PRODUCT MONOGRAPH

PrEPURIS®

Isotretinoin Capsules 10, 20, 30, 40 mg

Retinoid for treatment of acne

ATC code: D10B A01

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules 10, 20, 30, 40 mg	None *For a complete listing of non-medicinal ingredients see Dosage Forms, Composition and Packaging section*

INDICATIONS AND CLINICAL USE

EPURIS® (isotretinoin) is indicated for the treatment of:

- Severe Nodular and/or Inflammatory Acne
- Acne Conglobata
- Recalcitrant Acne

Because of significant side effects associated with its use, EPURIS® should be reserved for patients where the conditions listed above are unresponsive to conventional first line therapies. EPURIS® should not be substituted with other marketed formulations of isotretinoin.

EPURIS® should only be prescribed by physicians knowledgeable in the use of retinoids systemically, who understand the risk of teratogenicity in females of child bearing age and who are experienced in counselling young adults for whom isotretinoin is generally indicated (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS: Serious Warnings and Precautions and Special Populations, Pregnant Women).

A careful assessment of the patient's mental state should be made, including whether or not they have a history of previous psychiatric illness (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, Psychiatric).

It is strongly recommended that each EPURIS® prescription be limited to a one-month supply in order to encourage patients to return for follow-up to monitor side-effects.

The pharmacist must ensure that:

- Prescriptions of EPURIS for women of childbearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of EPURIS should occur on the same day.
- Dispensing of EPURIS should occur within a maximum of 7 days of the prescription

Pediatrics (12 – 17 years of age):
The use of EPURIS® in pediatric patients less than 12 years of age is not recommended. The use of isotretinoin 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: Special Populations, Pediatrics).

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

CONTRAINDICATIONS

EPURIS® (isotretinoin) is contraindicated in pregnancy.
- Females must not become pregnant while taking EPURIS® or for at least one month after its discontinuation. Isotretinoin causes severe birth defects in a very high percentage of infants born to women who became pregnant during treatment with isotretinoin in any amount, even for a short period of time. Potentially any exposed fetus can be affected. There are no accurate means of determining whether an exposed fetus has been affected (see WARNINGS AND PRECAUTIONS: Special Populations, Pregnant Women).
- If pregnancy does occur during treatment with EPURIS® or for one month after its discontinuation, EPURIS® treatment must be immediately stopped and the physician and patient should discuss the desirability of continuing the pregnancy.
- EPURIS® should only be prescribed by physicians knowledgeable in the use of retinoids systemically (see INDICATIONS AND CLINICAL USE).

EPURIS® is also contraindicated in the following conditions:

- breastfeeding women,
- hepatic and renal insufficiency,
- hypervitaminosis A,
- patients with excessively elevated blood lipid values,
- patients taking tetracyclines (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, Neurologic and DRUG INTERACTION: Drug-Drug Interactions).
- patients who are sensitive to isotretinoin, or to any of the excipients. EPURIS® capsules contain stearoyl macrogolglycerides, soybean oil, sorbitan monooleate and propyl gallate

(see DOSAGE FORMS, COMPOSITION AND PACKAGING: Composition).

WARNINGS AND PRECAUTIONS

The Information/Consent/Agreement should be signed by *all* patients prior to starting therapy with isotretinoin. This consent form is designed to ensure that patients have been counselled on and understand the psychiatric and teratogenic risks associated with isotretinoin, prior to starting treatment. The consent form can be obtained by downloading it from the EPURIS® PEER™ Program Website, www.epuris.ca, or by contacting Customer Service at 1-855-437-8747 (1-855-4EPURIS).

Serious Warnings and Precautions

- **Pregnancy Prevention*:*** Isotretinoin is a known teratogen contraindicated in pregnancy (see boxed CONTRAINDICATIONS). Physicians should **only** prescribe EPURIS® to females of childbearing potential if **ALL** the conditions described below under **"Conditions of use"** are met.

  It is mandatory that all female patients of childbearing potential treated with EPURIS have regular negative monthly pregnancy tests prior to receiving each 30-day EPURIS prescription and an additional test one month after the discontinuation of treatment.

  In addition, when prescribing this drug to female patients of childbearing potential, physicians **MUST** use the **EPURIS® Patient Engagement and Education Resource (PEER™) Program**, which includes the following:

  - **comprehensive information about the potential risks of this drug**
  - **a checklist for criteria which MUST be met prior to prescribing this drug to female patients of childbearing potential**
  - **detailed information on birth control options**
  - **a patient informed consent for review and signature**
  - **monthly pregnancy reminders for physicians to use at each patient visit during the treatment period**

  The information listed above may be obtained by accessing and downloading it from the EPURIS® PEER™ Program Website, www.epuris.ca, or by contacting Customer Service at 1-855-437-8747 (1-855-4EPURIS).

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

A Psychiatric Screening Checklist is available to assist physicians in screening patients for depression/suicidality prior to treatment and in monitoring for the development of psychiatric symptoms during treatment.

The following materials are available to physicians and pharmacists. Please contact your EPURIS® Representative or the Customer Service centre provided below.

- **Pregnancy Prevention Checklist**
- **Information/Consent/Agreement**
- **EPURIS® Treatment and Patient Monitoring Checklist**
- **Laboratory Monitoring Guide**
- **PEER™ Flowchart**
- **Patient Reminder Slips**
- **Psychiatric Screening Checklist**

Cipher Pharmaceuticals Inc. Customer Service:
209 Oak Park Blvd, Suite 501, Oakville, ON L6H 0M2
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www.epuris.ca

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

General

Serious Skin Reactions

There have been very rare post-marketing reports of severe skin reactions (e.g., erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)) associated with isotretinoin use. These events may be serious and result in hospitalization, life threatening events, disfiguration, disability and/or death. EPURIS® treatment should be discontinued if the patient develops any of the following reactions: rash, especially if associated with fever and/or malaise, conjunctivitis (red or inflamed eyes); blisters on legs, arms or face and/or sores in mouth, throat, nose or eyes; peeling skin or other serious skin reactions.

Conditions of Use:

EPURIS® is contraindicated in females of childbearing potential unless **ALL** of the following conditions apply:

1. The patient has severe disfiguring nodular and/or inflammatory acne, acne conglobata or recalcitrant acne that has not responded to standard therapy, including systemic antibiotics.
2. The patient is reliable in understanding and carrying out instructions.
3. All patients must sign the informed consent form prior to initiating therapy. **This form is**

provided to the physician via the www.epuris.ca website or by contacting Cipher Pharmaceuticals Inc.'s Information line at 1-855-437-8747 (1-855-4EPURIS).

4. The patient is able and willing to comply with the mandatory effective contraceptive measures.
5. The patient has received, and acknowledged understanding of, a careful oral and printed explanation of the hazards of fetal exposure to isotretinoin and the risk of possible contraception failure. This explanation may include showing a line drawing to the patient of an infant with the characteristic external deformities resulting from isotretinoin exposure during pregnancy.
6. The patient has been informed and understands the need to rapidly consult her physician if there is a risk of pregnancy.
7. The patient understands the need for rigorous follow-up on a monthly basis.
8. The patient uses effective contraception without any interruption for one month before beginning EPURIS® therapy, during EPURIS® therapy and for one month following discontinuation of EPURIS® therapy. It is recommended that two reliable forms of contraception be used simultaneously (see WARNINGS AND PRECAUTIONS: Special Populations, Pregnant Women).
9. The patient has had two negative pregnancy tests before starting EPURIS® therapy with the first pregnancy test conducted at initial assessment when the patient is qualified for EPURIS® therapy by the physician. The patient has had a second serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL with a negative result, performed in a licensed laboratory, within 11 days prior to initiating therapy. The patient has had two or three days of the next normal menstrual period before EPURIS® therapy is initiated.
10. In the event of relapse treatment, the patient must also use the same uninterrupted and effective contraceptive measures one month prior to, during and for one month after EPURIS®.

(Re items 2 to 9 see WARNINGS AND PRECAUTIONS: Special Populations, Pregnant Women).

Even female patients who normally do not employ contraception due to a history of infertility, or claim absence of sexual activity should be advised to employ contraception while taking EPURIS®, following the above guidelines. Even female patients who have amenorrhea must follow all the advice on effective contraception.

Information concerning the EPURIS® PEER™ Program (see boxed Serious Warnings and Precautions) has also been provided directly to patients *via* the EPURIS® compliance packaging. This "Patient Information" asks female patients of childbearing potential, who have not been counseled using the EPURIS® PEER™ Program, to contact their physician for further information.

Patients should also be informed that confidential contraception counseling (provided by a health care professional) is available from Cipher Pharmaceuticals Inc.

Special Populations

Pregnant Women: There is an extremely high risk (25% or greater) that major human fetal

abnormalities will occur if pregnancy occurs during treatment with isotretinoin or up to one month following its discontinuation. Potentially any exposed fetus can be affected. These abnormalities, associated with isotretinoin administration during pregnancy, have been reported and include:

CNS (hydrocephalus, hydranencephaly, microcephaly, posterior fossa abnormalities, cranial nerve dysfunction, cerebellar malformation); craniofacial (anotia, microtia, low set ears, small or absent external auditory canals, microphthalmia, facial dysmorphia, cleft palate); cardiac (septal defects, aortic arch abnormalities, tetralogy of Fallot); thymus gland abnormalities; and parathyroid hormone deficiency. Cases of IQ scores less than 85 with or without other abnormalities have been reported.

Pregnancy Tests: Female patients of childbearing potential must not be given EPURIS® until pregnancy is excluded. The patient must have two negative pregnancy tests before starting EPURIS® therapy with the first pregnancy test conducted at initial assessment when the patient is qualified for EPURIS® therapy by the physician. A second pregnancy test must be performed within 11 days prior to starting EPURIS® treatment. EPURIS® treatment should start on the second or third day of the next normal menstrual period following this negative pregnancy test.

It is mandatory that all female patients of childbearing potential treated with EPURIS® have regular monthly pregnancy tests during treatment and one month after the discontinuation of treatment. The dates and results of pregnancy tests should be documented. The blood monitoring chart can be used to document these results as well as to serve as a reminder of all the tests that should be carried out and their frequency.

These pregnancy tests will:

a) Serve primarily to reinforce to the patient the necessity of avoiding pregnancy.
b) In the event of accidental pregnancy, provide the physician and patient an immediate opportunity to discuss the serious risk to the fetus from this exposure to EPURIS® and the desirability of continuing the pregnancy in view of the potential teratogenic effect of EPURIS® (see CONTRAINDICATIONS and TOXICOLOGY: Reproduction and Teratology Studies).

Contraception: Effective contraception must be used for at least one month before starting EPURIS® treatment, during treatment and for at least one month following the discontinuation of EPURIS® treatment. It is recommended that two reliable forms of contraception be used simultaneously. At least 1 of these forms of contraception must be a primary form, unless the patient has undergone a hysterectomy. Effective forms of contraception include: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and topical/injectable/insertable hormonal birth control products. Barrier forms of contraception include diaphragms, latex condoms, and cervical caps; each must be used with a spermicide. Any birth control method can fail. **Therefore, it is critically important that women of childbearing potential use 2 effective forms of contraception simultaneously** (see DRUG INTERACTIONS: Drug-Drug Interactions).

Pregnancy occurring during treatment with isotretinoin and for one month after its discontinuation carries the risk of fetal malformation and the increased risk of spontaneous abortion (see CONTRAINDICATIONS and TOXICOLOGY: Reproduction and Teratology

Studies). EPURIS® treatment must be stopped and the patient should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. If pregnancy does occur during this time the physician and patient should discuss the desirability of continuing the pregnancy.

Nursing Women: It is not known whether isotretinoin is excreted in human milk. As isotretinoin is highly lipophilic, the passage of the drug in human milk is very likely. Because of the potential for adverse effects, women should not breast-feed if they are receiving EPURIS® (see CONTRAINDICATIONS).

Pediatrics (12 - 17 years of age): The long term safety of EPURIS®, in prepubertal children (< 12 years of age), has not been established.

In studies with isotretinoin, adverse reactions reported in pediatric patients ages 12 to 17 years were similar to those described in adults except for the increased incidence of back pain and arthralgia (both of which were sometimes severe) and myalgia in pediatric patients (see ADVERSE REACTIONS).

Pediatric patients and their caregivers should be informed that approximately 29% of pediatric patients treated with isotretinoin developed back pain in clinical trials. 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. In a clinical trial of isotretinoin, arthralgias were experienced in 22% (79/358) of pediatric patients, and 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 EPURIS® if any significant abnormality is found.

Geriatrics (> 65 years of age): Clinical studies of isotretinoin did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

Special Patient Groups: In high risk patients (with diabetes, obesity, alcoholism or lipid metabolism disorder) undergoing treatment with EPURIS®, more frequent checks of serum values for lipids (see WARNINGS AND PRECAUTIONS: Endocrine and Metabolism and Hepatic/Biliary/Pancreatic) and/or blood glucose may be necessary.

Male Patients: The available data suggest that the level of maternal exposure from the semen of the patients receiving isotretinoin is not of a sufficient magnitude to be associated with the teratogenic effects of isotretinoin. The threshold dose of isotretinoin exposure causing birth defects is not known. Postmarketing reports through 20 years include 4 with isolated defects compatible with features of retinoid exposed fetus; however 2 of these reports were incomplete and 2 had other possible explanations for the defects observed.

Male patients should be reminded that they must not share their medication with anyone, particularly not females.

Isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm.

Both male and female patients should be given a copy of the Consumer Information (Part III).

Blood Donation

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

Cardiovascular

Approximately 25% of patients receiving isotretinoin experienced an elevation in plasma triglycerides. Approximately 15% developed a decrease in high density lipoproteins and about 7% showed an increase in cholesterol levels. These effects on triglycerides, HDL and cholesterol were reversible upon cessation of isotretinoin therapy (see ADVERSE REACTIONS: Laboratory Abnormalities).

Patients with increased tendency to develop hypertriglyceridemia include those with diabetes mellitus, obesity, increased alcohol intake and familial history.

The cardiovascular consequences of hypertriglyceridemia are not well understood, but may increase the patient's risk status. Therefore, every attempt should be made to control significant triglyceride elevation (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests). Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in dose while continuing isotretinoin. An obese male patient with Darier's disease developed elevated triglycerides and subsequent eruptive xanthomas.

Ear/Nose/Throat

Impaired hearing at certain frequencies has been reported in some patients treated with isotretinoin. Patients who experience tinnitus or hearing impairment should discontinue EPURIS® treatment and be referred for specialized care for further evaluation.

Endocrine and Metabolism

Patients with diabetes or a family history of diabetes may experience problems with the control of their blood sugar during EPURIS® therapy. Therefore, known or suspected diabetics should have periodic blood sugar determinations. Although no causal relationship has been established, elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during isotretinoin therapy (see ADVERSE REACTIONS: Clinical Trial and Post-Market Adverse Reactions, Laboratory Abnormalities).

Gastrointestinal

Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis, colitis and hemorrhage) in patients without a prior history of intestinal disorders. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue EPURIS®

immediately. In some instances symptoms have been reported to persist after isotretinoin treatment has been stopped.

Hepatic/Biliary/Pancreatic

Liver function tests should be monitored before treatment and at regular intervals during treatment (one month after the start of treatment and at least three month intervals thereafter) unless more frequent monitoring is clinically indicated. Several cases of clinical hepatitis have been noted which are considered to be possibly or probably related to isotretinoin therapy. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials, some of which normalized with dosage reduction or continued administration of the drug. If normalization does not readily occur, or if hepatitis is suspected during treatment with EPURIS®, the drug should be discontinued and the etiology further investigated (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

There have been some reports of **acute pancreatitis**, which is known to be potentially fatal. This is sometimes associated with elevation of serum triglycerides in excess of 800 mg/dL or 9 mmol/L (see ADVERSE REACTIONS: Clinical Trial and Post-Market Adverse Drug Reactions, Laboratory Abnormalities). Therefore, every attempt should be made to control significant triglyceride elevation (see WARNINGS AND PRECAUTIONS: Cardiovascular). EPURIS® should be discontinued if uncontrolled hypertriglyceridemia or symptoms of pancreatitis occur.

Immune

Anaphylactic reactions have been reported with isotretinoin. These reactions were more serious after prior exposure to topical retinoids. Allergic cutaneous reactions and serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

Musculoskeletal

Effects of multiple courses of EPURIS® 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 (see also WARNINGS AND PRECAUTIONS: Special Populations, Pediatrics).

In the pivotal clinical trial (ISOCT 08.01) in 924 patients, adverse events related to the musculoskeletal system and connective tissue were reported in approximately 37% of patients, and musculoskeletal symptoms in approximately 24% of the patients. Elevations in levels of serum creatine kinase (≥350 U/L) were reported in approximately 29% of patients, and the AE "blood creatine kinase increase" in 6% of patients. In the same trial, 27/306 (8.8%) of adolescents had BMD declines, defined as ≥ 4% lumbar spine or total hip, or ≥ 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.
In an open-label clinical trial (N=217) of a single course of therapy with ACCUTANE for severe recalcitrant nodular acne in pediatric patients 12 to 17 years, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change >-4% and total hip change>-5%) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density >4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density >4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumber 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 this clinical trial transient elevations in CPK were observed in 12% of patients, including those undergoing strenuous physical activity in association with reported musculoskeletal adverse events such as back pain, arthralgia, limb injury, or muscle sprain. In these patients, approximately half of the CPK elevations returned to normal within 2 weeks and half returned to normal within 4 weeks. No cases of rhabdomyolysis were reported in this trial.

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

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

Physicians should use caution when prescribing EPURIS® to patients with a genetic predisposition for age related osteoporosis, a history of childhood osteoporosis conditions, osteomalacia, or other disorders of bone metabolism. This would include patients diagnosed with anorexia nervosa and those who are on chronic drug therapy that causes drug-induced osteoporosis/osteomalacia and/or affects vitamin D metabolism, such as systemic corticosteroids and any anticonvulsant. Patients may be at increased risk when participating in sports with repetitive impact where the risks of spondylolisthesis with and without pars fractures and hip growth plate injuries in early and late adolescence are known. There are spontaneous reports of fractures and/or delayed healing in patients while on treatment with EPURIS® or following cessation of treatment with EPURIS® while involved in these activities. While causality to EPURIS® has not been established, an effect cannot be ruled out.

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

of acne. Bone changes including, premature epiphyseal closure, hyperostosis and calcification of tendons and ligaments have occurred after several years of administration at high doses for treating disorders of keratinization. The dose levels, duration of treatment and total cumulative dose in these patients generally far exceeded those recommended for the treatment of acne.

In clinical trials of disorders of keratinization, with a mean dose of 2.24 mg/kg/day, a high prevalence of skeletal hyperostosis was noted. Two children showed x-ray findings suggestive of premature closure of the epiphysis. Additionally, skeletal hyperostosis was noted in six of eight patients in a prospective study of disorders of keratinization.

Minimal skeletal hyperostosis and calcification of tendons have also been observed by x-rays in prospective studies of cystic acne patients treated with a single course of therapy at recommended doses. There are spontaneous 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 clinical study of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, hyperostosis was not observed after 16 to 20 weeks of treatment with approximately 1 mg/kg/day of isotretinoin given in two divided doses. Hyperostosis may require a longer time frame to appear. The clinical course and significance remain unknown.

Myalgia and arthralgia (mild to moderate) may occur and may be associated with reduced tolerance to vigorous exercise (see ADVERSE REACTIONS: Clinical Trial and Post-Market Adverse Drug Reactions, Musculoskeletal). Instances of raised serum creatine phosphokinase (CPK) values have been reported in patients receiving isotretinoin, particularly those undertaking vigorous physical activity. Discontinuation of EPURIS® may be required.

Ophthalmologic

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. Dry eyes, corneal opacities, decreased night vision, keratitis, blepharitis and conjunctivitis usually resolve after discontinuation of therapy. Due to the possible occurrence of keratitis, patients with dry eyes should be monitored. All EPURIS® patients experiencing visual difficulties should discontinue the drug and have an ophthalmological examination. Approximately 3% of patients experienced a decrease in visual acuity that did not fully recover at the end of the study (see ADVERSE REACTIONS: Clinical Trial and Post-Market Adverse Drug Reactions, Ophthalmologic). Dry eyes, can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment

A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted after therapy (see ADVERSE REACTIONS: Clinical Trial and Post-Market Adverse Drug Reactions, Ophthalmologic). 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. EPURIS® patients experiencing visual impairment should discontinue treatment and have an ophthalmological examination. Visual problems should be carefully monitored.

Skin

Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually 7-10 days, and usually does not require dose adjustment.

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

It is recommended that aggressive chemical dermabrasion and cutaneous laser treatment be avoided in patients on EPURIS® and for a period of 5-6 months after the end of treatment because of the risk of hypertrophic scarring in atypical areas, and more rarely hyper- or hypo-pigmentation in treated areas.

It is recommended that wax epilation be avoided in patients on EPURIS® therapy and for a period of 5-6 months after treatment because of the risk of epidermal stripping, scarring or dermatitis.

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

Patients should be advised to use a skin-moisturizing ointment or cream and a lip balm from the start of treatment as isotretinoin is likely to cause dryness of the skin and lips.

There have been post-marketing reports of severe skin reactions. (see WARNINGS AND PRECAUTIONS: Serious Skin Reactions).

Monitoring and Laboratory Tests

Pregnancy tests: The patient should have two negative pregnancy tests (β-hCG in urine or serum) before starting EPURIS® therapy with the first pregnancy test conducted at initial assessment when the patient is qualified for EPURIS® therapy by the physician. The patient then should have a second pregnancy test with a sensitivity of at least 25 mIU/mL with a negative result, performed in a licensed laboratory, within 11 days prior to initiating therapy. The patient has had two or three days of the next normal menstrual period before EPURIS® therapy is initiated. **Pregnancy test must be repeated monthly for pregnancy detection** during EPURIS® treatment and at one month after discontinuation of treatment. The dates and results of the pregnancy tests should be documented.

Signs of Depression: sad mood, hopelessness, feeling of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, changes 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. If symptoms of depression develop or worsen during treatment with EPURIS®, the drug should be discontinued promptly and the patient referred for appropriate psychiatric treatment.

The following tests are required before starting EPURIS®, at first month, then as clinically indicated:

- Serum blood lipid determinations (under fasting conditions) should be performed before EPURIS® is given and then at intervals (one month after the start of therapy) until the lipid response to EPURIS® is established (which usually occurs within four weeks), and also at the end of treatment.
- Complete blood count and differential: for early detection of leukopenia, neutropenia, thrombocytopenia and anemia.
- Liver function tests: Increases in about 15% of ALT, AST, ALP baseline levels have been reported. Liver function tests should be monitored before treatment and at regular intervals during treatment (one month after the start of treatment and at least three month intervals thereafter) unless more frequent monitoring is clinically indicated.
- Blood glucose levels: all patients and in particular patients with known or suspected diabetes should have periodic blood sugar determinations.

A Psychiatric Screening Checklist is available to assist physicians in screening patients for depression/suicidality prior to treatment and in monitoring for the development of psychiatric symptoms during treatment.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse events listed below reflect the experience from the clinical studies conducted with EPURIS® (isotretinoin) and the post-marketing experience. The relationship of some of these events to EPURIS® therapy is unknown.

Many of the side effects and adverse events seen or expected in patients receiving isotretinoin are similar to those described in patients taking high doses of vitamin A.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Table 1 presents common adverse events (≥ 1%) reported in a double-blind, randomized, Phase III, parallel group study of EPURIS® compared to a Reference Product dosed under fed conditions, in 925 patients with severe recalcitrant nodular acne.

In the above-described study (ISOCT.08.01) almost all patients experienced at least one adverse event (AE) in both groups at similar rates (92% with EPURIS® and 90% with the Reference Product (a marketed formulation of isotretinoin)). Most of these AEs were treatment related (87% with EPURIS® and 84% with the reference drug).

Adverse events related to the musculoskeletal system and connective tissues were reported in approximately 37% of the patients, and musculoskeletal symptoms in approximately 24% of the patients. Elevations in levels of serum creatine kinase were reported as high alert laboratory

values (≥ 350 u/L) in approximately 29% of patients, and incidence of the AE "blood creatine kinase increase" in 6% of patients.

Systematic assessment of visual acuity (Snellen chart) was performed in most patients and revealed that 20% of patients in the EPURIS® group and 15% of patients in the Reference group experienced VA worsening that was reversible for most. However, 3.7% (17/464) of patients in the EPURIS® group and 3% (14/460) of patients in the Reference group did not fully recover baseline visual acuity values.

No deaths were reported during the study, and the rate of serious adverse events (SAE) was relatively low in both groups (1.1% to 1.5%). Three serious AEs were considered to be possibly related to EPURIS® and recovered completely: severe abdominal pain, severe upper abdominal pain and moderate migraine.

Adverse events leading to discontinuation were reported in 4.1% of patients with EPURIS®, and 3.3% of patients with the Reference Product. These AEs were classified as psychiatric events and gastrointestinal events in the EPURIS® group, and as psychiatric events and musculoskeletal/connective tissue events in the Reference Product group.

Table 1: Adverse Events Reported in ≥ 1% of Patients in the EPURIS® group versus the Reference Product Group in the Double-Blind, Phase III Study

Adverse Event	EPURIS® (N = 464)	Reference Product (N = 460)	Adverse Event	EPURIS® (N = 464)	Reference Product (N = 460)
Patients with any adverse events	428 (92.2)	413 (89.8)	Sunburn	10 (2.2)	8 (1.7)
Lip dry	209 (45.0)	210 (45.7)	Excoriation	10 (2.2)	4 (0.9)
Dry skin	205 (44.2)	206 (44.8)	Eye Pruritus	9 (1.9)	17 (3.7)
Back pain	96 (20.7)	89 (19.3)	Nasal congestion	9 (1.9)	5 (1.1)
Dry eye	87 (18.8)	78 (17.0)	X-ray limb abnormal	9 (1.9)	8 (1.7)
Arthralgia	64 (13.8)	60 (13.0)	Asparate aminotransferase increased	8 (1.7)	10 (2.2)
Epistaxis	54 (11.6)	42 (9.1)	Myalgia	8 (1.7)	7 (1.5)
Headache	37 (8.0)	36 (7.8)	Abdominal pain	8 (1.7)	3 (0.7)
Nasopharyngitis	36 (7.8)	48 (10.4)	Cough	7 (1.5)	12 (2.6)
Chapped lips	34 (7.3)	32 (7.0)	Joint sprain	7 (1.5)	10 (2.2)
Dermatitis	28 (6.0)	23 (5.0)	Musculoskeletal stiffness	7 (1.5)	6 (1.3)
Blood creatine kinase increased	26 (5.6)	27 (5.9)	Gastroenteritis viral	7 (1.5)	5 (1.1)
Cheilitis	26 (5.6)	19 (4.1)	Vomiting	7 (1.5)	4 (0.9)
Musculoskeletal discomfort	25 (5.4)	16 (3.5)	Influenza	6 (1.3)	11 (2.4)
Upper respiratory tract infection	25 (5.4)	14 (3.0)	Pharyngitis	6 (1.3)	11 (2.4)

Adverse Event	EPURIS®	Reference Product	Adverse Event	EPURIS®	Reference Product
Visual acuity reduced	23 (5.0)	25 (5.4)	Pharyngitis streptococcal	6 (1.3)	4 (0.9)
Nasal dryness	21 (4.5)	23 (5.0)	Night blindness	6 (1.3)	3 (0.7)
Fatigue	20 (4.3)	11 (2.4)	Erythema	6 (1.3)	2 (0.4)
Musculoskeletal pain	19 (4.1)	23 (5.0)	Migraine	6 (1.3)	0
Eczema	17 (3.7)	20 (4.3)	Hordeolum	5 (1.1)	10 (2.2)
Blood triglycerides increased	17 (3.7)	14 (3.0)	Constipation	5 (1.1)	8 (1.7)
Rash	17 (3.7)	14 (3.0)	Anxiety	5 (1.1)	7 (1.5)
Bone density decreased	17 (3.7)	7 (1.5)	Decreased appetite	5 (1.1)	7 (1.5)
Neck pain	14 (3.0)	22 (4.8)	Diarrhoea	5 (1.1)	7 (1.5)
Pain in extremity	14 (3.0)	15 (3.3)	Weight fluctuation	5 (1.1)	6 (1.3)
Vision blurred	14 (3.0)	15 (3.3)	Eye irritation	5 (1.1)	5 (1.1)
Nausea	14 (3.0)	10 (2.2)	Asthenopia	5 (1.1)	4 (0.9)
Insomnia	14 (3.0)	9 (2.0)	Ingrowing nail	5 (1.1)	4 (0.9)
Muscle strain	14 (3.0)	8 (1.7)	Pyrexia	5 (1.1)	4 (0.9)
Oropharyngeal pain	12 (2.6)	8 (1.7)	Bronchitis	5 (1.1)	3 (0.7)
Alanine aminotransferase increased	10 (2.2)	11 (2.4)	Conjunctivitis	5 (1.1)	2 (0.4)
Sinusitis	10 (2.2)	11 (2.4)	Ear infection	5 (1.1)	1 (0.2)
Dermatitis contact	10 (2.2)	9 (2.0)			

Some AEs tended to be reported with a differential in frequency according to gender in both treatment groups: For example, triglycerides increased, arthralgia, pain, and blurred vision tended to be more often reported in females, while chapped lips, cheilitis, epistaxis, creatine kinase increased, and bone density decreased tended to be more reported in males.

Reduced visual acuity, blurred vision, increased triglycerides, headache and fatigue tended to be more often reported in adults as compared to adolescents (12 to 17 years).

Decreased bone density was reported in adolescents of both treatment groups (4% to 8%) but not in adults.

Adverse reactions were generally reversible when therapy was discontinued; however, some have persisted after cessation of therapy.

Less Common (<1%) Clinical Trial Adverse Reactions
Adverse events in subjects receiving EPURIS® in any clinical trial are listed below.

Body as a Whole: Herpes simplex, irritability, oedema peripheral, thirst, chest pain, cyst, impaired healing, influenza like illness, lymphadenopathy, xerosis, discomfort, oedema, gravitational oedema, mucous membrane disorder and swelling.

Cardiovascular: Palpitations, tachycardia and coronary artery disease.

Endocrine and Metabolism: Increased appetite and thyroid disorder.

Gastrointestinal: Bleeding and inflammation of the gums, dry mouth, abdominal discomfort, dyspepsia, haemorrhoids, rectal haemorrhage, abdominal pain lower, lip swelling, mouth ulceration, oral pain, tooth impacted, abdominal distension, abdominal tenderness, anal fissure, frequent bowel movement, gastrooesophageal reflux disease, gingival recession, haematochezia, hypoaesthesia oral, lip haemorrhage, lip ulceration, oesophageal pain, painful defaecation, rectal fissure, tooth disorder and toothache.

Hearing Disorders: Tinnitus, ear pain, hypoacusis, ear discomfort, external ear inflammation, cerumen impaction, hyperacusis and vertigo.

Mucocutaneous and Dermatologic: Bruising, pruritus, alopecia, eczema nummular, scar, eczema asteatotic, acne, rash popular, skin exfoliation, acne cystic, blister, hair texture abnormal, intertrigo, pain of skin, photosensitivity reaction, pyogenic granuloma, skin discolouration, acrodermatitis, alopecia effluvium, androgenic alopecia, dermatitis atopic, dermatitis exfoliative, exfoliative rash, livedo reticularis, onycholysis, pityriasis rosea, psoriasis, rash follicular, paronychia, seborrhoea, skin depigmentation, skin fissures, skin irritation, skin infections, skin lesion, skin ulcer, swelling face and telangiectasia.

Musculoskeletal: Tendonitis, muscle spasms, arthropathy, joint stiffness, joint swelling, joint pain, muscle tightness, musculoskeletal chest pain, arthritis, bone pain, fibromyalgia, groin pain, intervertebral disc space narrowing, joint crepitation, limb discomfort, muscle atrophy, myositis, spinal osteoarthritis, synovial cyst and tendon pain.

Neurologic: Dizziness, drowsiness, malaise, memory impairment, nervousness, paresthesia, presyncope, sinus headache, syncope, weakness.

Ophthalmologic: Ocular hyperaemia, lacrimation increased, photophobia, xerophthalmia, blepharitis, eye pain, visual impairment, blepharospasm, conjunctival haemorrhage, conjunctival hyperaemia, conjunctivitis allergic, diplopia, eczema eyelids, eye haemorrhage, eye swelling, eyelid oedema, foreign body sensation in eyes, keratitis, myopia, orbital edema, photopsia, pinguecula and punctuate keratitis.

Psychiatric Disorders: Depression, attention deficit/hyperactivity disorder, mood swings, sleep disorder, panic attack, restlessness, stress, adjustment disorder, affect lability, anger, bradyphrenia, delusion, depressed mood, disorientation, dysthymic disorder, emotional distress, hallucination auditory, libido decreased, middle insomnia, obsessive thoughts, paranoia and substance abuse.

Respiratory: Rhinorrhoea, sinus congestion, asthma, respiratory tract congestion, dry throat, nasal mucosal disorder, rales, rhinitis seasonal, sleep apnoea syndrome, throat irritation, voice hoarseness and wheezing.

Reproductive System: Metrorrhagia, menstruation irregular, vulvovaginal bleeding, vulvovaginal discomfort, amenorrhoea, breast cyst, dysmenorrhoea, epididymitis, erectile dysfunction, menorrhagia, ovarian cyst, ovarian cyst ruptured, pruritus genital, testicular cyst, vaginal discharge and vulva cyst.

Urinary System: Proteinuria, haematuria, dysuria, nephrolithiasis and polyuria

Abnormal Laboratory Findings:

Blood potassium increased, blood alkaline phosphatase increased, blood bilirubin increased, blood urea increased, elevated platelet counts, eosinophil count increased, false positive tuberculosis test, gamma-glutamyltransferase abnormal, blood cholesterol increased, glucose urine present, haematocrit decreased, protein urine, thrombocytopenia, white blood cell count decreased.

Post-Marketing Adverse Drug Reactions

The following additional adverse reactions have been identified during post-approval use of EPURIS®.

Body as a whole: Weight loss, anemia, allergic responses and hypertriglyceridemia.

Cardiovascular: Transient pain in the chest and vascular thrombotic disease.

Endocrine and Metabolism: New cases of diabetes (see WARNING AND PRECAUTIONS: Endocrine and Metabolism).

Gastrointestinal: Inflammatory bowel disease, colitis, esophagitis/esophageal ulceration and other nonspecific gastrointestinal symptoms (see WARNINGS AND PRECAUTIONS: Gastrointestinal).

Hearing Disorders: Impaired hearing at certain frequencies.

Hepatic/Biliary/Pancreatic: Pancreatitis (see WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic).

Laboratory Abnormalities: Elevated fasting blood sugar and red blood cells in the urine.

Mucocutaneous and Dermatologic: Acne flare, hair loss, hypopigmentation, sweating and urticaria.

Musculoskeletal: Other types of bone abnormalities and rhabdomyolysis.

Neurologic: Seizures and benign intracranial hypertension (see WARNINGS AND PRECAUTIONS: Serious Warnings and Precautions, Neurologic).

Ophthalmologic: Visual disturbances.

Psychiatric Disorders: Emotional instability, suicidal ideation, suicide attempts, suicide, aggression and violent behaviors.

Urinary system: Nonspecific urogenital findings.

The following additional adverse reactions have been identified during the use of other isotretinoin products.

Body as a Whole: Allergic vasculitis, systemic hypersensitivity.

Cardiovascular: Stroke.

Dose-Relationship: Cheilitis and hypertriglyceridemia were usually dose related.

Gastrointestinal: Ileitis and other nonspecific gastrointestinal symptoms.

Hepatic/Biliary/Pancreatic: Patients treated with isotretinoin, especially those with high triglyceride levels are at risk of developing pancreatitis. Rare cases of fatal pancreatitis and several cases of clinical hepatitis have been reported (see WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic).

Laboratory Abnormalities: Decreases in red blood cell parameters, decrease in serum high density lipoprotein (HDL), hyperuricemia, elevated sedimentation rates, white blood cells in the urine and blood protein present.

A rise in serum levels of liver enzymes may occur, especially with higher dosages. Although the changes have usually been within the normal range, and may return to baseline levels despite continued treatment, significant increases have occurred in a few cases, necessitating dosage reduction or discontinuation of isotretinoin (see WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic).

Mucocutaneous and Dermatologic: Acne fulminans, desquamation, eruptive xanthomas, facial erythema, nail dystrophy, flushing, fragility of skin, hirsutism, hyperpigmentation, peeling of palms and soles, photoallergic, vasculitis (including Wegener's granulomatosis), abnormal wound healing (delayed healing or exuberant granulation tissue with crusting), erythema nodosum and exanthema. Erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported to be associated with isotretinoin (see WARNING AND PRECAUTIONS: Serious Skin Reactions).

Musculoskeletal: Calcification of tendons and ligaments, premature epiphyseal closure, skeletal hyperostosis (see WARNINGS AND PRECAUTIONS: Musculoskeletal, Hyperostosis) and other types of bone abnormalities. There have been post-marketing serious reports of rhabdomyolysis, often leading to hospitalization, particularly in those undergoing strenuous

physical activity.

Neurologic: Lethargy.

Ophthalmologic: Cataracts, colour vision disorder, optic neuritis, papilledema as a sign of benign intracranial hypertension and colour vision disturbances. Corneal opacities were reported in nodular and/or inflammatory acne patients (see WARNINGS AND PRECAUTIONS: Ophthalmologic). Decreases in night vision were reported and, in rare instances, persisted after cessation of therapy (see WARNINGS AND PRECAUTIONS: Ophthalmologic).

Respiratory: Voice alteration and bronchospasm, sometimes in patients with pre-history of asthma.

Urinary system: Glomerulonephritis.

DRUG INTERACTIONS

Drug-Drug Interactions

Tetracyclines: Rare cases of benign intracranial hypertension 'pseudotumor cerebri' have been reported after use of isotretinoin and/or tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see WARNINGS AND PRECAUTIONS: Serious Warnings and Precautions, Neurologic).

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

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

Norethindrone/ethinyl estradiol: In a study of 31 premenopausal women with severe recalcitrant nodular acne receiving OrthoNovum®7/7/7 Tablets 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). A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for isotretinoin.

Microdosed progesterone preparations (minipills): Are not a suitable method of contraception during EPURIS® therapy.

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

Drug-Food Interactions

Following administration of a single capsule of 40 mg EPURIS® with a high fat high calorie meal in healthy subjects, the mean (CV%) for isotretinoin AUC_T was 6095.2 ng•hr/mL (26%). The isotretinoin C_{max} was 394.3 ng/mL (39%), and the median time to peak of 4.5 hours.

When a single capsule of 40 mg EPURIS® was administered under fasting conditions the mean (CV%) for extent of isotretinoin exposure AUC_T was 4045 ng•hr/mL (20%) representing a decrease of 33% relative to high fat-fed conditions. The isotretinoin peak plasma concentration mean (CV%) for C_{max} was 313 ng/mL (26%) or a decrease of 20% over fed, with a median time to peak of 2.5 hours in healthy volunteers, representing a decrease of 45% over fasting.

Drug-Herb Interactions

St. John's Wort: Isotretinoin use is associated with depression in some patients (see WARNINGS AND PRECAUTIONS: Serious Warnings and Precautions, Psychiatric and ADVERSE REACTIONS: Psychiatric Disorders). 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The therapeutic response to isotretinoin is dose-related and varies between patients. This necessitates individual adjustment of dosage according to the response of the condition and the patient's tolerance of the drug. In most cases, complete or near-complete suppression of acne is achieved with a single 12 to 16 week course of therapy. If a second course of therapy is needed, it can be initiated eight or more weeks after completion of the first course, since experience has shown that patients may continue to improve while off the drug.

Due to possible differences in pharmacokinetic properties, EPURIS® capsules are not interchangeable with other isotretinoin-containing products.

Recommended Dose and Dosage Adjustment

Initial Therapy: The initial dose of EPURIS® should be individualized according to the patient's weight and severity of the disease.

In general, patients initially should receive EPURIS® 0.5 mg/kg body weight daily for a period of two to four weeks, when their responsiveness to the drug will usually be apparent. It should be noted that transient exacerbation of acne is occasionally seen during this initial period. For optimal absorption, the daily dose of EPURIS® should be taken with food. Taking EPURIS® without food decreases the rate and extent of absorption by 21% and 33% (Cmax and AUC_t). EPURIS® should be taken in the nearest number of whole capsules, either as a single dose or in

two divided doses during the day, whichever is more convenient.

Maintenance Therapy: Maintenance dose should be adjusted between 0.1 and 1 mg/kg body weight daily and, in exceptional instances, up to 2 mg/kg body weight daily, depending upon individual patient response and tolerance to the drug.

A complete course of therapy consists of 12-16 weeks of EPURIS® administration.

Patients may show additional improvement for up to several months after a course of EPURIS® has been completed. With effective treatment, appearance of new lesions will not normally be evident for a period of at least three to six months.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In the event of acute EPURIS® overdose, evacuation of the stomach should be considered during the first few hours after this overdose. Signs and symptoms of acute overdose have been associated with headache, vomiting, facial flushing, cheilitis, abdominal pain, dizziness and ataxia. To date, all symptoms have quickly resolved without apparent residual effects and usually without treatment. Elevated intracranial pressure has been reported with patients receiving therapeutic doses of isotretinoin. Patients with EPURIS® overdose should be monitored closely for signs of increased intracranial pressure. Signs of hypervitaminosis A could appear in cases of overdose.

Limited data exists on the pharmacokinetic characteristics of isotretinoin in an overdose situation. Following the oral administration of single 80, 160, 240 and 340 mg doses to 12 healthy male subjects C_{max} was 366, 820, 1,056 and 981 ng/mL, and $t_{1/2}$ was 13.6, 14.1, 14.4 and 16.5 hours for isotretinoin, respectively. Twenty-three compromised cancer patients received weekly oral doses of 200 (3 patients); 400 (7 patients); 660 (2 patients); 1,000 (3 patients); 1,400 (6 patients) and 1,800 (1 patient) mg/m^2. Normal body surface area for healthy subjects is 1.73 m^2. After the first dose, C_{max} was 1.5, 3.8, 3.5, 2.5, 2.7 and 4.6 µg/mL, and $t_{1/2}$ was 45, 9.1, 14.5, 57, 13.1 and 6.1 hours for isotretinoin, respectively. The absorption of isotretinoin appears to be a saturable process.

Since it is difficult to extrapolate from the results of these studies to the overdose situation, the following precautions should be taken with all female patients of childbearing potential who have taken an overdose of EPURIS®.

After a patient has been treated for an isotretinoin overdose, consideration should be given to the teratogenic potential of the drug. Female patients should be given pregnancy tests and advised that they need to use a designated method of birth control for at least 30 days after the overdose (the average half life of the drug is ~25 hours). Female patients who test positive on a pregnancy screen after an overdose should be fully counseled on the serious risk to the fetus from this exposure to isotretinoin and the physician and patient should discuss the desirability of continuing the pregnancy (See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS,

Special Populations, Pregnant Women and TOXICOLOGY: Reproduction and Teratology Studies).

Canadian Regional Poison Information Centres have been advised on the proper collection and handling of isotretinoin blood samples and also on the laboratory(s) equipped to assay these samples.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of isotretinoin is unknown. Vitamin A is important for functional integrity of the skin and is known to affect the keratinization process. In acne patients, improvement occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is temporary and is related to either the dose or duration of isotretinoin administration and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.

Pharmacokinetics

Absorption: Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when given with a high-fat meal. EPURIS® is equivalent in rate and extent of absorption to Accutane® (isotretinoin) capsule (Roche, USA) when both drugs are taken with a high-fat meal. EPURIS® is more bioavailable than Accutane® (isotretinoin) capsules (Roche, USA) when both drugs are taken fasted; the AUC_{0-t} of EPURIS® is approximately 83% greater than that of Accutane® (isotretinoin) capsules (Roche, USA). EPURIS® is therefore not interchangeable with other marketed isotretinoin products.

A single dose two-way crossover pharmacokinetic trial was conducted in healthy adult subjects comparing EPURIS® 40 mg (1 x 40 mg capsules), dosed under fasted and fed conditions. Under fasted conditions, it was observed that the mean AUC_{0-t} and C_{max} were approximately 33% and 20% lower than that observed under high fat-fed 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. In a single dose 4-way cross over study conducted in normal healthy adult subjects, a 40 mg dose of Accutane® (isotretinoin) capsules (Roche, USA) was administered under fasted conditions the mean AUC_{0-t} and C_{max} were approximately 62% and 64% lower than that observed under high fat-fed conditions.

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

EPURIS® (1 x 40 mg Capsules)	AUC_{0-t} (ng x hr/mL)* (CV)	C_{max} (ng/mL)* (CV)	T_{max} (hr)** (CV)	$T_{1/2}$ (hr)* (CV)
Fed	6095 (26 %)	395 (39 %)	6.4 (47 %)	22 (25 %)
Fasted	4055 (20 %)	314 (26 %)	2.9 (34 %)	24 (28 %)
Accutane® (Roche, USA)				

(1x40 mg Capsules)				
Fed	6146 (26%)	417 (41%)	6.8 (55%)	18 (16%)
Fasted	2349 (26%)	170 (29%)	3 (58%)	22 (21%)
*Mean Value **Median Value				

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 99.9% protein bound in human plasma, almost exclusively to 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 EPURIS® 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.

Following 40 mg of EPURIS® administered orally, maximum plasma concentrations of the 4-oxo-isotretinoin was 51 to 463 ng/mL and maximum concentrations were observed between 7 and 36 hours.

The mean minimum steady-state blood concentrations of EPURIS® were 171 ng/mL in 40 patients receiving 40 mg (2 x 20 mg) twice daily doses. After single and multiple doses, the mean ratio of areas under the curves of 4-oxo-isotretinoin to isotretinoin was between 3.2 and 3.8.

Excretion: After a single 40 mg (2 x 20 mg) oral dose of EPURIS® to 57 healthy adult subjects under fed conditions, the mean ± SD elimination half-lives ($t_{1/2}$) of isotretinoin and 4-*oxo*-isotretinoin under fed states were 18 hours and 38 hours, respectively. Following oral administration of ^{14}C-isotretinoin, ^{14}C activity in blood declined with a mean half-life of 90 hours. Approximately equal amounts of radioactivity were recovered in the urine and feces, with 65-83% of the dose recovered.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of isotretinoin were evaluated after single and multiple doses in 38 pediatric patients (12 to 15 years) and 19 adult patients (≥18 years) who received 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. The dose-normalized pharmacokinetic parameters for isotretinoin following single and multiple doses are summarized in Table 3 for pediatric patients. There were no statistically significant differences in the pharmacokinetics of isotretinoin between pediatric and adult patients.

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

Parameter	Isotretinoin (Single Dose)	Isotretinoin (Steady-State)
C_{max} (ng/mL)	573.25 (278.79)	731.98 (361.86)
$AUC_{(0-12)}$ (ng·hr/mL)	3033.37 (1394.17)	5082.00 (2184.23)
$AUC_{(0-24)}$ (ng·hr/mL)	6003.81 (2885.67)	–
T_{max} (hr)†	6.00 (1.00-24.60)	4.00 (0-12.00)
Css_{min} (ng/mL)	–	352.32 (184.44)
$T_{1/2}$ (hr)	–	15.69 (5.12)
CL/F (L/hr)	–	17.96 (6.27)

*The single and multiple dose data in this table were obtained following a non-standardized meal (non high-fat meal).

†Median (range)

In pediatric patients (12 to 15 years), the mean ± SD elimination half-lives ($t_{1/2}$) of isotretinoin and 4-oxo-isotretinoin were 15.7 ± 5.1 hours and 23.1 ± 5.7 hours, respectively. The accumulation ratios of isotretinoin ranged from 0.46 to 3.65 for pediatric patients.

STORAGE AND STABILITY

EPURIS® (isotretinoin) 10 mg, 20 mg, 30 mg and 40 mg capsules: Store at 20 - 25ºC . Protect from light. Keep in a safe place out of the reach of children.

SPECIAL HANDLING INSTRUCTIONS

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems” if available in your location.

Return any unused EPURIS® (isotretinoin) capsules to the pharmacist.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:

10 mg Capsules; Dark yellow opaque capsule imprinted with black ink “**G 240**” on cap and “**10**” on the body
Box of 30 capsules (3 x 10 Blister Cards)

20 mg Capsules; Red opaque capsule imprinted with black ink “**G 241**” on cap and “**20**” on the body
Box of 30 capsules (3 x 10 Blister Cards)

30 mg Capsules; Brown opaque capsule imprinted with white ink “**G 242**” on cap and “**30**” on the body
Box of 30 capsules (3 x 10 Blister Cards)

40 mg Capsules; Brown opaque cap and red opaque body imprinted with white ink "**G 325**" on cap and "**40**" on the body
Box of 30 capsules (3 x 10 Blister Cards)

Availability:
EPURIS® capsules 10 mg, 20 mg, 30 mg and 40 mg are available in boxes of 30 capsules (3 x 10 Blister Cards).

Active Ingredient: Isotretinoin, USP

Inactive Ingredients: Stearoyl macrogolglycerides, soybean oil, sorbitan monooleate and propyl gallate. Gelatin capsules contain the following dye systems: 10 mg – iron oxide (yellow) and titanium dioxide; 20 mg – iron oxide (red) and titanium dioxide; 30 mg – iron oxide (yellow, red and black) and titanium dioxide; and 40 mg – iron oxide (yellow, red, and black) and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

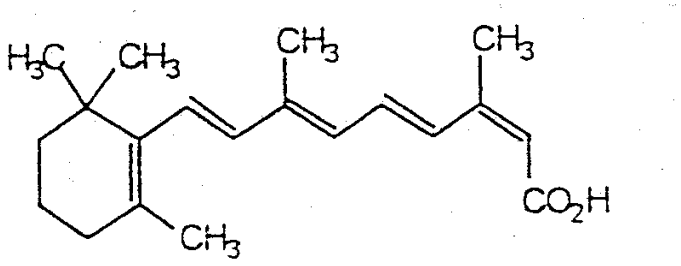
Proper Name: Isotretinoin, USP

Chemical Name: 3-7-dimethyl-9-(2,6,6-trimethyl-1-cyclo-hexen-1-yl)-2-cis-4-trans-6-trans-8-trans- nonatetraenoic acid

Molecular Formula: $C_{20}H_{28}O_2$

Molecular Weight: 300.44

Structural Formula:



Physiochemical properties: Orange crystalline powder, insoluble in water; soluble in chloroform (10g / 100 mL). Melting point approximately 175ºC; pKa approximately 4.

CLINICAL TRIALS

Study demographics and trial design

A double-blind, randomized, phase III, parallel group study was conducted under fed conditions, in patients with severe recalcitrant nodular acne to evaluate the efficacy and safety of EPURIS® compared to a Reference Product (currently marketed formulation of isotretinoin). A total of 925 (EPURIS®: 464 / Reference Product: 461) male and female patients between the ages of 12 and 54 years with at least 10 or more nodular lesions on the face and/or trunk were randomized into the study; 813 patients completed the full duration of the study. Patients were treated with EPURIS® or the Reference Product in a 1:1 ratio at an initial titration dose of 0.5 mg/kg/day for the first 4 weeks followed by 1 mg/kg/day for the following 16 weeks. The ITT population was defined as all randomized patients who were dispensed the study drug. The per protocol

population was defined as patients in the ITT population who completed the study without any major protocol deviations.

Safety assessments during the study included monitoring of adverse events, laboratory tests, psychiatric evaluations, bone mineral density and bone age assessments, questions about musculoskeletal symptoms, ophthalmic and audiology testing.

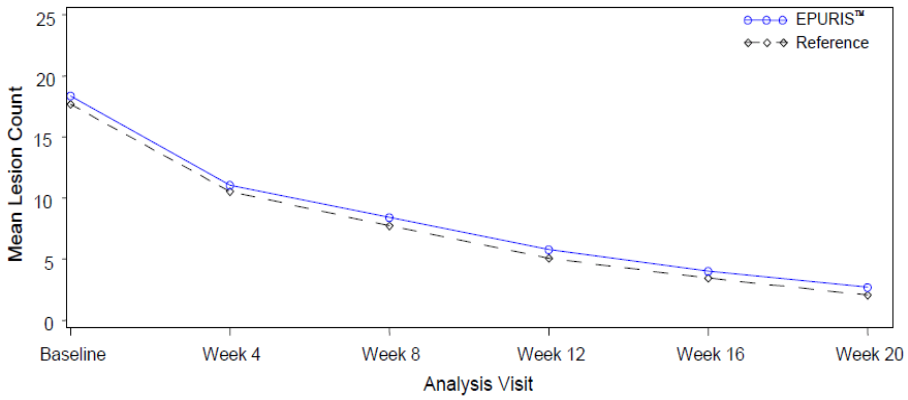
Results with both of the primary efficacy outcomes, change from Baseline to Week 20 in total nodular lesion count and the proportion of patients with at least a 90% reduction from Baseline in total nodular lesion count are shown below (Table 4).

Table 4: Efficacy Results in the Phase III clinical study (ISOCT.08.01): Total nodular lesion count (facial and truncal)

	PP		ITT	
	EPURIS® N = 363	**Reference N = 361**	**EPURIS® N = 464**	**Reference N = 461**
Number of nodules				
Baseline, Mean (SD)	18.4 (14.8)	17.7 (10.9)	18.4 (14.7)	17.7 (10.8)
Week 20, Mean (SD)	1.4 (3.4)	1.2 (2.5)	2.7 (6.8)	2.0 (4.8)
Change from baseline, Mean (SD)	-17.0 (14.26)	-16.5 (10.57)	-15.68 (14.02)	-15.62 (10.59)
Difference (95% C.I)	0.14 (-0.27, 0.55)		0.49 (-0.23, 1.21)	
Responder rates				
Responder rates* (95% C.I.)	78.8% (74.6, 83.0)	80.9% (76.8, 84.9)	69.8 % (65.7, 74.0)	74.6% (70.6, 78.6)
Difference (95% C.I)*	-2.10 (-7.94, 3.74)		-4.79 (-10.56, 0.97)	

*: responders are defined as a patients having ≥ 90% reduction from baseline to week 20 in total nodular (facial and truncal) lesion Count
PP: Per-protocol analysis, ITT: Intent-to-treat analysis

Figure 2: Total Nodular (Facial and Truncal) Lesion Count by Visit [ITT Population (LOCF)]



DETAILED PHARMACOLOGY

Isotretinoin exerts a specific action on the sebaceous glands of the hamster flank organs. Subcutaneous administration of isotretinoin to female hamsters treated simultaneously with testosterone enanthate prevents the androgen-induced growth of flank organ sebaceous glands without affecting other androgen dependent cells (i.e. does not inhibit development of pigment or larger hair follicles).

Doses up to 300 mg/kg orally of isotretinoin have no effect upon circulation and respiratory parameters in the anesthetized cat. A dose of 1 g/kg results in respiratory stimulation and a slight decrease in blood pressure, pulse rate, blood flow to the extremities as well as oxygen saturation.

TOXICOLOGY

Acute Toxicity Studies:

Animal	Route	LD50	Observation Period
mouse	oral	3,389 mg/kg	--
mouse	intraperitoneal	904 mg/kg	10, 20 days
rat	oral	> 4,000 mg/kg	14 days
rat	intraperitoneal	901 mg/kg	10, 20 days
rabbit	oral	approx. 1,960 mg/kg	14 days

(Signs and symptoms: sedation and respiratory depression)

Pyramiding doses of 4.8, 13.1, 41.2 and 79.8 mg/kg of isotretinoin were administered to dogs. All dogs survived. Diarrhea occurred in dogs treated with doses of 13.1 mg/kg or higher.

Long-Term Toxicity Studies:

55-week Oral Toxicity -Dog

In a 55-week toxicity study conducted in beagle dogs (9/sex/group), isotretinoin was administered as a dietary admix at doses of 3, 20 or 120 mg/kg/day. Severe toxicity developed in the high-dose group and administration was stopped at the end of week 4. Isotretinoin was restarted in this group at the end of 12 weeks, but at a reduced dosage of 60 mg/kg/day. After 7 weeks, administration again had to be stopped for 6 weeks. Administration continued uninterrupted until week 30. Thereafter, the high-dose group was maintained on a cycle of 2 weeks no treatment followed by 6 weeks of treatment with 60 mg/kg/day.

In the high-dose group (60/120 mg/kg/day), the following toxic manifestations were observed: weight loss, skin lesions, visible blood in feces, ophthalmological changes (epiphora, superficial punctate corneal opacities in the subepithelial stroma, vascularization of the subepithelial corneal stroma and congestion or hyperemia of the palpebral and/or bulbar conjunctiva), decreases in hematocrit and hemoglobin, decreased mean serum glucose levels, slight alterations in mean serum transaminase activity, elevations in mean serum alkaline phosphatase activity, and qualitative albuminuria.

Most clinical signs of toxicity disappeared or diminished when isotretinoin was withdrawn and reappeared when treatment was reactivated. Pathological changes in the high-dose group included: increased incidence of focal gross lesions in the gastrointestinal tract, testicular atrophy with evidence of spermatogenic arrest, increased mean liver weight, microscopic evidence for edema and/or erythrophago-cytosis of the lymph nodes, encephalomalacia limited to single microscopic foci in the brain of two dogs, and degeneration of elastic fibre in four dogs.

Many of the clinical and pathological signs, except for weight loss and corneal opacities, seen in the high dosage group were also evident in the dogs treated with 20 mg/kg/day. However, a tendency towards a decreased frequency and a longer time to first appearance than in the high-dose group was noted.

The low dosage (3 mg/kg/day) was well tolerated, but microscopic changes in the lymph nodes were observed in the same number of dogs as was recorded for the mid-dose group.

Two-year Oral Toxicity - Rat

Isotretinoin was administered to rats (80/sex/group) as a dietary admix for two years. All groups received 1 mg/kg/day for 13 weeks in order to avoid excessive bone fractures during the major period of growth. Thereafter, doses of 2, 8 and 32 mg/kg/day were administered. In the high-dose group, administration of drug was discontinued during weeks 29-41 and 67-73 due to long bone fracture.

All observed side effects of hypervitaminosis A syndrome were spontaneously reversible after withdrawal of isotretinoin. Even experimental animals in a poor general state had largely recovered within 1-2 weeks.

32 mg/kg/day

Upon completion of the study, the following **clinical and laboratory findings** were observed in the high dose group: increased mortality, decreased body weight gain and food consumption; altered gait (related to possible long bone fracture); decreased hemoglobin and hematocrit; elevated serum alkaline phosphatase, serum triglycerides, serum phosphate, and serum urea nitrogen; exacerbated age- and sialodacryoadenitis (SDA) virus-related eye changes; skin lesions; some increased organ weights. The following **histopathological findings** were noted: reduplication of small bile ducts; focal fibrosis and focal chronic inflammation of the heart; focal dilation of renal tubules and focal chronic inflammation of the kidney; adrenal medullary lesions (hyperplasia and pheochromocytomas); arteritis; calcification of arteries; focal calcification in tissues; focal osteolysis of bone.

8 mg/kg/day

When isotretinoin was administered to rats at 8 mg/kg/day as a dietary admix for two years, the **clinical and laboratory findings** were: increased mortality; decreased body weight gain; decreased hemoglobin and hematocrit; elevated serum alkaline phosphatase and serum triglycerides; exacerbated age- and SDA virus-related eye changes; skin lesions; some increased organ weights. The **histopathological findings** were: reduplication of small bile ducts; focal fibrosis and focal chronic inflammation in the heart; renal tubular dilation and focal chronic inflammation in the kidney; adrenal medullary lesions (hyperplasia and pheochromocytomas); arteritis; calcification of arteries; focal calcification in tissues; focal osteolysis of bone.

2 mg/kg/day
When isotretinoin was administered to rats at 2 mg/kg/day as a dietary admix for two years, the **clinical and laboratory findings** were: elevated serum alkaline phosphatase values, some increased organ weights. The **histopathological findings** were: reduplication of small bile ducts; increased focal chronic inflammation of the kidneys; arteritis; calcification of arteries; focal calcification in tissues.

Although an increased incidence of pheochromocytomas and adrenal medullary hyperplasia were observed at the high and mid doses, no increase was observed at the low dose. It is very likely that this increase in number of adrenal medullary proliferative lesions was mediated by an effect upon hormonal status in rats that were already hormonally abnormal because of their genetic origin and overfeeding, as well as other aspects of the environment of laboratory rats. Dose-related decreases in the incidence of liver adenomas and angiomas in male rats and leukemia in female rats were also noted.

Reproduction and Teratology Studies:
Like other Vitamin A derivatives, isotretinoin has been shown in animal experiments to be teratogenic and embryotoxic; however, there is a large species variation in the teratogenic effect. Rats have been reported to be less sensitive to the teratogenic effects of isotretinoin; whereas, humans have been reported to be the most sensitive. Differences in sensitivity are a result of interspecies differences in the pharmacokinetics and placental transfer of isotretinoin.

The following table provides the low dose (mg/kg) reported to elicit teratogenesis in animal models.

Species	Low dose to elicit teratogenic effect
Mouse/rat	75 - 150 mg/kg
Rabbit	10 mg
Monkey	2.5 – 5 mg
Human	0.4 – 1 mg/kg

Fertility and General Reproductive Performance - Rat
Isotretinoin at doses of 2, 8 or 32 mg/kg/day was administered orally to male rats for 63 days prior to mating and through the mating period and to females for 14 days prior to mating and through day 13 of gestation or day 21 of gestation or day 21 of lactation. No adverse effects on fertility and general reproductive performance were observed except for a slight reduction in the weight of weanlings in the high-dose group.

Teratology - Rat
A teratology study was conducted in rats with 5, 15 or 50 mg/kg/day of isotretinoin administered orally on gestation days 7 through 15. Doses of up to 50 mg/kg/day of isotretinoin were found to be nonteratogenic. In an earlier study a dose of 150 mg/kg/day was observed to be teratogenic.

Teratology - Rabbit
New Zealand white rabbits were administered isotretinoin at doses of 1, 3 or 10 mg/kg/day on

days 7 through 18 of gestation. No teratogenic or embryotoxic effects were observed at 1 and 3 mg/kg/day. At 10 mg/kg/day, 9/13 does aborted and teratogenicity and embryotoxicity were observed in the remaining four litters.

Perinatal and Postnatal Evaluation - Rat

Rats were administered isotretinoin at doses of 5, 15 or 32 mg/kg/day orally from gestation day 14 through day 21 of lactation. Increased pup mortality, considered secondary to reduced maternal food intake, was noted in all treated groups and particularly in the high-dose group. Body weight development of pups was impaired significantly in the high-dose group. Similarly, this effect was considered due to a reduced food intake by the dams.

Mutagenicity Testing

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* TA 100 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.

Carcinogenicity Testing

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.

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PART III: CONSUMER INFORMATION

PrEPURIS® Isotretinoin Capsules

This leaflet is part III of a three-part "Product Monograph" published when EPURIS® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about EPURIS®. Contact your doctor or pharmacist if you have any questions about the drug.

Read this Consumer Information every time you get a prescription or a refill for EPURIS®. There may be new information. This information does not take the place of talking with your doctor.

ABOUT THIS MEDICATION

What the medication is used for:

EPURIS® is a medicine used to treat severe acne (nodular and or inflammatory acne) that cannot be cleared up by other acne treatments, including antibiotics.

What it does:

- The mechanism of action of isotretinoin is not known. It is believed to act on the sebaceous glands (oil/wax producing glands) to reduce sebum excretion. This may indirectly reduce bacterial activity associated with acne and improve the condition.
- EPURIS® contains the active ingredient isotretinoin. This is a vitamin A derivative, belonging to the retinoid class of medicines. Retinoids are normally used to treat skin problems.
- During the first few weeks of treatment, your acne may seem to get worse. Redness and itching of the affected skin are common initial effects. These should disappear as you continue to take isotretinoin. Most often, the first signs of healing occur after two to three weeks of treatment. It may take one to two months before beneficial effects are seen. Most patients with severe acne notice a marked improvement after one or two courses of treatment with isotretinoin.

When it should not be used:

- **Do not use if pregnant.**
- **Do not get pregnant** while taking EPURIS® and stop taking immediately if you do get **pregnant** (See SERIOUS WARNINGS AND PRECAUTIONS).
- **Do not breast feed** while taking EPURIS® and for one (1) month after stopping isotretinoin. Isotretinoin may pass through your milk and harm the baby.
- **Do not take tetracyclines with isotretinoin.** For some antibiotics, you may have to stop taking isotretinoin until the antibiotic treatment is finished. Use of tetracyclines with isotretinoin together can increase the chances of getting increased pressure in the brain. Certain antibiotics interfere with the effectiveness of birth control pills.
- **Do not take Vitamin A** supplements. Vitamin A in high doses has many of the same side effects as isotretinoin. Taking both together may increase your chance of getting side effects.
- **Do not take** EPURIS® if you have liver or kidney disease.
- **Do not take** EPURIS® if you have high blood fat (lipid) levels.
- **Do not take** EPURIS® if you are sensitive to retinoids, or stearoyl macrogolglycerides, soybean oil, sorbitan monooleate or propyl gallate (See What the nonmedicinal ingredients are).

What the medicinal ingredient is:

Isotretinoin, USP

What the nonmedicinal ingredients are:

Stearoyl macrogolglycerides, soybean oil, sorbitan monooleate and propyl gallate. Gelatin capsules contain the following dye systems: 10 mg – iron oxide (yellow) and titanium dioxide; 20 mg – iron oxide (red) and titanium dioxide; 30 mg – iron oxide (yellow, red and black) and titanium dioxide; and 40 mg – iron oxide (yellow, red, and black) and titanium dioxide.

What dosage forms it comes in:

EPURIS® capsules 10 mg, 20 mg, 30 mg and 40 mg are available in boxes of 30 capsules (3 x 10 Blister Cards).

WARNINGS AND PRECAUTIONS

EPURIS® can cause serious side effects. Before starting EPURIS®, discuss with your doctor how bad your acne is, the possible benefits of EPURIS®, and its possible side effects, to decide if EPURIS® is right for you. Your doctor will ask you to read and sign a form indicating you understand some of the serious risks of EPURIS®.

Possible serious side effects of taking EPURIS® include birth defects and mental health problems.

Serious Warnings and Precautions

All patients must sign the informed consent form prior to initiating therapy.

All Females: Birth defects:
Isotretinoin can cause birth defects (deformed babies). It can also cause miscarriage, premature birth, or death of the baby. Therefore, adequate birth control measures are essential when taking EPURIS®. See **"What are the important warnings for females taking EPURIS®?"**

All Patients: Mental health problems and suicide:
Some patients, while taking isotretinoin or soon after stopping isotretinoin, have become depressed or developed other serious mental health problems. Signs of these problems include feelings of sadness, irritability, unusual tiredness, trouble concentrating, and loss of appetite. Some patients taking isotretinoin have had thoughts about putting an end to their own lives (suicidal thoughts), tried to end their own lives, and some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on isotretinoin becoming aggressive or violent. No one knows if isotretinoin caused these behaviors or if they would have happened even if the person did not take isotretinoin.
For other possible serious side effects of isotretinoin, see the table: "Serious side effects and what to do about them.:"

There have been reports of serious skin reactions occurring with the use of isotretinoin, such as erythema multiforme (EM), Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) which can result in hospitalization, disability and/or death.

Stop using EPURIS® and call your doctor immediately if you develop a serious skin reaction with symptoms such as blisters, peeling skin, severe red/purple rash, multiple lesions and sores, particularly in your mouth, nose, eyes and genitals, as well as facial and tongue swelling.

What are the important warnings for females taking EPURIS®?

- **Do not take isotretinoin if you are pregnant.**
- **If you become pregnant, stop taking isotretinoin and contact your doctor immediately.**
- **Isotretinoin can cause deformed babies. There is an extremely high risk that your baby will be deformed if you are pregnant while taking EPURIS®. This risk exists even if EPURIS® is taken for a short time. If you are a female of childbearing potential, your physician should have discussed this risk with you, and explained how to avoid becoming pregnant while taking EPURIS®.**
- **You must avoid becoming pregnant while you are taking EPURIS® and for at least one month after you stop taking EPURIS®.**
- **You must discuss effective birth control with your doctor before beginning EPURIS® treatment, and you must use effective birth control:**
  - **For at least one month before you start EPURIS®;**
  - **While you are taking EPURIS®; and**
  - **For at least one month after you stop taking EPURIS®;**

Bearing in mind that any method of birth control can fail:

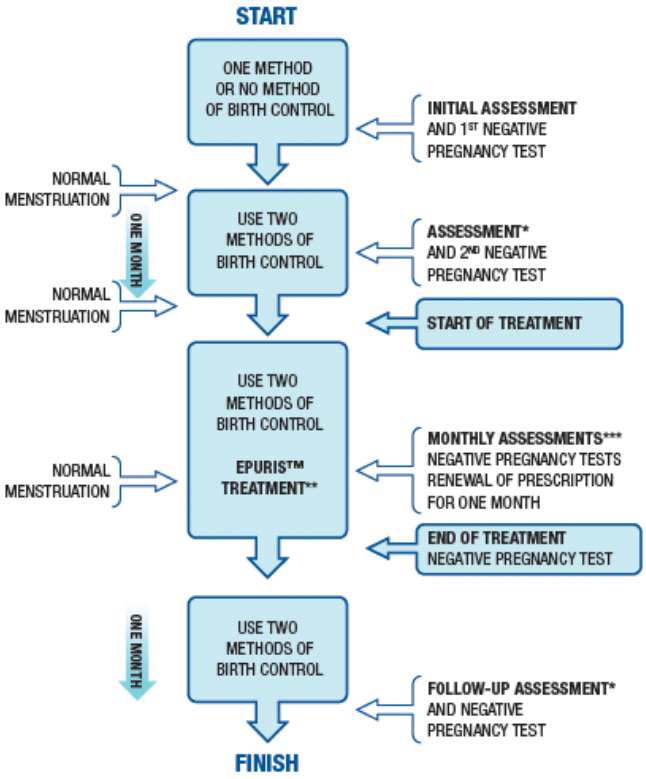
- **It is recommended that you either abstain from sexual intercourse or use two reliable methods of birth control at the same time, even if you have a history of infertility or are not sexually active.**
- **Do not take EPURIS® until you are sure that you are not pregnant.**
- **You must have two negative pregnancy tests before you start EPURIS®. You will need to take a test on a monthly basis while on the drug and one month after you stop taking EPURIS®. If your menstrual period is abnormal in length and intensity, first contact your doctor. (see the EPURIS® PEER™ PROGRAM)**
- **You must wait until the second or third day of your next normal menstrual period before you start EPURIS®.**
- **Stop taking EPURIS® and contact your doctor immediately if you do become pregnant while taking EPURIS® or during the first month after treatment has stopped, if you miss your period, or if you have sexual intercourse without using effective birth control. You should discuss with your doctor the serious risk of your baby having severe birth deformities because you are taking or have taken EPURIS®. You should also discuss the desirability of continuing with your pregnancy.**
- **Do not breast feed while taking EPURIS®.**

You should have been counseled using the EPURIS® PEER™ PROGRAM which includes:

- Comprehensive information about the risks of this drug
- A line drawing of a deformed baby
- A checklist of criteria you had to meet before receiving this drug
- Detailed information on birth control options
- A chart: "EPURIS® PEER ™ PROGRAM"
- An informed consent for you to review and sign. A copy of this form should be given to you by your doctor.

Please note that the manufacturer of EPURIS® provides confidential contraception counseling (from a health care professional). For more information, please contact Cipher Pharmaceuticals Inc at 1-855-437-8747 (1-855-4EPURIS).

If you were not counseled using the EPURIS® PEER™ PROGRAM, please contact your doctor for more information.



* To ensure that you are using two reliable methods of birth control at the same time.
** Duration of therapy is typically 3-4 months.
***To ensure that you are using two reliable methods of birth control at the same time and to detect any side effects tat you may have from the treatment.

All patients should read the rest of the Consumer Information.

Do not take EPURIS® unless you completely understand its possible risks

What should you tell your doctor before starting EPURIS®?

- Tell your doctor if you or someone in your family has ever had any mental illness, including depression, suicidal behavior, or psychosis. Psychosis means a loss of contact with reality, such as hearing voices or seeing things that are not there. Also, you should tell your doctor if you are taking medicines for any of these problems.
- Tell your doctor if you or any member of your family have liver disease, kidney disease, heart disease, high cholesterol, diabetes or asthma.
- Tell your doctor if you plan vigorous physical activity during treatment with EPURIS®.
- Tell your doctor if you have any food or drug allergies.
- Tell your doctor if you are taking any vitamin preparations or health food supplements that contain Vitamin A.
- Tell your doctor the brand of contraceptives you are taking. There are certain types of contraceptives that should not be taken while on EPURIS®.
- Tell your doctor if you are taking an antibiotic (particularly tetracyclines).

What should you avoid while taking EPURIS®?

- **Do not give blood** while you take EPURIS® and for one (1) month after stopping EPURIS®. If someone who is pregnant gets your donated blood, her baby may be exposed to isotretinoin and may be born with birth defects.
- **Do not have cosmetic procedures to smooth your skin, such as waxing, dermabrasion, or laser procedures, while you are using EPURIS® and for at least 6 months after you stop**. Isotretinoin can increase your chance of scarring or inflammation of the skin from these procedures. Check with your doctor for advice about when you can have cosmetic procedures.
- **Avoid the use of artificial ultraviolet lights** such as the ones used in tanning machines and **protect yourself from excessive sunlight**. Isotretinoin may make your skin more sensitive to ultraviolet light. When necessary, sunscreen with a high protection factor of at least SPF 15 should be used
- **Avoid the use of exfoliative anti-acne agents.**
- **Do not share EPURIS® with other people**. It can cause birth defects and other serious health problems.
- **Do not take Vitamin A.**
- **Do not take antibiotics unless you have discussed with your doctor. See "When it should not be used".**

INTERACTIONS WITH THIS MEDICATION

- **Do not use low dose birth control pills.** They may not work while you take EPURIS®.
- The following medications may interact with isotretinoin or isotretinoin may interfere with the actions of: low-dose contraceptives, antibiotics, corticosteroids, phenytoin, and natural health products such as herbs (i.e., St. John's Wort).

PROPER USE OF THIS MEDICATION

Usual dose:

- Read your prescription label carefully and be sure to take the exact amount of medicine prescribed by your doctor. Your doctor may change your prescribed dose from time to time, therefore, it is important that you check the label each time you fill your EPURIS® prescription. If you have any questions, call your doctor.
- If you are of childbearing age, your doctor will limit your EPURIS® prescription to 30 days, so that continued treatment will require a new prescription. Be sure to have your new prescription filled within 7 days after seeing your doctor.
- Take EPURIS® with food.
- Be sure to return to your doctor as scheduled. It is important for your doctor to see you regularly, every month, when you are taking EPURIS®. Blood tests and other tests allow your doctor to check your response to EPURIS®. Discuss your progress and any concerns with your doctor.

Overdose:

In case of an overdose or suspected overdose, contact your doctor, hospital emergency department or the regional poison control centre, even if there are no symptoms.

Missed Dose:
If you forget to take a dose of EPURIS® it may be taken later the same day, but, do not take more EPURIS® in one day than your doctor has prescribed.

Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Serious side effects you must immediately tell your doctor about:

If you get these symptoms, you must tell your doctor immediately because it may be necessary to stop EPURIS®. These symptoms could lead to serious health problems requiring treatment even if EPURIS® is stopped.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Effect	Signs and Symptoms	Tell your doctor immediately
Mental health problems such as depression or psychosis (severe mental disturbance)	• changes in your mood such as becoming depressed, feeling sad, or having crying spells, • losing interest in your usual activities, • changes in your normal sleep patterns, • becoming more irritable or aggressive than usual (for example, temper outbursts, thoughts of violence), • losing your appetite, • becoming unusually tired, • having trouble concentrating, • withdrawing from family and friends, • having thoughts about taking your own life (suicidal thoughts) Your doctor may recommend a consultation with a specialist if you become depressed or experience these changes in mood	√
Inflammation of the liver, pancreas, or intestines (bowel)	• severe stomach pain, diarrhea, rectal bleeding; yellowing of the skin or eyes and/or dark urine	√
Bone and muscle changes:	• aches or pains in bones or joints, back pain, or difficulty in moving, muscle pain, especially after vigorous exercise If a bone breaks tell your doctor.	√
Hypersensitivity (allergic) reactions	• hives, swollen face or mouth, trouble breathing, fever, rash, red patches, bruises. • In some patients a rash can be serious. These include; conjunctivitis (red or inflamed eyes, like "pink eye"), a rash with fever, blisters on legs, arms or face and/or sores in your mouth, throat, nose, eyes, or if your skin begins to peel.	√
Increased pressure in the brain	• bad headaches, blurred vision, dizziness, nausea, vomiting.	√
Hearing and vision differences	• Changes in your **hearing** or ringing in your ears. • Changes in your **vision** especially at night. Decreased night vision may occur and be sudden in some patients. Take caution when driving at night In addition, some loss may occur in the sharpness of your vision (acuity) which is most often reversible when you stop EPURIS™. In some cases this loss may not be completely reversible • persistent feelings of **dry eyes**	√
Heart Problems	• chest pain, palpitations, vascular thrombotic disease, stroke, leg swelling, seizures (convulsions), slurred speech, problems moving or any other serious unusual problems	√
Problems with blood sugar levels	fainting, become very thirsty, urinating a lot, feeling weak	√

EPURIS® may affect blood fat, cholesterol, or sugar levels. Therefore it is important for you to see your doctor at regularly scheduled visits.

What are the other possible side effects of isotretinoin?
It is important to watch for the special symptoms listed in the table above as these may be signs of serious side effects.

The side effects listed below are generally temporary and disappear when isotretinoin treatment is stopped; however, you must tell your doctor if any of your side effects do not clear up

in a few weeks after you stop taking isotretinoin. **You must also check with your doctor, if these effects become bothersome, to see if any change in your medication is needed.**

- **Some of the most common side effects are:** dryness of the skin, lips, mouth, and lining of the nose. It is recommended that you use a skin-moisturizing ointment or cream and a lip balm from the start of treatment of EPURIS®.
- Some other side effects that may occur include: facial or body rash, flaking of the skin, itching, peeling of the palms and soles, increased sensitivity to the sun, sunburn, inflammation of the lips, mild nose bleed, bleeding and inflammation of the gums, easily injured skin and increased fatigue. You may experience some redness, dryness, or irritation of the eyes
- In some patients variable amounts of hair loss have occurred. In rare cases, this hair loss persisted after treatment was completed.
- If you wear contact lenses, you may find them uncomfortable during treatment because isotretinoin may cause dry eyes. This may continue after treatment has stopped. Dry eyes can be helped by applying a lubricating eye ointment or tear replacement therapy.

These are not all of the possible side effects associated with isotretinoin. Your doctor or pharmacist can give you more detailed information that is written for health care professionals.

HOW TO STORE IT

Keep out of the reach and sight of children.

- EPURIS® should be stored at 20 - 25ºC. Store in the original package. Protect from light.
- EPURIS® does not need to be refrigerated.

SPECIAL HANDLING INSTRUCTIONS

It is recommended that EPURIS® not be disposed of in household waste or waste water. Please return any unused EPURIS® to the pharmacist or use an established "collection system" if available in your location.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following three (3) ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This Consumer Information is only a summary of some important information about EPURIS®. Medicines are sometimes prescribed for purposes other than those listed in a Consumer Information. If you have any concerns or questions about EPURIS®, ask your doctor. Do not use EPURIS® for a condition for which it was not prescribed.

This document plus the full product monograph, prepared for health professionals can be found at: www.epuris.ca, or by contacting Cipher Pharmaceuticals Inc. at 1-855-437-8747 (1-855-4EPURIS).

This leaflet was prepared by

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For information about birth control or for confidential counseling call Cipher Pharmaceuticals Inc. at 1-855-437-8747 (1-855-4EPURIS) or visit the EPURIS® website at www.epuris.ca