients receiving isotretinoin 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 of triglycerides, HDL and cholesterol were reversible upon cessation of isotretinoin therapy. Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in the dose while continuing isotretinoin.

Blood lipid determinations should be performed before ABSORICA is given and then at intervals until the lipid response to ABSORICA 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 of triglyceridemia during ABSORICA therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If ABSORICA therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended [see *Warnings and Precautions* (5.15)].

The cardiovascular consequences of hypertriglyceridemia associated with isotretinoin are unknown.

5.9 Hearing Impairment

Impaired hearing has been reported in patients taking isotretinoin; in some cases, the hearing impairment has been reported to persist after therapy has been discontinued. Mechanism(s) and causality for this reaction have not been established. Patients who experience tinnitus or hearing impairment should discontinue ABSORICA treatment and be referred for specialized care for further evaluation [see *Adverse Reactions* (6.1)].

5.10 Hepatotoxicity

Clinical hepatitis considered to be possibly or probably related to isotretinoin therapy has been reported. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials with isotretinoin, 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 ABSORICA, the drug should be discontinued and the etiology further investigated.

5.11 Inflammatory Bowel Disease

Isotretinoin 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 isotretinoin treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue ABSORICA immediately [see *Adverse Reactions* (6.1)].

5.12 Skeletal Abnormalities

Bone Mineral Density Changes

Isotretinoin may have a negative effect on bone mineral density (BMD) in some patients. In a clinical trial of ABSORICA and a generic product of Accutane® (isotretinoin), 27/306 (8.8%) of adolescents had BMD declines, defined as $\geq 4\%$ lumbar spine or total hip, or $\geq 5\%$ femoral neck, during the 20 week treatment period. Repeat scans conducted within 2-3 months after the post-treatment scan showed no recovery of BMD. Longer term data at 4-11 months showed that 3 out of 7 patients had total hip and femoral neck BMD below pre-treatment baseline, and 2 others did not show the increase in BMD above baseline expected in this adolescent population. Therefore, physicians

should use caution when prescribing ABSORICA to patients with 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 [see *Use in Specific Populations* (8.4)].

Musculoskeletal Abnormalities

Approximately 16% of patients treated with isotretinoin 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.

In a trial of pediatric patients treated with isotretinoin, approximately 29% (104/358) 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 ABSORICA. Consideration should be given to discontinuation of ABSORICA if any significant abnormality is found.

There have been spontaneous reports of osteoporosis, osteopenia, bone fractures and/or delayed healing of bone fractures in patients while on therapy with isotretinoin or following cessation of therapy with isotretinoin. While causality to isotretinoin has not been established, an effect cannot be ruled out.

Patients may be at an increased risk when participating in sports with repetitive impact where the risks of spondylolysis with and without pars fractures and hip growth plate injuries in early and late adolescence are known.

Effects of multiple courses of isotretinoin on the developing musculoskeletal system are unknown. There is some evidence that long-term, high-dose, or multiple courses of therapy with isotretinoin have more of an effect than a single course of therapy on the musculoskeletal system.

Longer term effects have not been studied. It is important that ABSORICA 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 of isotretinoin. Additionally, skeletal hyperostosis was noted 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 recommended doses. The skeletal effects of multiple isotretinoin treatment courses for acne are unknown.

In a clinical trial 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 isotretinoin 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 literature reports of premature epiphyseal closure in acne patients receiving recommended doses of isotretinoin. The effect of multiple courses of isotretinoin on epiphyseal closure is unknown.

In a 20-week clinical trial that included 289 adolescents on ABSORICA or a generic product of Accutane® (isotretinoin) who had hand radiographs taken to assess bone age, a total of 9 (3.11%) patients had bone age changes that were clinically significant and for which a drug-related effect cannot be excluded.

5.13 Ocular Abnormalities

Visual problems should be carefully monitored. All ABSORICA patients experiencing visual difficulties should discontinue ABSORICA treatment and have an ophthalmological examination [see *Adverse Reactions* (6.1)].

Corneal Opacities

Corneal opacities have occurred in patients receiving isotretinoin 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 isotretinoin have either completely resolved

or were resolving at follow-up 6 to 7 weeks after discontinuation of the drug [see *Adverse Reactions* (6.1)].

Decreased Night Vision

Decreased night vision has been reported during isotretinoin 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.

Dry Eye

Dry eye has been reported in subjects during isotretinoin therapy. Patients who wear contact lenses may have trouble wearing them while on ABSORICA treatment and afterwards.

5.14 Hypersensitivity

Anaphylactic reactions and other allergic reactions have been reported in isotretinoin-treated patients. 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.

5.15 Laboratory Monitoring for Adverse Reactions

Lipids Test

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 ABSORICA is established. The incidence of hypertriglyceridemia is 1 patient in 4 on isotretinoin [see *Warnings and Precautions* (5.8)].

Liver Function Test

Since elevations of liver enzymes have been observed during clinical trials, and hepatitis has been reported in patients on isotretinoin, pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to ABSORICA has been established [see *Warnings and Precautions* (5.10)].

Glucose

Some patients receiving isotretinoin have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during isotretinoin therapy, although no causal relationship has been established.

CPK

Some patients undergoing vigorous physical activity while on isotretinoin 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 an isotretinoin clinical trial of 924 patients, marked elevations in CPK (≥ 350 U/L) were observed in approximately 24% of patients. In another clinical trial of 217 pediatric patients (12 – 17 years) 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 clinical trial.

6 ADVERSE REACTIONS

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

- Embryofetal Toxicity [see *Warnings and Precautions* (5.1)]
- Psychiatric Disorders [see *Warnings and Precautions* (5.4)]
- Pseudotumor Cerebri [see *Warnings and Precautions* (5.5)]
- Serious Skin Reactions [see *Warnings and Precautions* (5.6)]
- Pancreatitis [see *Warnings and Precautions* (5.7)]
- Lipid Abnormalities [see *Warnings and Precautions* (5.8)]
- Hearing Impairment [see *Warnings and Precautions* (5.9)]
- Hepatotoxicity [see *Warnings and Precautions* (5.10)]
- Inflammatory Bowel Disease [see *Warnings and Precautions* (5.11)]
- Skeletal Abnormalities [see *Warnings and Precautions* (5.12)]
- Ocular Abnormalities [see *Warnings and Precautions* (5.13)]
- Hypersensitivity [see *Warnings and Precautions* (5.14)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of ABSORICA cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The adverse reactions listed below reflect both clinical experience with ABSORICA, and consider other adverse reactions that are known from clinical trials and the post-marketing surveillance with oral isotretinoin. The relationship of some of these events to isotretinoin therapy is unknown. Many of the side effects and adverse events seen in patients receiving isotretinoin are similar to those described in patients taking very high doses of vitamin A (dryness of the skin and mucous membranes, e.g., of the lips, nasal passage, and eyes).

Dose Relationship

Cheilitis and hypertriglyceridemia are adverse reactions that are usually dose related. Most adverse reactions reported in clinical trials with isotretinoin were reversible when therapy was discontinued; however, some persisted after cessation of therapy.

Body as a Whole

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): fatigue, irritability, pain. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: allergic reactions, including vasculitis, systemic hypersensitivity, edema, lymphadenopathy, weight loss.

Cardiovascular

The following adverse reactions have been reported with isotretinoin: vascular thrombotic disease, stroke, palpitation, tachycardia.

Endocrine/Metabolism and Nutritional

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): decreased appetite, weight fluctuation, hyperlipidaemia. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: hypertriglyceridemia, alterations in blood sugar.

Gastrointestinal

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): lip dry, chapped lips, cheilitis, nausea, constipation, diarrhea, abdominal pain, vomiting. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: inflammatory bowel disease, hepatitis, pancreatitis, bleeding and inflammation of the gums, colitis, esophagitis/esophageal ulceration, ileitis, and other nonspecific gastrointestinal symptoms.

Hematologic

The following adverse reactions have been reported with isotretinoin: allergic reactions, anemia, thrombocytopenia, neutropenia, rare reports of agranulocytosis.

Infections and infestations

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): nasopharyngitis, hordeolum, upper respiratory tract infection. In addition to the above adverse reactions, the following adverse reaction has been reported with isotretinoin: infections (including disseminated herpes simplex).

Laboratory Abnormalities

The following changes in laboratory tests have been noted in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): blood creatine phosphokinase (CPK) increased, blood triglycerides increased, alanine aminotransferase (SGPT) increased, aspartate aminotransferase (SGOT) increased, gamma-glutamyltransferase (GGTP) increased, blood cholesterol increased, low density lipoprotein (LDL) increased, white blood cell count decreased, blood alkaline phosphatase increased, blood bilirubin increased, blood glucose increased, high density lipoprotein (HDL) decreased, bone mineral density decreased. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: increased LDH, elevation of fasting blood sugar, hyperuricemia, decreases in red blood cell parameters, decreases in white blood cell counts (including severe neutropenia and rare reports of agranulocytosis), elevated sedimentation rates, elevated platelet counts, thrombocytopenia, white cells in the urine, proteinuria, microscopic or gross hematuria.

Musculoskeletal and Connective Tissue

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane® (isotretinoin): decreases in bone mineral density, musculoskeletal symptoms (sometimes severe) including back pain, athralgia, musculoskeletal discomfort, musculoskeletal pain, neck pain, pain in extremity, myalgia, musculoskeletal stiffness [see *Warnings and Precautions (5.12)*]. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, tendonitis, arthritis, transient pain in the chest, and rare reports of rhabdomyolysis.

Neurological

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane® (isotretinoin): headache, syncope. In addition to the above adverse reactions, other adverse reactions reported with isotretinoin include: pseudotumor cerebri, dizziness, drowsiness, lethargy, malaise, nervousness, paresthesias, seizures, stroke, weakness.

Psychiatric

The following adverse reactions have been reported in clinical trials conducted with ABSORICA and a generic product of Accutane® (isotretinoin): suicidal ideation, insomnia, anxiety, depression, irritability, panic attack, anger, euphoria, violent behaviors, emotional instability. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: suicide attempts, suicide, aggression, psychosis and hallucination auditory. Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstatement of therapy.

Reproductive System

The following adverse reaction has been reported with isotretinoin: abnormal menses.

Respiratory

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane® (isotretinoin): epistaxis, nasal dryness. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: bronchospasms (with or without a history of asthma), respiratory infection, voice alteration.

Skin and Subcutaneous Tissue

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane® (isotretinoin): dry skin, dermatitis, eczema, rash, dermatitis contact, alopecia, pruritus, sunburn, erythema. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: acne fulminans, alopecia (which in some cases persists), bruising, dry nose, eruptive xanthomas, erythema multiforme, flushing, fragility of skin, hair abnormalities, hirsutism, hyperpigmentation and hypopigmentation, 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), abnormal wound healing (delayed healing or exuberant granulation tissue with crusting).

Special Senses

Hearing: The following adverse reactions have been reported with isotretinoin: tinnitus and hearing impairment.

Ocular: The following adverse reactions have been reported in clinical trials conducted with ABSORICA and a generic product of Accutane® (isotretinoin): dry eye, visual acuity reduced, vision blurred, eye pruritus, eye irritation, asthenopia, decreased night vision, ocular hyperemia, increased lacrimation, and conjunctivitis. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: corneal opacities, decreased night vision which may persist, cataracts, color vision disorder, conjunctivitis, eyelid inflammation, keratitis, optic neuritis, photobia, visual disturbances.

Renal and Urinary

The following adverse reactions have been reported in clinical trials conducted with isotretinoin: glomerulonephritis, nonspecific urogenital findings.

7 DRUG INTERACTIONS

7.1 Vitamin A

ABSORICA is closely related to vitamin A. Therefore, the use of both vitamin A and ABSORICA at the same time may lead to vitamin A side effects. Patients should be advised against taking vitamin supplements containing Vitamin A to avoid additive toxic effects.

7.2 Tetracyclines

Concomitant treatment with ABSORICA and tetracyclines should be avoided because isotretinoin use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines.

7.3 Phenytoin

Isotretinoin has not been shown to alter the pharmacokinetics of phenytoin in a trial 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 CYP2C9 human hepatic P450 enzyme. 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 St. John's Wort

Isotretinoin use is associated with depression in some patients. 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.

7.5 Systemic Corticosteroids

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

7.6 Norethindrone/ethinyl estradiol

In a trial of 31 premenopausal female patients with severe recalcitrant nodular acne receiving Norethindrone/ethinyl estradiol as an oral contraceptive agent, isotretinoin 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see *Contraindications (4) and Warnings and Precautions (5.1)*].

Risk Summary

ABSORICA is contraindicated during pregnancy because isotretinoin can cause fetal harm when administered to a pregnant woman. There is an increased risk of major congenital malformations, spontaneous abortions, and premature births following isotretinoin exposure during pregnancy in humans. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to a fetus.

Clinical Considerations

If pregnancy does occur during treatment of a female patient who is taking ABSORICA, ABSORICA must be discontinued immediately and she should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Human Data

Major 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 (including anotia, micropinna, small or absent external auditory canals); eye (including microphthalmia); facial dysmorphism and cleft palate. Internal abnormalities include: CNS (including 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.

Isotretinoin is found in the semen of male patients taking isotretinoin, but the amount delivered to a female partner 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 and 20 years of post-marketing reports include four reports with isolated defects compatible with features of retinoid exposed fetuses, two of these reports were incomplete and two had other possible explanations for the defects observed.

Cases of IQ scores less than 85 with or without other abnormalities have been reported. An increased risk of spontaneous abortion and premature births have been documented with isotretinoin exposure during pregnancy.

8.3 Nursing Mothers

It is not known whether this drug is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from ABSORICA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The use of ABSORICA in pediatric patients less than 12 years of age has not been studied. The use of ABSORICA 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 *Warnings and Precautions* (5.12)]. Use of ABSORICA in this age group for severe recalcitrant nodular acne is supported by evidence from a clinical trial of ABSORICA compared to a generic product of Accutane® (isotretinoin) in 397 pediatric patients (12 to 17 years). Results from this trial demonstrated that both ABSORICA and the other isotretinoin drug product, at a dose of 1 mg/kg/day given in two divided doses, was effective in treating severe recalcitrant nodular acne in pediatric patients.

In trials with isotretinoin, 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. In a trial of pediatric patients treated with isotretinoin, approximately 29% (104/358) 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 ABSORICA. Consideration should be given to discontinuation of ABSORICA if any significant abnormality is found.

The effect on bone mineral density (BMD) of a 20-week course of therapy with ABSORICA or a generic product of Accutane® (isotretinoin) was evaluated in a double-blind, randomized clinical trial involving 396 adolescents with severe recalcitrant nodular acne (mean age 15.4, range 12-17, 80% males). Following 20 weeks of treatment, there were no statistically significant differences between the treatment groups. The mean changes in BMD from baseline for the overall trial population were 1.8% for lumbar spine, -0.1% for total hip and -0.3% for femoral neck. Mean BMD Z-scores declined from baseline at each of these sites (-0.053, -0.109 and -0.104 respectively). Out of 306 adolescents, 27 (8.8%) had clinically significant BMD declines defined as $\geq 4\%$ lumbar spine or total hip, or $\geq 5\%$ femoral neck, including 2 subjects for lumbar spine, 17 for total hip and 20 for femoral neck. Repeat DXA scans within 2-3 months after the post treatment scan showed no recovery of BMD. Longer-term follow up at 4-11 months showed that 3 out of 7 patients had total hip and femoral neck BMD below pre-treatment baseline, and 2 others did not show the increase in 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 *Warnings and Precautions* (5.12)].

In an open-label clinical trial (N=217) of a single course of therapy with isotretinoin for adolescents with 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 trials performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range -1.6% to -7.6%) in 5 of 8 patients (62.5%).

In a separate open-label extension trial of 10 patients, ages 13 to 18 years, who started a second course of isotretinoin 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25%.

There are spontaneous literature reports of premature epiphyseal closure in acne patients receiving recommended doses of isotretinoin. The effect of multiple courses of isotretinoin on epiphyseal closure is unknown. In a 20-week clinical trial that included 289 adolescents who had hand radiographs taken to assess bone age, a total of 9 patients had bone age changes that were clinically significant and for which a drug-related effect cannot be excluded [see *Warnings and Precautions* (5.12)].

8.5 Geriatric Use

Clinical trials of ABSORICA 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 ABSORICA therapy.

8.6 Females of Childbearing Potential

All females of childbearing potential must comply with the iPLEDGE program requirements [see *Warnings and Precautions* (5.2)].

Pregnancy Testing

ABSORICA must only be prescribed to female patients who are known not to be pregnant as confirmed by a negative CLIA-certified laboratory conducted pregnancy test. Female patients of childbearing potential must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial ABSORICA prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for ABSORICA. 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, perform the second pregnancy test during the first 5 days of the menstrual period immediately preceding the beginning of ABSORICA 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, perform the second pregnancy test immediately preceding the beginning of ABSORICA therapy and after the patient has used 2 forms of contraception for 1 month.

Each month of continued ABSORICA 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 female patient 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 isotretinoin.

Contraception

Females of childbearing potential must use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless the patient commits to continuous abstinence from heterosexual contact, or the patient has undergone a hysterectomy or bilateral oophorectomy, or has been medically confirmed to be post-menopausal. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of ABSORICA therapy, during ABSORICA therapy, and for 1 month after discontinuing ABSORICA therapy. Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) are an inadequate method of contraception during isotretinoin therapy [see *Warnings and Precautions* (5.3)].

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

Primary forms	Secondary forms
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<ul style="list-style-type: none"> • Tubal sterilization • Partner's vasectomy • Intrauterine device • Hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring) 	Barrier: <ul style="list-style-type: none"> • male latex condom with or without spermicide • diaphragm with spermicide • cervical cap with spermicide Other: <ul style="list-style-type: none"> • Vaginal sponge (contains spermicide)
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Any birth control method can fail. There have been reports of pregnancy from female patients who have used combination oral contraceptives, as well as transdermal patch/ injectable/ implantable/ vaginal ring hormonal birth control products; these pregnancies occurred while taking isotretinoin. These reports are more frequent for female patients who use only a single method of contraception. Therefore, it is critically important for female patients of childbearing potential use 2 effective forms of contraception simultaneously.

Using two forms of contraception simultaneously substantially reduces the chances that a female 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 isotretinoin. 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 [see *Drug Interactions* (7.4)].

If the patient has unprotected heterosexual intercourse at any time 1 month before, during, or 1 month after therapy, she must:

- Stop taking ABSORICA immediately, if on therapy
- Have a pregnancy test at least 19 days after the last act of unprotected heterosexual intercourse
- Start using 2 forms of effective contraception simultaneously again for 1 month before resuming ABSORICA therapy
- Have a second pregnancy test after using 2 forms of effective contraception for 1 month as described above depending on whether she has regular menses or not.

If a pregnancy does occur during ABSORICA treatment, ABSORICA 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 1 month after ABSORICA 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) [see *Warnings and Precautions* (5.2)].

10 OVERDOSAGE

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.

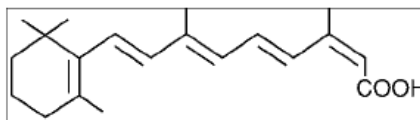
ABSORICA causes serious birth defects at any dosage (see Boxed CONTRAINDICATIONS AND WARNINGS). Female patients of childbearing potential who present with ABSORICA overdose must be evaluated for pregnancy. Patients who are pregnant should receive counseling about the risks to the fetus, as described 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 *Warnings and Precautions* (5). 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 1 month after the overdose. All patients with ABSORICA overdose should not donate blood for at least 1 month.

11 DESCRIPTION

ABSORICA (isotretinoin) Capsules contain 10 mg, 20 mg, 25 mg, 30 mg, 35 mg or 40 mg of isotretinoin (a retinoid) in hard gelatin capsules for oral administration. In addition to the active ingredient, isotretinoin, each capsule contains the following inactive ingredients: propyl gallate, sorbitan monooleate, soybean oil and stearyl polyoxyglycerides. The gelatin capsules contain the following dye systems:

- 10 mg – iron oxide (yellow) and titanium dioxide;
- 20 mg – iron oxide (red), and titanium dioxide;
- 25 mg – FD&C Blue #1, FD&C Yellow #5, FD&C Yellow #6 and titanium dioxide;
- 30 mg – iron oxide (black, red and yellow) and titanium dioxide;
- 35 mg – FD&C Blue #2, iron oxide (black, red and yellow) and titanium dioxide;
- 40 mg – iron oxide (black, red and yellow) and titanium dioxide.

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. It is practically insoluble in water, soluble in chloroform and sparingly soluble in alcohol and in isopropyl alcohol. The structural formula is:



Meets USP Dissolution Test 3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ABSORICA is a retinoid, which when administered in pharmacologic dosages of 0.5 to 1 mg/kg/day, inhibits sebaceous gland function and keratinization. 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 isotretinoin and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation. The exact mechanism of action of ABSORICA is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of ABSORICA are unknown.

12.3 Pharmacokinetics

Absorption

Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when given with a high-fat meal. ABSORICA is bioequivalent to Accutane® (isotretinoin) capsule when both drugs are taken with a high-fat meal. ABSORICA is more bioavailable than Accutane® (isotretinoin) capsules when both drugs are taken fasted; the AUC_{0-t} of ABSORICA is approximately 83% greater than that of Accutane®. ABSORICA is therefore not interchangeable with generic products of Accutane®.

A single dose two-way crossover pharmacokinetic trial was conducted in 14 healthy adult male subjects comparing ABSORICA 40 mg (1 x 40 mg capsules), dosed under fasted and fed conditions. Under fed conditions after a high-fat meal, it was observed that the mean AUC_{0-t} and C_{max} were approximately 50% and 26% higher, than that observed under fasting conditions (Table 2). The observed elimination half-life (T_{1/2}) was slightly lower in the fed state versus fasted. The time to peak concentration (T_{max}) increased with food and this may be related to a longer absorption phase.

Table 2: Pharmacokinetic parameters of ABSORICA mean (%CV) following administration of 40 mg strength, N=14

ABSORICA (1 x 40 mg capsules)	AUC _{0-t} (ng x hr/mL)	C _{max} (ng/mL)	T _{max} (hr)	T _{1/2} (hr)
Fed	6095 (26 %)	395 (39 %)	6.4 (47 %)	22 (25 %)
Fasted	4055 (20 %)	314 (26 %)	2.9 (34 %)	24 (28 %)

Published clinical literature has shown that there is no difference in the pharmacokinetics of isotretinoin between patients with nodular acne and healthy subjects with normal skin.

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 40 mg oral dose of ABSORICA to 57 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.

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 14C-isotretinoin as a liquid suspension, 14C-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 40 mg (2 x 20 mg) oral dose of ABSORICA to 57 healthy adult subjects under fed conditions, the mean \pm SD elimination half-lives ($T_{1/2}$) of isotretinoin and 4-*oxo*-isotretinoin under fed states were 18 hours and 38 hours, respectively.

Special Patient Populations

The pharmacokinetics of isotretinoin were evaluated after single and multiple doses in 38 pediatric patients (12 to 15 years) and 19 adult patients (\geq 18 years) who received isotretinoin 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. There were no statistically significant differences in the pharmacokinetics of isotretinoin between pediatric and adult patients.

13 NONCLINICAL TOXICOLOGY

13.1 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 1.6 x 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 trials 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 isotretinoin therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose.

13.2 Animal Toxicology

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).

14 CLINICAL STUDIES

A double-blind, randomized, parallel group trial (Study 1) was conducted in patients with severe recalcitrant nodular acne to evaluate the efficacy and safety of ABSORICA compared to a generic product of Accutane[®] under fed conditions. Enrolled patients had a weight of 40 to 110 kg with at least 10 nodular lesions on the face and/or trunk. A total of 925 patients were randomized 1:1 to receive ABSORICA or a generic product of Accutane[®] (isotretinoin). Study patients ranged from 12 to 54 years of age, were approximately 60% male, 40% female, and were 87% White, 4% Black, 6% Asian, and 3% Other. Patients were treated an initial dose of 0.5 mg/kg/day in two divided doses for the first 4 weeks followed by 1 mg/kg/day in two divided doses for the following 16 weeks.

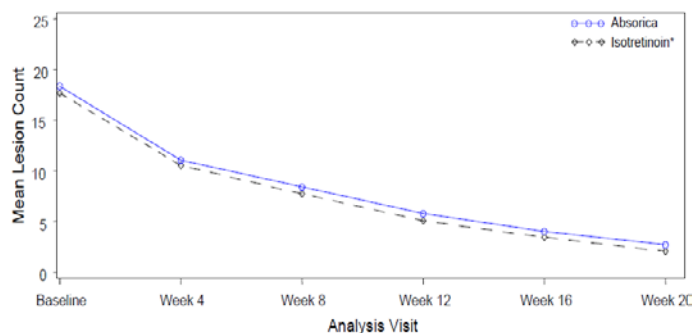
Change from Baseline to Week 20 in total nodular lesion count and proportion of patients with at least a 90% reduction in total nodular lesion count from Baseline to Week 20 are presented in Table 3. Total nodular lesion counts by visit are presented in Figure 1.

Table 3: Efficacy Results at Week 20 (Study 1)

	ABSORICA N=464	Isotretinoin* N=461
Nodular Lesions		
Mean Baseline Count	18.4	17.7
Mean Reduction	-15.68	-15.62
Patients Achieving 90% Reduction	324 (70%)	344 (75%)

*A generic product of Accutane[®]

Figure 1: Total Nodular (Facial and Truncal) Lesion Count by Visit in Study 1



*A generic product of Accutane[®]

16 HOW SUPPLIED/STORAGE AND HANDLING

ABSORICA (isotretinoin) Capsules are supplied as follows:

- **10 mg:** Dark yellow, opaque, capsule imprinted with black ink "G 240" on cap and "10" on the body
Box of 30 capsules (3 x 10 Prescription Packs): NDC 10631-115-31
- **20 mg:** Red, opaque, capsule imprinted with black ink "G 241" on cap and "20" on the body

Box of 30 capsules (3 x 10 Prescription Packs): NDC 10631-116-31

- **25 mg:** Green, opaque, capsule imprinted with white ink “G 342” on cap and “25” on the body
Box of 30 capsules (3 x 10 Prescription Packs): NDC 10631-133-31
- **30 mg:** Brown, opaque, capsule imprinted with white ink “G 242” on cap and “30” on the body
Box of 30 capsules (3 x 10 Prescription Packs): NDC 10631-117-31
- **35 mg:** Dark blue, opaque, capsule imprinted with white ink “G 343” on cap and “35” on the body
Box of 30 capsules (3 x 10 Prescription Packs): NDC 10631-134-31
- **40 mg:** Brown and red, capsule imprinted with white ink “G 325” on cap and “40” on the body
Box of 30 capsules (3 x 10 Prescription Packs): NDC 10631-118-31

Storage and Handling

Store at 20° C - 25° C (68° F - 77° F), excursion permitted between 15° C - 30° C (59° F - 86° F) [see USP controlled room temperature]. Protect from light.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide)

Advise the patient that ABSORICA is only available through a restricted program called iPLEDGE.

- As a component of the iPLEDGE program, prescribers must instruct patients to read the Medication Guide, the iPLEDGE program patient educational booklets, and watch the DVD with the following videos — “Be Prepared, Be Protected” and “Be Aware: The Risk of Pregnancy While on Isotretinoin”. The DVD includes information about contraception, the most common reasons that contraception fails, and the importance of using 2 forms of effective contraception when taking teratogenic drugs and comprehensive information about types of potential birth defects which could occur if a female patient who is pregnant takes ABSORICA at any time during pregnancy.
- Male patients and Female patients not of childbearing potential must understand the risks and benefits of ABSORICA, comply with the REMS requirements described in the booklet entitled *The iPLEDGE Program Guide to Isotretinoin for Male Patients and Female Patients Who Cannot Get Pregnant*, and sign a Patient Information/Informed Consent form.
- Female patients of childbearing potential must be instructed that they must not be pregnant when ABSORICA therapy is initiated or plan to become pregnant while receiving ABSORICA therapy. Additionally, they must use 2 forms of effective contraception simultaneously for 1 month before starting ABSORICA, while taking ABSORICA, and for 1 month after ABSORICA has been stopped, unless they commit to continuous abstinence from heterosexual intercourse. They should also sign a Patient Information/Informed Consent form and Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form prior to beginning ABSORICA therapy. Female patients 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 ABSORICA prescription is written. Additionally, a pregnancy test must be completed at the end of the entire course of ABSORICA therapy and 1 month after discontinuation of therapy.
- Advise the patient that isotretinoin is found in the semen of male patients taking isotretinoin, but the amount delivered to a female partner 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 post-marketing 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.
- Advise the patient that ABSORICA is available only from pharmacies that are certified in the iPLEDGE program, and provide them with the telephone number (1-866-495-0654) and website (www.ipledgeprogram.com) for information on how to obtain.
- Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the iPLEDGE program.
- 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 ABSORICA 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. Inform patients that **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 treatment 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 ABSORICA 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 ABSORICA therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of ABSORICA therapy.

- Patients must be informed that some patients, while taking isotretinoin or soon after stopping isotretinoin, 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 have tried to end their own lives, and some 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. There have also been reports of psychotic symptoms, which indicate a loss of contact with reality. Psychotic symptoms include feelings of suspiciousness toward others, strange beliefs, hearing voices or other noises without an obvious source, and seeing unusual objects or people with no explanation. No one knows if isotretinoin caused these behaviors and symptoms or if they would have happened even if the person did not take isotretinoin. If any of these behaviors or symptoms occur, the patient should stop treatment and the patient or family member should contact the prescriber promptly without waiting until the next visit [see *Warnings and Precautions* (5.4)]. Some people have had other signs of depression while taking isotretinoin.
- Patients must be informed that they must not share ABSORICA with anyone else because of the risk of birth defects and other serious adverse reactions.
- Patients must be informed not to donate blood during therapy and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to ABSORICA.
- ABSORICA may be taken without regard to meals [see *Dosage and Administration* (2.1)]. To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid.
- Patients should be informed that inflammatory bowel disease (including regional ileitis) may occur without a prior history of intestinal disorders. In rare instances, symptoms have been reported to persist after treatment has stopped. Patients should be informed that if they experience abdominal pain, rectal bleeding or severe diarrhea, they should discontinue ABSORICA immediately.
- 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 ABSORICA therapy and for at least 6 months thereafter due to the possibility of scarring.
- Patients should be advised to avoid prolonged exposure to UV rays or sunlight.
- Patients should be informed that they may experience dry eye, corneal opacities, and decreased night vision. Contact lens wearers may experience decreased tolerance to contact lenses during and after therapy.
- Patients should be informed that 16% of patients treated with isotretinoin 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 therapy, but in some cases persisted.

- There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity.
- Pediatric patients and their caregivers should be informed that approximately 17% to 29% of pediatric patients treated with isotretinoin developed back pain. In a clinical trial, back pain was severe in 13.5% 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 treatment. Consideration should be given to discontinuation of isotretinoin if any significant abnormality is found.
- Neutropenia and rare cases of agranulocytosis have been reported in patients treated with isotretinoin. ABSORICA 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 in patients treated with isotretinoin. Treatment with ABSORICA should be discontinued if clinically significant skin reactions occur.
- Adolescent patients who participate in sports with repetitive impact should be informed that isotretinoin use may increase their risk of spondylolisthesis or hip growth plate injuries. There are spontaneous reports of fractures and/or delayed healing in patients while on therapy with isotretinoin or following cessation of therapy with isotretinoin while involved in these activities [*see Warnings and Precautions (5.12)*].

Manufactured for: **RANBAXY**
LABORATORIES INC.

By: Jacksonville, FL 32257 USA
Galephar P R, Inc.
Juncos, Puerto Rico 00777