

TRETINOIN- tretinoin capsule, liquid filled
Teva Pharmaceuticals USA, Inc.

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 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. Advise females of reproductive potential to use two effective methods of contraception during treatment with tretinoin and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with tretinoin 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. 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 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 α 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/m² 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 α 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 α 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 has 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 Teva at 1-888-838-2872 or FDA at 1-800-FDA-1088 or 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: 2/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: EMBRYO-FETAL TOXICITY and DIFFERENTIATION SYNDROME

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Information

2.2 Recommended Dosage

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

5.2 Differentiation Syndrome

5.3 Patients Without t(15;17) Translocation or PML/RAR α Fusion

5.4 Leukocytosis

5.5 Intracranial Hypertension

5.6 Lipid Abnormalities

5.7 Hepatotoxicity

5.8 Thromboembolic Events

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Tretinoin

7.2 Concomitant Use of Products Known to Cause Intracranial Hypertension

7.3 Vitamin A

7.4 Anti-fibrinolytic Agents

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Use in Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY and DIFFERENTIATION SYNDROME

- **Tretinoin 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. Advise females of reproductive potential to use two effective methods of contraception during treatment with tretinoin and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with tretinoin 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. 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 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 α 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/m² 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 α 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

Capsules: 10 mg, two-piece hard gelatin capsule with brown opaque cap and dark yellow opaque body, filled with yellow viscous oily suspension. Imprinted in black ink with stylized barr 808.

4 CONTRAINDICATIONS

Tretinoin capsules are contraindicated in patients with a known hypersensitivity to tretinoin, 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 can cause embryo-fetal loss and malformations when administered to a pregnant woman. Tretinoin is 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/m² 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 and for 1 month following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with tretinoin 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 [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 for moderate and severe differentiation syndrome until resolution [see *Adverse Reactions (6.1)*].

5.3 Patients Without t(15;17) Translocation or PML/RAR α 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 α fusion using molecular diagnostic techniques. Tretinoin is 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 [see *Adverse Reactions (6.1)*]. Patients who present with a baseline white blood cell count (WBC) > 5 × 10⁹/L have an increased risk. Patients who receive chemotherapy with tretinoin 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, 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 [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 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 was evaluated in patients with APL who received tretinoin at a dose of 22.5 mg/m² 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 (%)
Nervous system disorders	
Headache	86
Dizziness	20
Paresthesias	17
Anxiety	17
Insomnia	14
Depression	14
Confusion	11
General disorders	
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
Musculoskeletal and connective tissue disorders	
Bone pain	77
Myalgia	14
Respiratory, thoracic and mediastinal disorders	
Upper respiratory tract disorders	63
Dyspnea	60
Respiratory insufficiency	26
Pleural effusion	20
Rales	14
Expiratory wheezing	14
Pneumonia	14
Vascular disorders	
Hemorrhage	60
Gastrointestinal hemorrhage	34
Flushing	23
Hypotension	14
Hypertension	11
Phlebitis	11
Infections and infestations	
Infections	58
Gastrointestinal disorders	
Nausea/vomiting	57
Abdominal pain	31
Other gastrointestinal disorders	26
Diarrhea	23
Constipation	17
Dyspepsia	14
Abdominal distention	11

Skin and subcutaneous tissue disorders	
Rash	54
Pruritus	20
Increased sweating	20
Alopecia	14
Skin changes	14
Blood and lymphatic system disorders	
Leukocytosis	49
Differentiation syndrome ¹	26
Disseminated intravascular coagulation	26
Ear and labyrinth disorders	
Earache or feeling of fullness in the ears	23
Cardiac disorders	
Arrhythmias	23
Eye disorders	
Visual disturbances	17
Ocular disorders	17
Renal and urinary disorders	
Renal insufficiency	11
¹ 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 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

Strong CYP3A Inhibitors

The coadministration of tretinoin with ketoconazole, a strong CYP3A4 inhibitor, increased tretinoin plasma concentration, which may increase the risk of adverse reactions [see *Clinical Pharmacology (12.3)*]. Avoid coadministration of tretinoin with strong CYP3A inhibitors if possible. Monitor patients taking a strong CYP3A inhibitor with tretinoin more frequently for adverse reactions.

Strong CYP3A Inducers

The coadministration of tretinoin with strong CYP3A4 inducers may decrease tretinoin plasma concentrations, which may reduce its efficacy. Avoid coadministration 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 and concomitant use of other products that can cause intracranial hypertension, such as tetracyclines, may increase the risk. Avoid concomitant use of tretinoin 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 may lead to vitamin A related adverse reactions. Avoid concomitant use of tretinoin with vitamin A.

7.4 Anti-fibrinolytic Agents

Fatal thrombotic complications have been reported in patients who have received tretinoin and concomitant use of anti-fibrinolytic agents may increase the risk. Avoid concomitant use of tretinoin 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 can cause embryo-fetal loss and malformations when administered to a pregnant woman. Tretinoin is 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/m² 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 is 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/m² 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 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. Females of reproductive potential must have a negative pregnancy test within 1 week prior to initiating tretinoin 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 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 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, 21% were 60 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

10 OVERDOSAGE

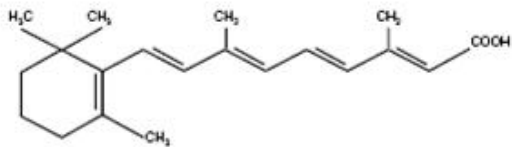
In case of overdose with tretinoin, reversible signs of hypervitaminosis A (headache, nausea, vomiting, mucocutaneous symptoms) can appear. Overdosage with other retinoids has been associated with transient headache, facial flushing, cheilosis, abdominal pain, dizziness and ataxia. These symptoms have 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 that induces maturation of acute promyelocytic leukemia (APL) cells in culture. It is available in a 10 mg gelatin capsule for oral administration. Each capsule contains the following inactive ingredients: butylated hydroxyanisole, edetate disodium, gelatin, hydrogenated vegetable oil, polysorbate 80, soybean oil, vitamin E, and white wax (beeswax). The ingredients in the capsule shell include black iron oxide, red iron oxide, titanium dioxide and yellow iron oxide. The ingredients in the edible imprinting ink include D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, iron oxide black, propylene glycol and shellac glaze.

Chemically, tretinoin, USP is *all-trans* retinoic acid and is related to retinol (Vitamin A) and has the following chemical name: 3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. It is a yellow to light orange crystalline powder, and has the following structural formula:



$C_{20}H_{28}O_2$

Molecular Weight: 300.44

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 have not been characterized.

12.3 Pharmacokinetics

Following the administration of tretinoin 22.5 mg/m² 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 was approximately 50%.

Effect of Food

The effect of food on the absorption of tretinoin 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 m²), 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

Coadministration of ketoconazole (strong CYP3A inhibitor) increased tretinoin AUC by 72%.

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/m² 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/m² 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/m²).

14 CLINICAL STUDIES

The efficacy of tretinoin 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 22.5 mg/m² 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	
	De		De		De	

	Relapsed N = 20	De Novo n = 15	Relapsed* N = 48	De Novo n = 14	Relapsed n = 46	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, 10 mg are available as two-piece hard gelatin capsule with brown opaque cap and dark yellow opaque body, filled with yellow viscous oily suspension. Imprinted in black ink with stylized barr 808. Available in bottles of 100 capsules (NDC 0555-0808-02).

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

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.

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 α Fusion

Advise patients that tretinoin capsules are not recommended for use in patients without t(15;17) translocation or PML/RAR α 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.

Brands listed are the trademarks of their respective owners.

Manufactured For:

Teva Pharmaceuticals

Parsippany, NJ 07054

Rev. C 2/2023

PRINCIPAL DISPLAY PANEL

NDC 0555-0808-02

Tretinoin Capsules 10 mg

Rx Only

100 Capsules

3 0 5 5 5 - 0 8 0 8 - 0 2 2

3 2 0 7 9 8 6 3 0 1

Serialization Coding Area

Each capsule contains 10 mg tretinoin, USP.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°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.

Manufactured For:
Teva Pharmaceuticals
 Parsippany, NJ 07054
 Rev. C 2/2023
 32079863_01

NDC 0555-0808-02

Tretinoin Capsules

10 mg

CAUSES BIRTH DEFECTS
DO NOT GET PREGNANT

Rx only
100 Capsules

teva

TRETINOIN

tretinoin capsule, liquid filled

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0555-0808
Route of Administration	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)	
GELATIN (UNII: 2G86QN327L)	
HYDROGENATED SOYBEAN OIL (UNII: A2M91M918C)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SOYBEAN OIL (UNII: 241ATL177A)	
ALPHA-TOCOPHEROL (UNII: H4N855PNZ1)	
WHITE WAX (UNII: 7G1J5DA97F)	
FERROSO FERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
D&C YELLOW NO. 10 ALUMINUM LAKE (UNII: CQ3XH3DET6)	
FD&C BLUE NO. 1 ALUMINUM LAKE (UNII: J9EQA3S2JM)	
FD&C BLUE NO. 2--ALUMINUM LAKE (UNII: 4AQJ3LG584)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	

SHELLAC (UNII: 46N107B71O)

Product Characteristics

Color	brown, yellow (dark yellow)	Score	no score
Shape	CAPSULE	Size	18mm
Flavor		Imprint Code	barr;808
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0555-0808-02	100 in 1 BOTTLE; Type 0: Not a Combination Product	06/26/2007	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077684	06/26/2007	

Labeler - Teva Pharmaceuticals USA, Inc. (001627975)

Revised: 2/2023

Teva Pharmaceuticals USA, Inc.