Product Monograph

Including Patient Medication Information

PrEPURIS®

Isotretinoin Capsules

Capsules
Oral use
10, 20, 30, 40 mg

Retinoid for treatment of acne

Cipher Pharmaceuticals Inc.
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Canada

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Recent Major Label Changes

Section 7 Warnings and Precautions, Reproductive Health: Female and Male Potential, Function	2025-05
Section 7 Warnings and Precautions, Musculoskeletal	2025-05

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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Part 1: Healthcare Professional Information

1. INDICATIONS

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

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

Because of significant adverse reactions 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 2. Contraindications, 3. Serious Warnings and Precautions Box and 7.1.1. 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 3. Serious Warnings and Precautions)

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 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® occur within a maximum of 7 days of the prescription.

1.1. Pediatrics

Pediatrics (< 12 years of age): The safety and efficacy of EPURIS® in pediatric patients less than 12 years of age have not been established. The use of EPURIS® in these patients is not recommended.

Pediatrics (12 to 17 years of age): 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 7.1.3. Pediatrics).

1.2. Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of isotretinoin-containing products did not include sufficient numbers of geriatric subjects aged 65 years and over to determine whether they respond differently from younger subjects. Although reported clinical experience has not identified differences in responses between elderly and younger patients, effects of aging might be expected to increase some risks associated with isotretinoin therapy (see 7.1.4. Geriatrics).

2. 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 7.1.1. 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 1. Indications).

EPURIS® is also contraindicated in:

- breast-feeding women
- hepatic insufficiency
- renal insufficiency
- hypervitaminosis A
- patients with excessively elevated blood lipid values
- patients taking tetracyclines (see 3. Serious Warnings and Precautions Box and 9.4. Drug-Drug Interactions)
- patients who are sensitive to isotretinoin or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Table 2.

3. Serious Warnings and Precautions Box

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 2. Contraindications). Physicians should **only** prescribe EPURIS® to females of childbearing potential if **ALL** the conditions described under Conditions of Use are met. See also Contraception.

  Females must use 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.

  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 before and during therapy (see Psychiatric). Physicians should determine whether the patient may be depressed or has a history of depression including a family history of major depression before starting therapy with EPURIS®. 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 as necessary. However, discontinuation of EPURIS® may not alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

  A Mental Health Questionnaire 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**
  - **Mental Health Questionnaire**

Cipher Pharmaceuticals Inc. Customer Service:

5750 Explorer Drive, Suite 404, Mississauga, Ontario, L4W 0A9
Tel: 1-855-437-8747 (1-855-4EPURIS)
Fax: 1-855-337-8747

- **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 2. Contraindications and 9.4. 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 2. Contraindications and 9.4. Drug-Drug Interactions)

4. Dosage and Administration

4.1. Dosing Considerations

- Carefully assess the patient's mental state, including whether or not they have a history of previous psychiatric illness (see 3. Serious Warnings and Precautions Box and 7. Warnings and Precautions, Psychiatric).
- 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

The following laboratory testing **must** be completed prior to EPURIS® use:

- **Pregnancy testing:**
  Ensure patient is not pregnant prior to administering EPURIS® (see 2. Contraindications, Monitoring and Laboratory Tests, and 7.1.1. Pregnant Women)
- A fasting lipid profile including triglycerides
- Liver function tests
- Renal function tests
- Blood glucose levels (see 2. Contraindications, Monitoring and Laboratory Tests)

4.2. 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 AUCt). 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.

4.4. Administration

EPURIS® is for oral use only.

4.5. Missed Dose

If a patient misses a dose of EPURIS®, it may be taken later the same day, but, the patient should be instructed to not take more EPURIS® in one day than what has been prescribed. The patient should then administer the next dose on the usual scheduled dosing day. The patient should not take a double dose to make up for a missed dose.

5. Overdose

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

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 of isotretinoin 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 an 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 2. Contraindications, 7.1.1. Pregnant Women and 16. Non-Clinical Toxicology, Reproductive and Developmental Toxicology).

Patients who test positive on a pregnancy screen after an overdose should be fully counselled 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 2. Contraindications, 7.1.1. Pregnant Women and 16. Non-Clinical Toxicology, Reproductive and Developmental Toxicology).

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.

6. Dosage Forms, Strengths, Composition and Packaging

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsules of 10 mg, 20 mg, 30 mg and 40 mg containing Isotretinoin, USP as an active ingredient	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.

Table 2: Hard Gelatin Capsule Shell: Description

Description
10 mg A size 2, Dark yellow opaque capsule imprinted with black ink "**G 240**" on cap and "**10**" on the body
20 mg A size 0, Red opaque capsule imprinted with black ink "**G 241**" on cap and "**20**" on the body
30 mg A size 0EL Brown opaque capsule imprinted with white ink "**G 242**" on cap and "**30**" on the body
40 mg A size 00EL, Brown opaque cap and red opaque body imprinted with white ink "**G 325**" on cap and "**40**" on the body.

7. Warnings and Precautions

Please see 3. Serious Warnings and Precautions Box

General

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

Conditions of Use

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 7.1.1. 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®.

(For items 4 to 9 above, please see 7.1.1. Pregnant Women).

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.

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 3. Serious Warnings and Precautions Box) has also been provided directly to patients *via* the EPURIS® compliance packaging or could be found via www.epuris.ca website. 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.

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 8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

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 7. 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 8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data)

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 7. 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 7. Warnings and Precautions, Monitoring and Laboratory Tests). Therefore, every attempt should be made to control significant triglyceride elevation (see 7. 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.

Monitoring and Laboratory Tests

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 7. Warnings and Precautions, Endocrine and Metabolism and Hepatic/Biliary/Pancreatic) and/or blood glucose may be necessary.

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.

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 7.1.3. 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.

There have been post-marketing serious reports of rhabdomyolysis, often leading to hospitalization and some with fatal outcome, particularly in those undergoing strenuous physical activity. Patients should abstain from vigorous exercise activity during isotretinoin treatment (see 8.5. Post-Market Adverse Reactions, Musculoskeletal).

Sacroiliitis has been reported in patients exposed to isotretinoin. To differentiate sacroiliitis from other causes of back pain, in patients with clinical signs of sacroiliitis, further evaluation may be needed including imaging modalities such as MRI. In cases reported post-marketing, sacroiliitis improved after discontinuation of isotretinoin and appropriate treatment.

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 8.2. Clinical Trial Adverse Reactions and 8.5. 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.

Neurologic

See 3. Serious Warnings and Precautions Box.

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 8.2. Clinical Trial Adverse Reactions and 8.5. Post-Market Adverse Drug Reactions, Eye Disorders). 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 8.2. Clinical Trial Adverse Reactions and 8.5. Post-Market Adverse Drug Reactions, Eye Disorders). 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.

Psychiatric

See 7. Warning and Precautions, Signs of Depression and 3. Serious Warnings and Precautions Box.

A Mental Health Questionnaire 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.

Renal

EPURIS® is contraindicated in patients with renal insufficiency (see 2. Contraindications).

Reproductive Health: Female and Male Potential

Both male and female patients should be given a copy of the Patient Medication Information.

- **Contraception**
  Females:
  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 9.4 Drug-Drug Interactions).

  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 3 Serious Warnings and Precautions Box) 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.

- **Fertility**

  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 Patient Medication Information.

- **Function**

Risk of Sexual Side Effects
Cases of sexual dysfunction including erectile dysfunction, decreased/loss of libido, vulvovaginal dryness, orgasm difficulties, and genital hypoaesthesia have been reported in patients with the use of isotretinoin. There have been reports of persistence of these events following drug discontinuation. While causality to isotretinoin could not be definitively established, an effect cannot be ruled out. When deciding on treatment with isotretinoin, patients, and where appropriate, parents or caregivers, should be informed about this potential risk. All patients should be screened and monitored, and advised to monitor themselves, for signs and symptoms of sexual dysfunction before and during therapy.

- **Teratogenic Risk**

Embryo-Fetal Toxicity

EPURIS® is contraindicated in pregnancy (see 2 Contraindications). Based on human data, there is an extremely high risk EPURIS® can cause fetal harm when administered to a pregnant patient (see 3 Serious Warnings and Precautions Box, Conditions of Use, and 7.1.1 Pregnant Women).

Male Patients

The threshold dose of isotretinoin exposure causing birth defects is not known. Since the extent to which isotretinoin may be found in semen is not known, it is recommended that male patients being treated with EPURIS® use a condom or avoid reproductive sexual activity to avoid possible transmission to a female partner.

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

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 hypopigmentation 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.

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. Patients treated with EPURIS® should be monitored closely for severe skin reactions. 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.

7.1. Special Populations

7.1.1. 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:

1. Serve primarily to reinforce to the patient the necessity of avoiding pregnancy.
2. 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 2. Contraindications and 16. Toxicology, Reproduction and Developmental Toxicology).

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 2. Contraindications and 16. Toxicology, Reproduction and Developmental Toxicology). 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.

7.1.2. Breastfeeding

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 breastfeed if they are receiving EPURIS® (see 2. Contraindications).

7.1.3. Pediatrics

Pediatrics (< 12 years of age): The safety and efficacy of EPURIS® in pediatric patients less than 12 years of age have not been established. The use of EPURIS® in these patients is not recommended.

Pediatrics (12 to 17 years of age): 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 8. Adverse Reactions).

Pediatric patients and their caregivers should be informed that approximately 29% of pediatric patients treated with isotretinoin developed back pain. Back pain was severe in 13.5% of the cases and occurred at a higher frequency in female patients than male patients. Arthralgias were experienced in 22% (79/358) of pediatric patients. Arthralgias were severe in 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system should be done in patients who present with these symptoms during or after a course of EPURIS®. Consideration should be given to discontinuation of EPURIS® if any significant abnormality is found.

7.1.4. Geriatrics

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 geriatric and younger adults, effects of aging may increase some risks associated with EPURIS®.

8. Adverse Reactions

8.1. Adverse 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.

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

See 7. Warnings and Precautions regarding psychiatric events (Signs of Depression), Gastrointestinal events (association with inflammatory bowel disease), impact on Hepatic/Biliary/Pancreatic function (acute pancreatitis), Neurologic (benign intracranial hypertension), Skin.

The following adverse reactions have been identified 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. The most commonly reported adverse events with EPURIS® use were dry lip (45%) and dry skin (44.2%). Adverse events related to the musculoskeletal system and connective tissues were reported in approximately 37% of the patients.

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.

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.

Discontinuation: 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.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Table 3 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 phosphocreatine kinase increased” 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 3: Adverse Events Reported in ≥ 1% of Patients in the EPURIS® group versus the Reference Product Group in the Double-Blind, Phase III Study

Body System **Adverse Reactions** Preferred Term	**EPURIS®**	**Reference Product**
	(N = 464)	**(N = 460)**
Eye disorders		
Dry eye	87 (18.8)	78 (17.0)
Visual acuity reduced	23 (5.0)	25 (5.4)
Vision blurred	14 (3.0)	15 (3.3)
Eye Pruritus	9 (1.9)	17 (3.7)
Night blindness	6 (1.3)	3 (0.7)
Asthenopia	5 (1.1)	4 (0.9)
Eye irritation	5 (1.1)	5 (1.1)
Gastrointestinal disorders		
Lip dry	209 (45.0)	210 (45.7)
Chapped lips	34 (7.3)	32 (7.0)
Cheilitis	26 (5.6)	19 (4.1)
Nausea	14 (3.0)	10 (2.2)
Abdominal pain	8 (1.7)	3 (0.7)
Vomiting	7 (1.5)	4 (0.9)
Constipation	5 (1.1)	8 (1.7)
Diarrhoea	5 (1.1)	7 (1.5)
General disorders and administration site conditions		
Fatigue	20 (4.3)	11 (2.4)
Pyrexia	5 (1.1)	4 (0.9)

Body System Adverse Reactions Preferred Term	EPURIS®	Reference Product
	(N = 464)	(N = 460)
Infections and infestations		
Nasopharyngitis	36 (7.8)	48 (10.4)
Upper respiratory tract infection	25 (5.4)	14 (3.0)
Sinusitis	10 (2.2)	11 (2.4)
Gastroenteritis viral	7 (1.5)	5 (1.1)
Influenza	6 (1.3)	11 (2.4)
Pharyngitis	6 (1.3)	11 (2.4)
Pharyngitis streptococcal	6 (1.3)	4 (0.9)
Bronchitis	5 (1.1)	3 (0.7)
Conjunctivitis	5 (1.1)	2 (0.4)
Ear infection	5 (1.1)	1 (0.2)
Hordeolum	5 (1.1)	10 (2.2)
Injury, poisoning and procedural complications		
Muscle strain	14 (3.0)	8 (1.7)
Excoriation	10 (2.2)	4 (0.9)
Sunburn	10 (2.2)	8 (1.7)
Joint sprain	7 (1.5)	10 (2.2)
Investigations		
Blood creatine phosphokinase increased	26 (5.6)	27 (5.9)
Blood triglycerides increased	17 (3.7)	14 (3.0)
Bone density decreased	17 (3.7)	7 (1.5)
Alanine aminotransferase increased	10 (2.2)	11 (2.4)
X-ray limb abnormal	9 (1.9)	8 (1.7)
Asparate aminotransferase increased	8 (1.7)	10 (2.2)
Metabolism and nutrition disorders		
Decreased appetite	5 (1.1)	7 (1.5)
Weight fluctuation	5 (1.1)	6 (1.3)
Musculoskeletal and connective tissue disorders		
Back pain	96 (20.7)	89 (19.3)
Arthralgia	64 (13.8)	60 (13.0)
Musculoskeletal discomfort	25 (5.4)	16 (3.5)
Musculoskeletal pain	19 (4.1)	23 (5.0)
Neck pain	14 (3.0)	22 (4.8)
Pain in extremity	14 (3.0)	15 (3.3)
Myalgia	8 (1.7)	7 (1.5)
Musculoskeletal stiffness	7 (1.5)	6 (1.3)
Nervous system disorders		
Headache	37 (8.0)	36 (7.8)
Migraine	6 (1.3)	0
Psychiatric disorders		
Insomnia	14 (3.0)	9 (2.0)
Anxiety	5 (1.1)	7 (1.5)

Body System Adverse Reactions Preferred Term	EPURIS®	Reference Product
	(N = 464)	(N = 460)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	54 (11.6)	42 (9.1)
Nasal dryness	21 (4.5)	23 (5.0)
Oropharyngeal pain	12 (2.6)	8 (1.7)
Nasal congestion	9 (1.9)	5 (1.1)
Cough	7 (1.5)	12 (2.6)
Skin and subcutaneous tissue disorders		
Dry skin	205 (44.2)	206 (44.8)
Dermatitis	28 (6.0)	23 (5.0)
Eczema	17 (3.7)	20 (4.3)
Rash	17 (3.7)	14 (3.0)
Dermatitis contact	10 (2.2)	9 (2.0)
Erythema	6 (1.3)	2 (0.4)
Ingrowing nail	5 (1.1)	4 (0.9)

Some adverse events 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.

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

See 8.2. Clinical Trial Adverse Reactions.

8.3. Less Common Clinical Trial Adverse Reactions

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

Blood and lymphatic system disorders: lymphadenopathy

Cardiac Disorders: Palpitations, tachycardia and coronary artery disease.

Ear and labyrinth disorders: Tinnitus, ear pain, hypoacusis, ear discomfort, external ear inflammation, cerumen impaction, hyperacusis and vertigo.

Eye disorders: 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 punctate keratitis.

Gastrointestinal disorders: 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, gastroesophageal reflux disease, gingival recession, haematochezia, hypoaesthesia oral, lip haemorrhage, lip ulceration, oesophageal pain, painful defaecation, rectal fissure, tooth disorder and toothache.

General disorders and administration site conditions: oedema peripheral, thirst, chest pain, cyst, impaired healing, influenza like illness, xerosis, discomfort, oedema, gravitational oedema, mucous membrane disorder and swelling.

Metabolism and nutrition disorders: Increased appetite and thyroid disorder.

Musculoskeletal and connective tissue disorders: 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.

Nervous system disorders: Dizziness, drowsiness, malaise, memory impairment, nervousness, paresthesia, presyncope, sinus headache, syncope, weakness.

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, substance abuse and irritability.

Renal and urinary disorders: Proteinuria, haematuria, dysuria, nephrolithiasis and polyuria

Reproductive system and breast disorders: 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.

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

Skin and subcutaneous tissue disorders: Bruising, pruritus, alopecia, eczema nummular, scar, eczema asteatotic, acne, rash papular, 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.

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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.

8.5. Post-Market Adverse Reactions

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

Blood and lymphatic system disorders: anemia.

Ear and labyrinth disorders: Impaired hearing at certain frequencies.

Eye disorders: Visual disturbances.

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

General disorders and administration site conditions: chest pain.

Immune system disorders: allergic responses

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

Metabolism and nutrition disorders: New cases of diabetes (see Warnings and Precautions: Endocrine and Metabolism), hypertriglyceridemia.

Nervous system disorders: Seizures and benign intracranial hypertension, seizures (see Warnings and Precautions: Serious Warnings and Precautions, Neurologic).

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

Renal and urinary disorders: Nonspecific urogenital findings.

Reproductive system: Sexual dysfunction.

Skin and subcutaneous tissue disorders: Acne flare, hair loss, hypopigmentation, sweating and urticaria.

Vascular disorders: vascular thrombotic disease.

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

Eye disorders: Cataracts, colour vision disorder, optic neuritis, papilledema as a sign of benign intracranial hypertension and colour vision disturbances. Corneal opacity were reported in nodular and/or inflammatory acne patients (see 7. Warnings and Precautions: Ophthalmologic). Decreases in night vision were reported and, in rare instances, persisted after cessation of therapy (see 7. Warnings and Precautions: Ophthalmologic).

Gastrointestinal disorders: Ileitis, cheilitis and other nonspecific gastrointestinal symptoms. Patients treated with isotretinoin, especially those with high triglyceride levels are at risk of developing pancreatitis. Rare cases of fatal pancreatitis have been reported (see 7. Warnings and Precautions: Hepatic/Biliary/Pancreatic).

Hepatobiliary disorders: Several cases of clinical hepatitis have been reported (see 7. Warnings and Precautions: Hepatic/Biliary/Pancreatic).

Immune system disorders: systemic hypersensitivity

Investigations: 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 7. Warnings and Precautions: Hepatic/Biliary/Pancreatic).

Metabolism and nutrition disorders: hypertriglyceridemia (usually was dose-related).

Musculoskeletal and connective tissue disorders: 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.

Renal and urinary disorders: Glomerulonephritis.

Reproductive system: Sexual dysfunction.

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

Skin and subcutaneous tissue disorders: 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 7. Warnings and Precautions: Serious Skin Reactions).

9. Drug Interactions

9.1. Serious Drug Interactions

Serious Drug Interactions

- Tetracyclines (see 3. Serious Warnings and Precautions Box, 9.4. Drug-Drug Interactions)

9.2. Drug Interactions Overview

Tetracyclines (e.g., minocycline, tetracycline), vitamin A-type drugs and supplements, phenytoin, and systemic corticosteroids (e.g., prednisone) may interact with isotretinoin (see 9.4. Drug-Drug Interactions).

9.4. Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

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 7. 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.

9.5. 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.

9.6. Drug-Herb Interactions

St. John's Wort: Isotretinoin use is associated with depression in some patients (see 7. Warnings and Precautions, Psychiatric and 8.3. Less Common Clinical Trial 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.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. 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.

10.2. Pharmacodynamics

The pharmacodynamics of EPURIS® is unknown.

10.3. 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 4). 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 4: 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)**[1] **(CV)**	**C_{max}** **(ng/mL)**[1] **(CV)**	**T_{max}** **(hr)**[2] **(CV)**	**$T_{1/2}$** **(hr)**[1] **(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)**				

EPURIS® **(1 x 40 mg Capsules)**	**AUC_{0-t}** **(ng x hr/mL)**[1] **(CV)**	**C_{max}** **(ng/mL)**[1] **(CV)**	**T_{max}** **(hr)**[2] **(CV)**	**$T_{1/2}$** **(hr)**[1] **(CV)**
Fed	6146 (26%)	417 (41%)	6.8 (55%)	18 (16%)
Fasted	2349 (26%)	170 (29%)	3 (58%)	22 (21%)
[1] Mean Value [2] 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.

Elimination

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 5 for pediatric patients. There were no statistically significant differences in the pharmacokinetics of isotretinoin between pediatric and adult patients.

Table 5: Pharmacokinetic Parameters of Isotretinoin Following Single and Multiple Dose Administration in Pediatric Patients, 12 to 15 Years of Age Mean (SD), N=38[1]

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)[2]	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)

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

[2] Median (range)

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

11. Storage, Stability and Disposal

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

12. 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.

Part 2: Scientific Information

13. Pharmaceutical Information

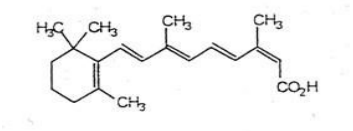
Drug Substance

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 and molecular mass: $C_{20}H_{28}O_2$
300.44

Structural formula:



Physicochemical properties: Orange crystalline powder, insoluble in water; soluble in chloroform (10g / 100 mL).

Melting point: approximately 175ºC;

pKa: approximately 4.

14. Clinical Trials

14.1. Clinical Trials by Indication

Treatment of Severe Recalcitrant Nodule Acne

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.

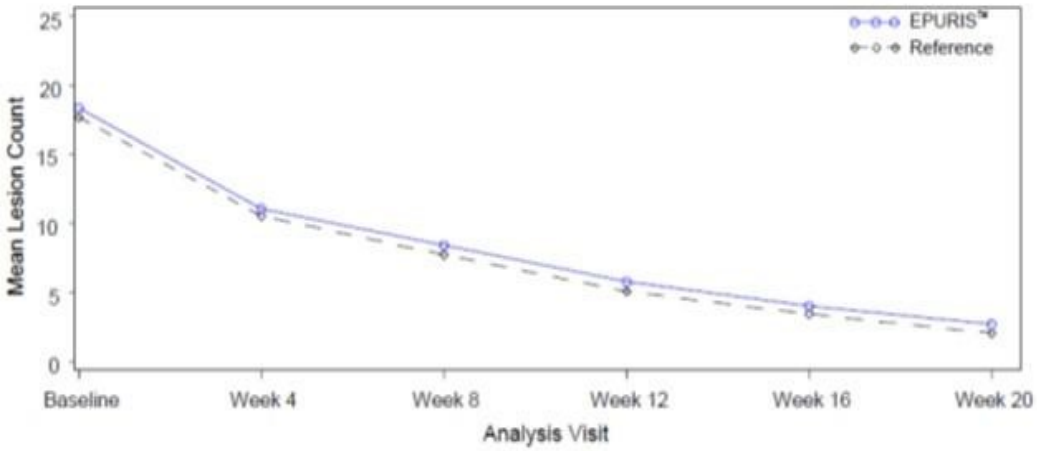
Safety assessments during the study included monitoring of adverse events, laboratory tests, psychiatric evaluations, bone mineral density and bone age assessments, questions about musculoskeletal symptoms, ophthalmic and audiology testing.

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 6).

Table 6: 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[1] (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)[1]	-2.10 (-7.94, 3.74)		-4.79 (-10.56, 0.97)	
[1] 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 1: Total Nodular (Facial and Truncal) Lesion Count by Visit [ITT Population (LOCF)]



15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General Toxicology

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:

Table 7: Acute Toxicity Studies

Animal	Route	LD_{50}	Observation Period[1]
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
[1] 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.

Carcinogenicity:

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.

Genotoxicity:

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.

Reproductive and Developmental Toxicology:

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.

Table 8 provides the low dose (mg/kg) reported to elicit teratogenesis in animal models.

Table 8: 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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]EPURIS®

Isotretinoin Capsules

This patient medication information is written for the person who will be taking EPURIS®. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about EPURIS®, talk to a healthcare professional.

Serious warnings and precautions box

Informed Consent Form:

- You must sign the informed consent form before you start taking EPURIS®. Your doctor will explain the birth defect and mental health risks with EPURIS®. They will provide you with the form and have you sign it.

Pregnancy Prevention:

- EPURIS® can cause birth defects (deformed babies). It can also cause miscarriage, premature birth, or death of the baby. You must not take EPURIS® if you are pregnant or plan to become pregnant. You must prevent pregnancy while you are taking EPURIS®. Your doctor will only prescribe EPURIS® to you if you meet all conditions of use. See "Other warnings you should know about, *Pregnancy Prevention in Females*", below for more information.

Mental Health Problems including Depression and Suicide:

- Some patients treated with isotretinoin have become depressed. Some have attempted suicide or have committed suicide. Before you take EPURIS® your doctor will assess you for mental health problems including depression. Tell your doctor if you are depressed, have ever been depressed or if a family member is depressed. Stop taking EPURIS® and get immediate medical help if you have symptoms of depression. These include feeling sad, having crying spells, losing interest in your usual activities, changes in sleep patterns, losing your appetite or becoming unusually tired, having trouble concentrating, withdrawing from family and friends, having thoughts about taking your life (suicidal thoughts).

Brain Problems (benign intracranial hypertension):

- EPURIS® can cause a serious brain condition called benign intracranial hypertension. This is where there is increased pressure in the brain. Stop taking EPURIS® and get immediate medical help if you get any symptoms of benign intracranial hypertension. These include headaches, blurred vision, dizziness, nausea, vomiting, seizures (convulsions) and stroke. Symptoms of stroke include sudden numbness or weakness of your arm, leg or face, trouble walking or loss of balance

What EPURIS® is used for:

EPURIS® is used to treat patients with the following conditions of severe acne:

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

EPURIS® can cause serious side effects. It is only used in patients whose acne cannot be cleared up by other medicines.

EPURIS® will be prescribed to you by a doctor with experience in treating patients with medicines like EPURIS®. They will talk to you about the possible serious side effects of EPURIS® including birth defects and mental health problems. Your doctor will also assess your mental health including if you have had mental illness in the past. You will be given an informed consent form that you must sign before taking EPURIS®.

It is not known if EPURIS® is safe and effective in patients under 12 years of age.

How EPURIS® works:

EPURIS® belongs to a group of medicines called retinoids (vitamin A derived). The way EPURIS® works is not known. It is thought to treat acne by reducing oil production in the skin.

During the first few weeks of treatment, your acne may seem to get worse. It may take one to two months before you see improvement.

The ingredients in EPURIS® are:

Medicinal ingredient: isotretinoin

Non-medicinal ingredients: propyl gallate, sorbitan monooleate, soybean oil and stearoyl macrogolglycerides

Gelatin capsule shells contain the following ingredients:

- 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.

EPURIS® comes in the following dosage forms:

Capsules in 10 mg, 20 mg, 30 mg and 40 mg of isotretinoin

Do not use EPURIS® if:

- you are pregnant or plan to become pregnant.
- you become pregnant while taking EPURIS®. You must stop taking EPURIS® immediately if you become pregnant (see Serious Warnings and Precautions).
- you are breastfeeding.
- you have high levels of vitamin A in your body which can happen if you take supplements that contain vitamin A.
- you are taking a tetracycline medicine which is an antibiotic used to treat infections.

- you have liver problems.
- you have kidney problems.
- you have high blood fat levels.
- you are allergic to isotretinoin or to any of the other ingredients in EPURIS®.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EPURIS®. Talk about any health conditions or problems you may have, including if:

- you or a family member has ever had any mental illness, including depression, mood disturbances, loss of contact with reality or aggression (see Serious Warnings and Precautions).
- you or a family member has diabetes.
- you are obese.
- you regularly drink alcohol.
- you have dry eyes.
- you have any bone problems, including a condition called osteoporosis or osteomalacia.
- you are taking medicines called corticosteroids used to treat various conditions.
- you are taking anti-epileptic medicines used to treat seizures.
- you have an eating disorder called anorexia that causes low body weight.
- you play or plan to play high impact sports or engage in vigorous exercise.
- you plan to donate blood. You should not donate blood while you are taking EPURIS® and for one month after you stop taking it.
- you are taking supplements that contain vitamin A. You should not take these while you are taking EPURIS®.

Other warnings you should know about:

Pregnancy Prevention in Females:

- You must not take EPURIS® if you are pregnant or plan to become pregnant.
- EPURIS® can cause miscarriage and birth defects. There is an extremely high risk that your baby will be deformed if you take isotretinoin while pregnant. This risk exists even if EPURIS® is taken for a short time.
- Your doctor will only prescribe EPURIS® to you if you meet all conditions for pregnancy prevention.
- You must not get pregnant:
    - 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®.
- You must discuss effective birth control with your doctor before taking EPURIS®. You must use two effective forms of birth control at the same time. At least one of these needs to be a primary form of birth control. These include birth control pills or injections and intrauterine devices. Secondary forms include condoms and diaphragms.

- Before you start taking EPURIS® you must take two pregnancy tests in a licensed laboratory. Both tests need to show that you are not pregnant. The first test will be done once your doctor agrees that EPURIS® treatment may be right for you. The second test must be done within 11 days of you starting to take EPURIS®.
- You must wait until the second or third day of your next normal menstrual period before you start taking EPURIS®.
- You will need to take a pregnancy test every month while taking EPURIS®. You will receive a 30-day prescription if this test shows you are not pregnant. You will need to take an additional test one month after you stop taking EPURIS®.
- Stop taking EPURIS® and contact your doctor immediately if:
    - you become pregnant while taking EPURIS®.
    - you become pregnant during the first month after stopping your treatment.
    - you miss your period.
    - you have sex without using effective birth control.

Talk with your doctor about the risk of your baby having birth defects and whether you want to continue with your pregnancy.

Your doctor will counsel you using the EPURIS® PEER™ PROGRAM before you take EPURIS®. This includes the following:

- Information on the risks of EPURIS®
- A line drawing of a deformed baby
- A checklist of conditions you must meet before receiving EPURIS®
- Detailed information on birth control options
- A flowchart detailing the steps in the EPURIS® PEER™ PROGRAM
- Monthly pregnancy reminder slips
- An informed consent form from your doctor for you to review and sign

Confidential birth control counselling is available. For more information, please contact Cipher Pharmaceuticals Inc. at 1-855-437-8747 (1-855-4EPURIS).

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

Male patients:

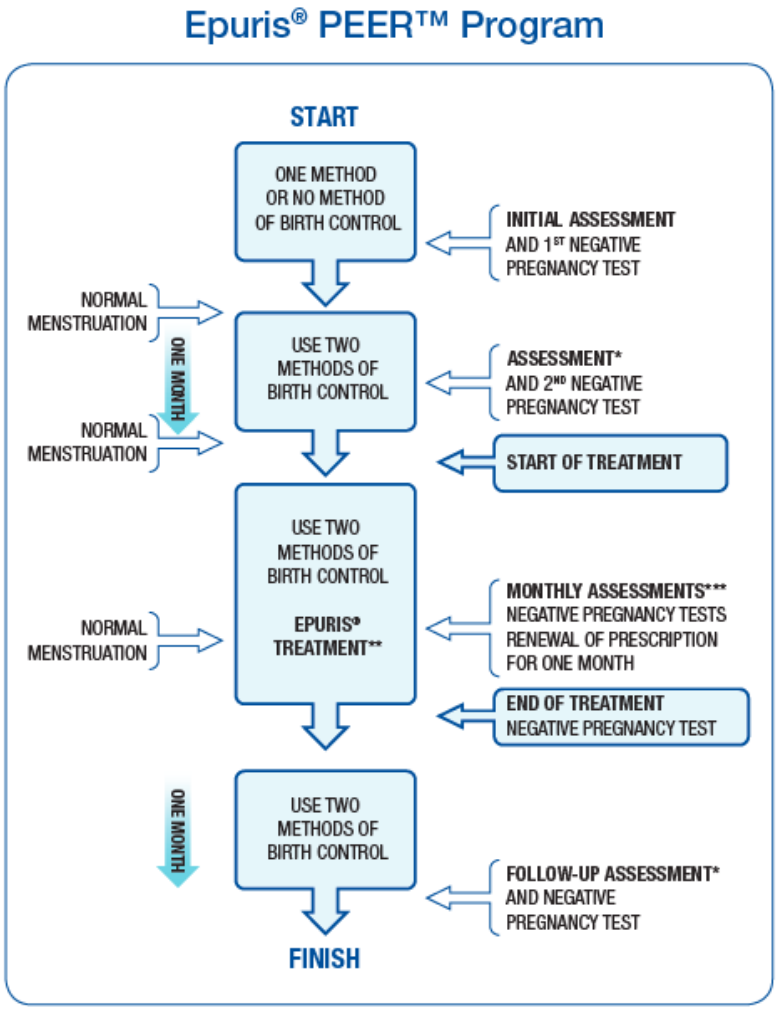
EPURIS® may be released into semen. Male patients should use a condom or avoid sex to prevent passing EPURIS® to a female partner.

Tests and Check-ups:

Stay under your doctor's care while you are taking EPURIS®. You must see your doctor regularly. For most patients this means seeing your doctor every month. For female patients, a pregnancy test is needed every month and at one month after stopping treatment.

Your doctor will perform the following tests before you start taking EPURIS®, at one month and then as decided by your doctor:

- check of blood fat levels, including triglyceride levels
- check of liver function
- check of kidney function
- check of sugar levels in your blood



* 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 that you may have from the treatment

Eyes:

EPURIS® may change your vision and ability to drive at night. Be cautious when driving any vehicle at night. EPURIS® can make your eyes dry. This can be helped by using lubricating eye ointment or artificial tears. Talk to your doctor about how to help your dry eyes. You might need to wear glasses during treatment instead of contact lenses if your eyes get dry.

Hair:

EPURIS® can cause hair loss. This can persist after you stop treatment.

Skin:

- Your acne may get worse when you first start taking EPURIS®. This should last only a short while. Talk with your doctor if this is a concern for you.
- You should not have chemical procedures on your skin, dermabrasion or laser treatments while you are taking EPURIS®. This is because EPURIS® can increase your chance of scarring from these procedures. Check with your doctor for advice about when you can have cosmetic procedures.
- Avoid the use of artificial ultraviolet (UV) lights such as the ones used in tanning machines and protect yourself from excessive sunlight. EPURIS® may make your skin more sensitive to UV light. When necessary, use sunscreen with a high protection factor of at least SPF 15.
- Avoid the use of anti-acne products for acne that exfoliate your skin since this can irritate your skin.
- You should use moisturizing skin cream and lip balm while you are taking EPURIS®. This is because EPURIS® can make your skin and lips dry.

Serious Skin Reactions:

EPURIS® can cause serious skin reactions such as erythema multiforme (EM),

Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). These can result in hospitalization, disability or death. Stop taking EPURIS® and get immediate medical help if you get any symptoms of a serious skin reaction. These include severe red / purple rash especially if associated with fever and not feeling well, red or inflamed eyes, blisters, peeling skin, multiple lesions and sores (especially in your mouth, nose, eyes and genitals), and facial and tongue swelling.

Sexual Dysfunction:

While taking EPURIS®, you may have the inability to get or maintain an erection, dryness in the vagina or vulva, reduced interest in sex, orgasm difficulties and loss of sensation or tingling in the genital area. This may continue after treatment. Tell your healthcare professional if you experience signs of sexual dysfunction before, during or after taking EPURIS®.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with EPURIS®:

- Low dose birth control pills. Low dose birth control pills that contain progesterone only (mini pills) may not work while you are taking EPURIS®.
- Antibiotics (such as Tetracyclines; e.g., minocycline, tetracycline) used to treat infections.
- Corticosteroids (such as hydrocortisone, prednisone, etc.) used to treat inflammatory conditions.
- Phenytoin, used to treat seizures.
- Vitamin supplements that contain vitamin A
- St. John's Wort, used to treat depression.

How to take EPURIS®:

- Always take EPURIS® exactly as your doctor has told you to.
- It will be prescribed to you by a doctor who knows how to safely use products like EPURIS®. They will discuss the risks of EPURIS® with you.
- You must sign the informed consent form before you start taking EPURIS®.
- Swallow the capsules whole with a full glass of liquid.
- Do not chew or open the capsules.
- You can take EPURIS® with or without food.
- Check with your doctor if you are not sure how to take EPURIS®.
- You must stay under your doctor's care while you are taking EPURIS®.
- Do not change between EPURIS® and other isotretinoin products. EPURIS® is not the same as other isotretinoin products.

Usual dose:

The dose you receive will be specific to you. It will depend on your weight and other factors. Your doctor will prescribe the dose that is right for you. They will tell you when to take EPURIS® and for how long. Most patients take EPURIS® for 12 to 16 weeks. Your doctor may change your dose during treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much EPURIS®, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you forget to take a dose of EPURIS® take it later that same day. Then, take your next dose at the regular time. Do not take a double dose to make up for a missed dose.

Possible side effects from using EPURIS®:

These are not all the possible side effects you may have when taking EPURIS®. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- dryness of the skin, lips, mouth, and lining of the nose
- 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
- fatigue
- redness, dryness, or irritation of the eyes
- upper respiratory tract infection (common cold)
- inability to develop and maintain an erection

You may experience following side effects while EPURIS® and even after you stop taking it: inability to have or maintain an erection during sex, dryness in the vagina or vulva, reduced sexual drive interest, orgasm difficulties and loss of sensation or tingling in the genital area.

Serious side effects and what to do about them

Symptom / Effect	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Mental health problems such as depression or psychosis (a 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)			√
Liver problems: Nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, light coloured bowel motions, dark coloured urine			√
Pancreatitis (Inflammation of the pancreas): Severe upper stomach pain, often with nausea and vomiting			√
Intestine (bowel) problems: Fever, abdominal pain, diarrhea (usually with blood and mucus), loss of weight, rectal bleeding			√

Symptom / Effect	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Bone and muscle problems: Aches or pains in bones or joints, back pain, or difficulty in moving, muscle pain, especially after vigorous exercise, dark coloured urine that is brown, red or tea-coloured, muscle weakness with or without pain can be a sign of serious muscle damage, breaking of a bone			√
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			√
Benign intracranial hypertension (Increased pressure in the brain): Headaches, blurred vision, dizziness, nausea, vomiting, seizures (convulsions) and stroke. Symptoms of stroke include sudden numbness or weakness of your arm, leg or face, trouble walking or loss of balance.			√
Hearing and vision problems: Changes in your hearing or ringing in your ears, changes in your vision especially at night, decreased night vision may occur suddenly in some patients (take caution when driving at night), persistent feelings of dry eyes. In addition, some loss may occur in the sharpness of your vision (acuity).			√
Heart problems: Chest pain, palpitations, stroke, leg swelling, seizures (convulsions), slurred speech, problems moving or any other serious unusual problems, vascular thrombotic disease (formation of a blood clot within the blood vessels that can occur both within the arteries and veins): pain in one leg (usually the calf or inner thigh), swelling in the leg or arm, chest pain, numbness or weakness on one side of the body, sudden change in your mental state			√
Pregnancy issues during or after treatment: Birth defects, miscarriage, premature birth or death of baby			√
Problems with blood sugar levels: Fainting, become very thirsty, urinating a lot, feeling weak			√

Symptom / Effect	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Serious Skin Reactions such as erythema multiforme (EM), Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN): Severe red / purple rash, fever or not feeling well, red or inflamed eyes, facial and tongue swelling, blisters, peeling skin, multiple lesions and sores, especially in your mouth, nose, eyes and genitals			√
Unknown Frequency			
Sexual Dysfunction: Inability to get or maintain an erection, dryness in the vagina or vulva, reduced interest in sex, orgasm difficulties and loss of sensation or tingling in the genital area.	√		
Sacroiliitis (inflammation in the lower spine and pelvis joints): Pain in lower back or buttocks. Pain may travel down legs.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children.

- EPURIS® should be stored at 20 - 25°C. Store in the original package. Protect from light.
- Return any unused EPURIS® to your pharmacist.

If you want more information about EPURIS®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website 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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Mississauga ON L4W 0A9

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