

# TRETINOIN- tretinoin capsule

## Glenmark Pharmaceuticals Inc., USA

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### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TRETINOIN capsules, for oral use

Initial U.S. Approval: 1995

#### **WARNING: EMBRYO-FETAL TOXICITY and DIFFERENTIATION SYNDROME**

*See full prescribing information for complete boxed warning.*

- **Embryo-Fetal Toxicity:** Tretinoin capsules can cause embryo-fetal loss and malformations when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Females of reproductive potential must have a negative pregnancy test before initiating tretinoin capsules. Advise females of reproductive potential to use two effective methods of contraception during treatment with tretinoin capsules and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with tretinoin capsules and for 1 week after the last dose. (5.1, 8.1, 8.3)
- **Differentiation Syndrome, which can be life-threatening or fatal, occurred in about 26% of patients with APL who received tretinoin capsules. At first signs or symptoms of this syndrome, immediately initiate high-dose corticosteroid therapy and hemodynamic monitoring until resolution of signs and symptoms. Consider withholding tretinoin capsules for moderate and severe Differentiation Syndrome until resolution. (5.2)**

#### **INDICATIONS AND USAGE**

Tretinoin capsules are a retinoid indicated for induction of remission in adults and pediatric patients 1 year of age and older with acute promyelocytic leukemia (APL), characterized by presence of t(15;17) translocation or presence of PML/RAR $\alpha$  gene expression, and who are refractory to or who have relapsed from anthracycline chemotherapy or for whom anthracycline-based chemotherapy is contraindicated. (1)

#### **DOSAGE AND ADMINISTRATION**

- The recommended dosage of tretinoin capsules is 22.5 mg/m<sup>2</sup> orally twice daily until complete remission. (2.2)
- Discontinue 30 days after achievement of complete remission or after 90 days of treatment, whichever occurs first. (2.2)

#### **DOSAGE FORMS AND STRENGTHS**

Capsules: 10 mg (3)

#### **CONTRAINDICATIONS**

Hypersensitivity to tretinoin, any of its components, or other retinoids (4)

#### **WARNINGS AND PRECAUTIONS**

- Patients Without t(15;17) Translocation or PML/RAR $\alpha$  Fusion: Tretinoin capsules may be initiated based on morphological diagnosis of APL. Confirm diagnosis by detection of the t(15;17) translocation or PML/RAR $\alpha$  fusion. (5.3)
- Leukocytosis: Consider administering cytoreductive chemotherapy (including an anthracycline if not contraindicated or hydroxyurea) with tretinoin capsules in the setting of leukocytosis, as clinically indicated. (5.4)
- Intracranial Hypertension: Tretinoin capsules have been associated with benign intracranial hypertension, especially in pediatric patients. Consider interruption, dose reduction, or discontinuation of tretinoin capsules as appropriate. (5.5)
- Lipid Abnormalities: Patients experienced hypercholesterolemia and/or hypertriglyceridemia, which may be reversible upon completion of treatment. Monitor fasting triglycerides and cholesterol at baseline and periodically during treatment. (5.6)

- Hepatotoxicity: Monitor liver function test results at baseline and during treatment as clinically indicated. (5.7)
- Thromboembolic Events: Venous and arterial events have been reported; these events may occur during the first month of treatment with tretinoin capsules. (5.8, 7.4)

-----**ADVERSE REACTIONS**-----

The most common adverse reactions ( $\geq 30\%$ ) are headache, fever, skin/mucous membrane dryness, bone pain, malaise, shivering, upper respiratory tract disorders, dyspnea, hemorrhage, infections, nausea/vomiting, rash, peripheral edema, leukocytosis, pain, gastrointestinal hemorrhage, chest discomfort, abdominal pain (6.1).

**To report SUSPECTED ADVERSE REACTIONS, contact Glenmark Pharmaceuticals Inc., USA at 1 (888) 721-7115 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

-----**DRUG INTERACTIONS**-----

- Strong CYP3A Inhibitors and Inducers: Avoid coadministration with strong CYP3A inhibitors and inducers. (7.1)
- Concomitant Use of Products Known to Cause Intracranial Hypertension: Avoid concomitant use with other products that can cause intracranial hypertension. (7.2)
- Vitamin A: Avoid concomitant use with vitamin A. (7.3)
- Anti-fibrinolytic Agents: Avoid concomitant use with anti-fibrinolytic agents. (7.4)

-----**USE IN SPECIFIC POPULATIONS**-----

Lactation: Advise not to breastfeed. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 6/2025**

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## **FULL PRESCRIBING INFORMATION**

### **WARNING: EMBRYO-FETAL TOXICITY and DIFFERENTIATION SYNDROME**

- **Tretinoin capsules can cause embryo-fetal loss and malformations when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Females of reproductive potential must have a negative pregnancy test before initiating tretinoin capsules. Advise females of reproductive potential to use two effective methods of contraception during treatment with tretinoin capsules and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with tretinoin capsules and for 1 week after the last dose [see Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3)].**
- **Differentiation Syndrome, which can be life-threatening or fatal, occurred in about 26% of patients with APL who received tretinoin capsules. At first signs or symptoms of this syndrome, immediately initiate high-dose corticosteroid therapy and hemodynamic monitoring until resolution of signs and symptoms. Consider withholding tretinoin capsules for moderate and severe Differentiation Syndrome until resolution [see Warnings and Precautions (5.2)].**

## **1 INDICATIONS AND USAGE**

Tretinoin capsules are indicated for the induction of remission in adults and pediatric patients 1 year of age and older with acute promyelocytic leukemia (APL) characterized by the presence of the t(15;17) translocation or PML/RAR $\alpha$  gene expression, and who are refractory to or who have relapsed from anthracycline chemotherapy or for whom anthracycline-based chemotherapy is contraindicated.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Important Safety Information**

Verify pregnancy status in females of reproductive potential prior to initiating tretinoin capsules. Females of reproductive potential must have a negative pregnancy test before initiating tretinoin capsules [see *Use in Specific Populations (8.3)*].

### **2.2 Recommended Dosage**

The recommended dosage of tretinoin capsules is 22.5 mg/m<sup>2</sup> orally twice daily until complete remission is documented. Discontinue tretinoin capsules 30 days after achievement of complete remission or after 90 days of treatment, whichever occurs first.

Discontinue tretinoin capsules if the t(15;17) translocation or PML/RAR $\alpha$  fusion has not been identified [see *Warnings and Precautions (5.3)*]. Take tretinoin capsules with a meal. Swallow tretinoin capsules whole with water. Do not chew, dissolve, or open capsule.

Do not take a missed dose of tretinoin capsules unless it is more than 10 hours until the next scheduled dose. If vomiting occurs after tretinoin capsules administration, do not take an additional dose, but continue with the next scheduled dose.

## **3 DOSAGE FORMS AND STRENGTHS**

Tretinoin Capsules are available as:

10 mg: Pink, oval, soft-gelatin capsules printed with black 'T 10' filled with yellow to orange, opaque, viscous suspension.

## **4 CONTRAINDICATIONS**

Tretinoin capsules are contraindicated in patients with a known hypersensitivity to tretinoin capsules, any of its components, or other retinoids. Reactions have included rash, pruritus, face edema, and dyspnea. [see *Adverse Reactions (6.1)*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Embryo-Fetal Toxicity**

Tretinoin capsules can cause embryo-fetal loss and malformations when administered to a pregnant woman. Tretinoin capsules are a retinoid and there is an increased risk of major congenital malformations, spontaneous abortions and premature births following exposure to retinoids during pregnancy in humans. Tretinoin has teratogenic and

embryotoxic effects in mice, rats, hamsters, rabbits and pigtail monkeys at doses less than the human dose on a mg/m<sup>2</sup> basis.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use 2 effective methods of contraception during treatment with tretinoin capsules and for 1 month following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with tretinoin capsules and for 1 week following the last dose [see *Use in Specific Populations (8.1, 8.3)*].

## **5.2 Differentiation Syndrome**

Differentiation Syndrome, which may be life-threatening or fatal, occurred in about 26% of patients with APL who received tretinoin capsules [see *Adverse Reactions (6.1)*]. Symptoms include fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, edema, and hepatic, renal, and multi-organ failure. This syndrome has been accompanied by impaired myocardial contractility and episodic hypotension and it has been observed with or without concomitant leukocytosis. This syndrome generally occurs during the first month of treatment, as early as following the first dose. Endotracheal intubation and mechanical ventilation were required in some cases due to progressive hypoxemia and several patients have died with multi-organ failure.

At the first signs or symptoms of this syndrome, immediately administer dexamethasone 10 mg intravenously every 12 hours until signs and symptoms have abated for at least 3 days and initiate hemodynamic monitoring until resolution of signs and symptoms. Consider withholding tretinoin capsules for moderate and severe differentiation syndrome until resolution [see *Adverse Reactions (6.1)*].

## **5.3 Patients Without t(15;17) Translocation or PML/RAR $\alpha$ Fusion**

Tretinoin capsules may be initiated based on the morphological diagnosis of acute promyelocytic leukemia (APL). Confirm the diagnosis of APL by detection of the t(15;17) translocation using cytogenetic studies or PML/RAR $\alpha$  fusion using molecular diagnostic techniques. Tretinoin capsules are not recommended for use in patients without these genetic markers [see *Indications and Usage (1)*].

## **5.4 Leukocytosis**

Rapidly evolving leukocytosis, which can be life-threatening, occurred in about 40% of patients with APL who received tretinoin capsules [see *Adverse Reactions (6.1)*]. Patients who present with a baseline white blood cell count (WBC) > 5 × 10<sup>9</sup>/L have an increased risk. Patients who receive chemotherapy with tretinoin capsules may be at a reduced risk. Rapidly evolving leukocytosis is associated with a higher risk of life-threatening complications.

Consider administering cytoreductive chemotherapy (including an anthracycline if not contraindicated or hydroxyurea) with tretinoin capsules in the setting of leukocytosis, as clinically indicated.

## **5.5 Intracranial Hypertension**

Retinoids, including tretinoin capsules, have been associated with intracranial

hypertension, especially in pediatric patients. Early signs and symptoms include papilledema, headache, nausea, vomiting, and visual disturbances. Evaluate patients with these symptoms for intracranial hypertension, and, if present, institute appropriate care in concert with neurological assessment. Consider interruption, dose reduction, or discontinuation of tretinoin capsules as appropriate.

The concomitant use of other products (e.g., tetracyclines) that can cause intracranial hypertension may increase the risk. Avoid concomitant use of tretinoin capsules with other products that can cause intracranial hypertension [see *Drug Interactions (7.2)*].

## 5.6 Lipid Abnormalities

Hypercholesterolemia and/or hypertriglyceridemia has occurred in up to 60% of patients who received tretinoin capsules. These changes may be reversible upon completion of treatment. The clinical consequences of increased triglycerides and cholesterol are unknown, but venous thrombosis and myocardial infarction have been reported in patients who ordinarily are at low risk for such complications.

Monitor fasting triglycerides and cholesterol at baseline and periodically during treatment.

## 5.7 Hepatotoxicity

Elevated liver function test results occurred in 50% to 60% of patients during treatment with tretinoin capsules. Most of these abnormalities resolved without interruption of tretinoin capsules or after completion of treatment.

Monitor liver function test at baseline and during treatment as clinically indicated. Consider withholding tretinoin capsules if liver function test results increase to greater than 5 times the upper limit of normal values until resolution.

## 5.8 Thromboembolic Events

Venous and arterial thromboembolic events, including cerebrovascular accident, myocardial infarction and renal infarct have been reported with tretinoin capsules [see *Adverse Reactions (6.2)*]. These events may occur during the first month of treatment. Patients taking anti-fibrinolytic agents may have an increased risk.

Avoid concomitant use of tretinoin capsules and anti-fibrinolytic agents, such as tranexamic acid, aminocaproic acid or aprotinin [see *Drug Interactions (7.4)*].

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Differentiation Syndrome [see *Warnings and Precautions (5.2)*]
- Leukocytosis [see *Warnings and Precautions (5.4)*]
- Intracranial hypertension [see *Warnings and Precautions (5.5)*]
- Lipid abnormalities [see *Warnings and Precautions (5.6)*]
- Hepatotoxicity [see *Warnings and Precautions (5.7)*]
- Thromboembolic events [see *Warnings and Precautions (5.8)*]

## 6.1 Clinical Trials Experience

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

### Acute Promyelocytic Leukemia

The safety of tretinoin capsules was evaluated in patients with APL who received tretinoin capsules at a dose of 22.5 mg/m<sup>2</sup> orally twice daily [see *Clinical Studies (14)*].

The most common adverse reactions (≥30%) were headache, fever, skin/mucous membrane dryness, bone pain, malaise, shivering, upper respiratory tract disorders, dyspnea, hemorrhage, infections, nausea/vomiting, rash, peripheral edema, leukocytosis, pain, gastrointestinal hemorrhage, chest discomfort, abdominal pain.

Table 1 summarizes the adverse reactions for patients with APL.

**Table 1. Adverse Reactions (≥ 10%) Occurring in Patients with APL Who Received Tretinoin Capsules**

Adverse Reaction	Tretinoin Capsules
	All Grades (%)
<b>Nervous system disorders</b>	
Headache	86
Dizziness	20
Paresthesias	17
Anxiety	17
Insomnia	14
Depression	14
Confusion	11
<b>General disorders</b>	
Fever	83
Skin/mucous membrane dryness	77
Malaise	66
Shivering	63
Peripheral edema	52
Pain	37
Chest discomfort	32
Edema	29
Mucositis	26
Weight increase	23
Anorexia	17
Weight decrease	17
<b>Musculoskeletal and connective tissue disorders</b>	
Bone pain	77
Myalgia	14
<b>Respiratory, thoracic and mediastinal disorders</b>	
Upper respiratory tract disorders	63

Dyspnea	60
Respiratory insufficiency	26
Pleural effusion	20
Rales	14
Expiratory wheezing	14
Pneumonia	14
<b>Vascular disorders</b>	
Hemorrhage	60
Gastrointestinal hemorrhage	34
Flushing	23
Hypotension	14
Hypertension	11
Phlebitis	11
<b>Infections and infestations</b>	
Infections	58
<b>Gastrointestinal disorders</b>	
Nausea/vomiting	57
Abdominal pain	31
Other gastrointestinal disorders	26
Diarrhea	23
Constipation	17
Dyspepsia	14
Abdominal distention	11
<b>Skin and subcutaneous tissue disorders</b>	
Rash	54
Pruritus	20
Increased sweating	20
Alopecia	14
Skin changes	14
<b>Blood and lymphatic system disorders</b>	
Leukocytosis	49
Differentiation syndrome <sup>1</sup>	26
Disseminated intravascular coagulation	26
<b>Ear and labyrinth disorders</b>	
Earache or feeling of fullness in the ears	23
<b>Cardiac disorders</b>	
Arrhythmias	23
<b>Eye disorders</b>	
Visual disturbances	17
Ocular disorders	17
<b>Renal and urinary disorders</b>	
Renal insufficiency	11

<sup>1</sup>Differentiation syndrome can be associated with other commonly reported events such as fever, leukocytosis, dyspnea, pneumonia, pleural effusion, pericardial effusion,

hypotension, edema, weight gain, and renal failure.

Adverse reactions that occurred in <10% of patients who received tretinoin capsules include:

- *Hepatobiliary disorders:* Hepatosplenomegaly (9%), hepatitis (3%), unspecified liver disorder (3%).
- *Musculoskeletal and connective tissue disorders:* Flank pain (9%), bone inflammation (3%).
- *Nervous system disorders:* Agitation (9%), cerebral hemorrhage (9%), intracranial hypertension (9%), hallucination (6%), abnormal gait, agnosia, aphasia, asterixis, cerebellar edema, cerebellar disorders, convulsions, coma, CNS depression, dysarthria, encephalopathy, facial paralysis, hemiplegia, hyporeflexia, hypotaxia, no light reflex, neurologic reaction, spinal cord disorder, stroke, tremor, leg weakness, unconsciousness, dementia, forgetfulness, somnolence, and slow speech (3% each).
- *Renal and urinary disorders:* Dysuria (9%), acute renal failure, micturition frequency, renal tubular necrosis, and enlarged prostate (3% each).
- *Respiratory, thoracic and mediastinal disorders:* Lower respiratory tract disorders (9%), pulmonary infiltration (6%), bronchial asthma, pulmonary edema, larynx edema, and unspecified pulmonary disease (3% each).
- *Infections and infestations:* Cellulitis (8%).
- *Blood and lymphatic system disorders:* Lymph disorders (6%).
- *Cardiovascular disorders:* Cardiac failure (6%), cardiac arrest, myocardial infarction, enlarged heart, heart murmur, myocarditis, pericarditis, and secondary cardiomyopathy (3% each).
- *Ear and labyrinth disorders:* Hearing loss and other unspecified auricular disorders (6%), irreversible hearing loss (<1%).
- *General disorders:* Face edema (6%), pallor (6%), hypothermia (3%).
- *Metabolism and nutrition disorders:* Fluid imbalance (6%), acidosis (3%).
- *Eye disorders:* Changed visual acuity (6%), visual field defects (3%).
- *Gastrointestinal disorders:* Ascites, ulcer (3% each).
- *Vascular disorders:* Ischemia and pulmonary hypertension (3% each).

## 6.2 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Erythema nodosum, basophilia and hyperhistaminemia, Sweet's Syndrome, organomegaly, hypercalcemia, pancreatitis, myositis, thrombosis (both venous and arterial), thrombocytosis, genital ulceration and vasculitis, predominantly involving the skin.

## 7 DRUG INTERACTIONS

### 7.1 Effects of Other Drugs on Tretinoin Capsules

#### Strong or moderate CYP3A Inhibitors

Avoid concomitant use of tretinoin capsules with strong CYP3A inhibitors if possible and

monitor more frequently if concomitant use is unavoidable. Monitor patients taking moderate CYP3A inhibitors concomitantly with tretinoin capsules more frequently for adverse reactions.

Tretinoin is a CYP3A substrate. Concomitant use with a strong CYP3A4 inhibitor increases tretinoin plasma concentrations, which may increase the risk of adverse reactions [see *Clinical Pharmacology* (12.3)].

### Strong CYP3A Inducers

Concomitant use of tretinoin capsules with strong CYP3A4 inducers may decrease tretinoin plasma concentrations, which may reduce its efficacy. Avoid concomitant use with strong CYP3A inducers if possible.

## **7.2 Concomitant Use of Products Known to Cause Intracranial Hypertension**

Intracranial hypertension has been reported in patients who received tretinoin capsules and concomitant use of other products that can cause intracranial hypertension, such as tetracyclines, may increase the risk. Avoid concomitant use of tretinoin capsules with other products agents that can cause intracranial hypertension [see *Warnings and Precautions* (5.5)].

## **7.3 Vitamin A**

The concomitant use of vitamin A with tretinoin capsules may lead to vitamin A related adverse reactions. Avoid concomitant use of tretinoin capsules with vitamin A.

## **7.4 Anti-fibrinolytic Agents**

Fatal thrombotic complications have been reported in patients who have received tretinoin capsules and concomitant use of anti-fibrinolytic agents may increase the risk. Avoid concomitant use of tretinoin capsules with anti-fibrinolytic agents [see *Warnings and Precautions* (5.8)].

# **8 USE IN SPECIFIC POPULATIONS**

## **8.1 Pregnancy**

### Risk Summary

Based on findings in animals and its mechanism of action [see *Clinical Pharmacology* (12.1)], tretinoin capsules can cause embryo-fetal loss and malformations when administered to a pregnant woman. Tretinoin capsules are a retinoid and there is an increased risk of major congenital malformations, spontaneous abortions and premature births following exposure to retinoids during pregnancy in humans. Tretinoin was teratogenic and embryotoxic in mice, rats, hamsters, rabbits and pigtail monkeys at doses less than the human dose on a mg/m<sup>2</sup> basis (see *Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to

4% and 15% to 20%, respectively.

## Data

### *Human Data*

Tretinoin capsules are a retinoid and increased spontaneous abortions and major fetal abnormalities related to the use of retinoids have been documented in humans. Reported malformations include abnormalities of the central nervous system, musculoskeletal system, external ear, eye, thymus and great vessels; and facial dysmorphism, cleft palate, and parathyroid hormone deficiency. Some of these abnormalities were fatal.

IQ scores less than 85, with or without obvious CNS abnormalities, have been reported in pediatrics exposed to retinoids in utero.

### *Animal Data*

Tretinoin causes fetal resorptions and a decrease in live fetuses in all animals studied. Gross external, soft tissue and skeletal alterations occurred at doses higher than 0.7 mg/kg/day in mice, 2 mg/kg/day in rats, 7 mg/kg/day in hamsters, and at a dose of 10 mg/kg/day, the only dose tested, in pigtail monkeys (about 1/20, 1/4, and 1/2 and 4 times the human dose, respectively, on a mg/m<sup>2</sup> basis).

## **8.2 Lactation**

There are no data on the presence of tretinoin in human milk, the effects on the breastfed child or the effects on milk production. Because of the potential for serious adverse reactions from tretinoin in breastfed infants, advise women not to breastfeed during treatment with tretinoin capsules and for 1 week after the last dose.

## **8.3 Use in Females and Males of Reproductive Potential**

Tretinoin capsules can cause embryo-fetal loss and malformations when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

### Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating tretinoin capsules. Females of reproductive potential must have a negative pregnancy test within 1 week prior to initiating tretinoin capsules with a sensitivity of at least 50 mIU/mL.

### Contraception

#### *Females*

Advise females of reproductive potential to abstain continuously from sexual intercourse or to use two effective methods of contraception. Counsel patients to use two effective methods of contraception during treatment with tretinoin capsules and for 1 month after the last dose. Two methods of effective contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Refer females of reproductive potential to a qualified provider of contraceptive methods, if needed.

#### *Males*

Advise males with female partners of reproductive potential to use effective contraception during and after treatment with tretinoin capsules and for 1 week after

the last dose.

## Infertility

### *Males*

Based on testicular toxicities observed in dogs, tretinoin capsules may impair male fertility [see *Nonclinical Toxicology (13.1)*]. The reversibility of effect on fertility is unknown.

## **8.4 Pediatric Use**

Safety and effectiveness of tretinoin capsules has been established in pediatric patients 1 year of age and older and the information on this use is discussed throughout the labeling. The maximum tolerated dose is lower in pediatric patients compared to adults. Some pediatric patients experience severe headache and intracranial hypertension, which required management with an analgesic and a lumbar puncture. Dose reduction may be considered for pediatric patients experiencing serious and/or intolerable adverse reactions.

Safety and effectiveness in pediatric patients less than 1 year of age have not been established.

## **8.5 Geriatric Use**

Across clinical studies of tretinoin capsules, 21% were 60 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

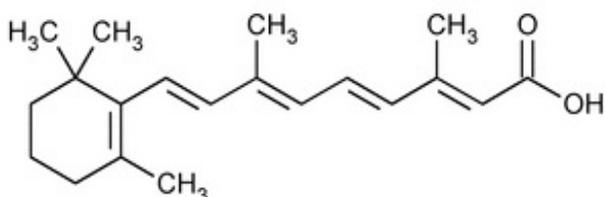
## **10 OVERDOSAGE**

In case of overdose with tretinoin capsules, reversible signs of hypervitaminosis A (headache, nausea, vomiting, mucocutaneous symptoms) can appear. Overdosage with other retinoids has been associated with transient headache, facial flushing, cheilosis, abdominal pain, dizziness and ataxia. These symptoms have quickly resolved without apparent residual effects.

There is no specific treatment in the case of an overdose; however, it is important that the patient be treated in a special hematological unit.

## **11 DESCRIPTION**

Tretinoin, USP is a retinoid. The chemical name is all-trans retinoic acid. The molecular formula is  $C_{20}H_{28}O_2$  and the molecular weight is 300.44 g/mol. The structural formula is:



It is a yellow to yellow-orange, crystalline powder with melting point at about 182°C (with decomposition). Tretinoin, USP is very sparingly soluble in water.

Tretinoin is available as capsules containing 10 mg tretinoin for oral use. Each capsule contains the following inactive ingredients: butylated hydroxyanisole, edetate disodium, hydrogenated vegetable oil, refined soybean oil and yellow wax. The ingredients in the capsule shell include gelatin, glycerin, sorbitol, red iron oxide, titanium dioxide. The ingredients in the edible imprinting ink include ammonium hydroxide, black iron oxide, propylene glycol and shellac. The ingredients in the processing aid Phosal 53 include lecithin, caprylic/capric triglycerides, ethanol, sunflower mono/diglycerides, oleic acid, ascorbyl palmitate and tocopherol.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Tretinoin induces cytodifferentiation and decreased proliferation of APL cells in culture and in vivo. In APL patients, tretinoin treatment produces an initial maturation of the primitive promyelocytes derived from the leukemic clone, followed by a repopulation of the bone marrow and peripheral blood by normal, polyclonal hematopoietic cells in patients achieving complete remission (CR). The exact mechanism of action of tretinoin in APL is unknown.

### **12.2 Pharmacodynamics**

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of tretinoin capsules have not been characterized.

### **12.3 Pharmacokinetics**

Following the administration of tretinoin capsules 22.5 mg/m<sup>2</sup> orally twice daily, the mean  $\pm$  SD peak tretinoin concentrations after the first dose was 394  $\pm$  89 and after 1 week of continuous treatment was 138  $\pm$  139 ng/mL, while area under the curve (AUC) after the first dose was 537  $\pm$  191 ng·h/mL and after 1 week of continuous treatment was 249  $\pm$  185 ng·h/mL.

#### Absorption

Time to reach peak concentration was between 1 and 2 hours. The absolute bioavailability of tretinoin capsules was approximately 50%.

#### *Effect of Food*

The effect of food on the absorption of tretinoin capsules has not been characterized. Food increases the absorption of retinoids, as a class.

#### Distribution

The apparent volume of distribution of tretinoin has not been determined. Protein binding is greater than 95%, predominately to albumin. Plasma protein binding remains constant over the concentration range of 10 to 500 ng/mL.

#### Elimination

The terminal elimination half-life of tretinoin following initial dosing is 0.5 to 2 hours in patients with APL.

## *Metabolism*

Tretinoin induced its own metabolism with plasma concentrations after 1 week of continuous therapy decreased to one-third of their day 1 values. Tretinoin is metabolized by cytochrome P450 enzymes, CYP3A4, 2C8, and 2E and undergoes glucuronidation by UGT2B7. Metabolites include 9-*cis* retinoic acid, 13-*cis* retinoic acid, 4-oxo *trans* retinoic acid, 4-oxo *cis* retinoic acid, and 4-oxo *trans* retinoic acid glucuronide. The metabolites 4-oxo retinoic acid and 4-oxo *trans* retinoic acid glucuronide have one-third of the pharmacological activity of the parent compound.

## *Excretion*

Following administration of radiolabeled tretinoin 2.75 mg and 50 mg (0.53 to 9.6 times the approved recommended dosage based on 1.7 m<sup>2</sup>), approximately 63% of radioactivity was recovered in the urine within 72 hours and 31% appeared in the feces within 6 days.

## Specific Populations

The effect of age, sex, race, renal impairment, and hepatic impairment on the pharmacokinetics of tretinoin is unknown.

## Drug Interaction Studies

### *Clinical Studies and Post Marketing Experience*

Strong CYP3A inhibitors: Tretinoin AUC increased by 72% following concomitant use with ketoconazole (strong CYP3A inhibitor). Increased tretinoin toxicity has also been reported post-marketing with strong CYP3A inhibitors including certain antimycotics.

Moderate CYP3A Inhibitors: Increased tretinoin toxicity following concomitant use of tretinoin capsules with certain antimycotics that are moderate CYP3A4 inhibitors has been reported post-marketing.

### *In Vitro Studies*

*Effect of Tretinoin on Transporters:* Tretinoin does not inhibit P-gp and BCRP *in vitro*.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No 2-year carcinogenicity studies in rodents have been conducted with tretinoin. In a carcinogenicity study, female B5D2F1 mice pretreated with a carcinogen diethylnitrosamine (DEN, intraperitoneal 50 mg/kg and 100 mg/kg) received dietary supplement of all-*trans*-retinoic acid (tretinoin) for 12 months. Tretinoin at a dose of 30 mg/kg/day in the diet (about 2 times the human dose on a mg/m<sup>2</sup> basis) was shown to increase the rate of DEN-induced mouse hepatocellular carcinomas. Tretinoin in combination with 50 mg/kg of DEN also increased the incidence of hemangiomas and hemangiosarcomas.

Tretinoin was negative when tested in the Ames and Chinese hamster V79 cell HGPRT assays for mutagenicity. A 2-fold increase in the sister chromatid exchange (SCE) has been demonstrated in human diploid fibroblasts, but other chromosome aberration assays, including an *in vitro* assay in human peripheral lymphocytes and an *in vivo*

mouse micronucleus assay, did not show a clastogenic or aneuploidogenic effect.

Adverse effects on fertility and reproductive performance were not observed in studies conducted in rats at doses up to 5 mg/kg/day (about 2/3 the human dose on a mg/m<sup>2</sup> basis). In a 6-week toxicology study in dogs, testicular degeneration, with increased numbers of immature spermatozoa, were observed at 10 mg/kg/day (about 4 times the equivalent human dose in mg/m<sup>2</sup>).

## 14 CLINICAL STUDIES

The efficacy of tretinoin capsules has been evaluated in 114 previously treated patients and in 67 previously untreated (“de novo”) patients with APL in one open-label, uncontrolled single investigator clinical study (Memorial Sloan-Kettering Cancer Center [MSKCC]) and in two cohorts of compassionate cases treated by multiple investigators under the auspices of the National Cancer Institute (NCI). Patients received tretinoin capsules 22.5 mg/m<sup>2</sup> orally twice daily for up to 90 days following the first dose or 30 days following achievement of complete remission. Efficacy results are shown Table 2.

**Table 2. Efficacy Results in a Controlled Clinical Trial (MSKCC) and Compassionate Use**

	MSKCC		NCI Cohort 1		NCI Cohort 2	
	Relapsed n=20	De Novo n=15	Relapsed* n=48	De Novo n=14	Relapsed n=46	De Novo† n=38
Complete Remission	16 (80%)	11 (73%)	24 (50%)	5 (36%)	24 (52%)	26 (68%)
Median Survival (months)	10.8	NR	5.8	0.5	8.8	NR
Median Follow-up (months)	9.9	42.9	5.6	1.2	8.0	13.1

NR = Not Reached

NA = Not Available

\* Including 9 chemorefractory patients

† Including 8 patients who received chemotherapy but failed to enter remission

The median time to complete remission was between 40 and 50 days (range: 2 to 120 days). Most patients received cytotoxic chemotherapy during the remission phase.

Ten of 15 pediatric cases achieved complete remission (8 of 10 males and 2 of 5 females).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Tretinoin Capsules are available as:

10 mg:	Pink, oval, soft-gelatin capsule printed with black ‘T 10’ filled with yellow to orange, opaque, viscous suspension.
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NDC 68462-792-01 Bottle of 100 capsules with child-resistant closure

Store at 20°C to 25°C (68° F to 77°F); excursions permitted to 15°C to 30°C (59° F to 86°F) [see USP Controlled Room Temperature].

Keep bottle tightly closed. Protect from light.

## **17 PATIENT COUNSELING INFORMATION**

### Embryo-Fetal Toxicity

Advise female patients of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)*].

Advise females of reproductive potential to use 2 methods of effective contraception during treatment with tretinoin capsules and for 1 month after the last dose [see *Use in Specific Populations (8.3)*].

Advise males with female partners of reproductive potential to use effective contraception during treatment with tretinoin capsules and for 1 week after the last dose [see *Use in Specific Populations (8.3)*].

### Differentiation Syndrome

Advise patients that tretinoin capsules can cause differentiation syndrome. Ask patients to immediately report any symptoms suggestive of differentiation syndrome, such as fever, cough or difficulty breathing, decreased urinary output, low blood pressure, rapid weight gain, or swelling of their arms or legs, to their healthcare provider for further evaluation [see *Warnings and Precautions (5.2)*].

### Patients Without t(15;17) Translocation or PML/RAR $\alpha$ Fusion

Advise patients that tretinoin capsules are not recommended for use in patients without t(15;17) translocation or PML/RAR $\alpha$  fusion [see *Warnings and Precautions (5.3)*].

### Leukocytosis

Inform patients that rapidly evolving leukocytosis, which can be life-threatening, can occur during treatment with tretinoin capsules [see *Warnings and Precautions (5.4)*].

### Intracranial Hypertension

Advise patients that tretinoin capsules can cause intracranial hypertension, especially in pediatric patients. Ask patients to immediately report any symptoms suggestive of intracranial hypertension, such as headache, nausea, vomiting, and visual disturbances [see *Warnings and Precautions (5.5)*].

### Lipid Abnormalities

Inform patients that hypercholesterolemia and/or hypertriglyceridemia can occur during treatment with tretinoin capsules. Advise patients on the need for monitoring fasting triglycerides and cholesterol [see *Warnings and Precautions (5.6)*].

### Hepatotoxicity

Advise patients that tretinoin capsules can cause elevated liver function tests. Advise

patients on the need for monitoring of liver function tests [see *Warnings and Precautions* (5.7)].

### Thromboembolic Events

Inform patients that venous and arterial thromboembolic events, including cerebrovascular accident, myocardial infarction and renal infarct can occur during treatment with tretinoin capsules [see *Warnings and Precautions* (5.8)].

### Lactation

Advise women not to breastfeed during treatment with tretinoin capsules and for 1 week after the last dose [see *Use in Specific Populations* (8.2)].

### Administration Instructions

Advise patients to swallow tretinoin capsules whole with water. Advise patients not to chew, dissolve, or open capsules. Advise patients not to take a missed dose of tretinoin capsules unless it is more than 10 hours until the next scheduled dose. Advise patients that if vomiting occurs after tretinoin capsules administration, that they should not take an additional dose, but continue with the next scheduled dose [see *Dosage and Administration* (2.2)].

### Effects on Ability to Drive and Use Machines

Advise patients that the ability to drive or operate machinery might be impaired when treated with tretinoin capsules, particularly if patients are experiencing dizziness or severe headache.

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Manufactured by:

#### **Douglas Manufacturing Limited**

Lincoln, Auckland 0610, New Zealand

Distributed by:

#### **Glenmark Pharmaceuticals Inc., USA**

Elmwood Park, NJ 07407

Questions? 1 (888) 721-7115

[www.glenmarkpharma-us.com](http://www.glenmarkpharma-us.com)

June 2025

### **PACKAGE/LABEL PRINCIPAL DISPLAY PANEL**

68462-792-01

Tretinoin Capsules  
10 mg

**CAUSES BIRTH DEFECTS. DO NOT GET PREGNANT.**

NDC 68462-792-01

# Tretinoin Capsules

CAUSES BIRTH DEFECTS



DO NOT GET PREGNANT

**10 mg**

PHARMACIST: Dispense the patient information leaflet provided separately to each patient.



Rx only

100 Capsules

Each capsule contains 10 mg Tretinoin, USP.

**Usual Dosage:** See package insert for prescribing information.

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

**PROTECT FROM LIGHT.**

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Distributed by: **Glenmark Pharmaceuticals Inc., USA**  
Elmwood Park, NJ 07407

Product of Germany

Questions? 1 (888) 721-7115  
www.glenmarkpharma-us.com



08/25  
312395



## TRETINOIN

tretinoin capsule

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:68462-792
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TRETINOIN (UNII: 5688UTC01R) (TRETINOIN - UNII:5688UTC01R)	TRETINOIN	10 mg

### Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
HYDROGENATED SOYBEAN OIL (UNII: A2M91M918C)	
SOYBEAN OIL (UNII: 241ATL177A)	
YELLOW WAX (UNII: 2ZA36H0S2V)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
GLYCERIN (UNII: PDC6A3C0OX)	
SORBITOL (UNII: 506T60A25R)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
SOYBEAN LECITHIN (UNII: 1DI56QDM62)	
MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)	

<b>OLEIC ACID</b> (UNII: 2UMI9U37CP)	
<b>ASCORBYL PALMITATE</b> (UNII: QN83US2B0N)	
<b>TOCOPHEROL</b> (UNII: R0ZB2556P8)	
<b>SUNFLOWER OIL</b> (UNII: 3W1JG795YI)	

### Product Characteristics

<b>Color</b>	PINK (Opaque Cap)	<b>Score</b>	no score
<b>Shape</b>	CAPSULE	<b>Size</b>	10mm
<b>Flavor</b>		<b>Imprint Code</b>	T;10
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68462-792-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/23/2016	

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA208279	12/23/2016	

### Labeler - Glenmark Pharmaceuticals Inc., USA (130597813)

### Establishment

Name	Address	ID/FEI	Business Operations
Douglas Manufacturing Limited		590829388	MANUFACTURE(68462-792)

Revised: 1/2026

Glenmark Pharmaceuticals Inc., USA