

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

EXTINA® (ketoconazole) foam, 2%

For topical use

Initial U.S. Approval: 1981

INDICATIONS AND USAGE

EXTINA® Foam is indicated for topical treatment of seborrheic dermatitis in immunocompetent patients 12 years of age and older (1).

Limitations of Use

Safety and efficacy of EXTINA Foam for treatment of fungal infections have not been established.

DOSAGE AND ADMINISTRATION

- EXTINA Foam should be applied to the affected area(s) twice daily for four weeks (2).
- EXTINA Foam is not for ophthalmic, oral, or intravaginal use (2).

DOSAGE FORMS AND STRENGTHS

Foam: 2% ketoconazole in 50 g and 100 g containers (3).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- EXTINA Foam may result in contact sensitization, including photoallergenicity (5.1, 6.2).
- The contents of EXTINA Foam are flammable. Avoid fire, flame, or smoking during and immediately following application. (5.2).

ADVERSE REACTIONS

The most common adverse reactions observed in clinical studies (incidence > 1%) were application site burning and application site reaction (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 06/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EXTINA (ketoconazole) Foam, 2% is indicated for the topical treatment of seborrheic dermatitis in immunocompetent patients 12 years of age and older.

Limitations of Use

Safety and efficacy of EXTINA Foam for treatment of fungal infections have not been established.

2 DOSAGE AND ADMINISTRATION

EXTINA Foam should be applied to the affected area(s) twice daily for four weeks.

Hold the container upright, and dispense EXTINA Foam into the cap of the can or other cool surface in an amount sufficient to cover the affected area(s). Dispensing directly onto hands is not recommended, as the foam will begin to melt immediately upon contact with warm skin. Pick up small amounts of EXTINA Foam with the fingertips, and gently massage into the affected area(s) until the foam disappears. For hair-bearing areas, part the hair, so that EXTINA Foam may be applied directly to the skin (rather than on the hair).

Avoid contact with the eyes and other mucous membranes. EXTINA Foam is not for ophthalmic, oral or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

EXTINA (ketoconazole) Foam, 2% contains 20 mg of ketoconazole, USP per gram, supplied in 50 g and 100 g containers.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Contact Sensitization

EXTINA Foam may result in contact sensitization, including photoallergenicity [*see Adverse Reactions (6.2)*].

5.2 Flammable Contents

The contents of EXTINA Foam include alcohol and propane/butane, which are flammable. Avoid fire, flame and/or smoking during and immediately following application. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C).

5.3 Systemic Effects

Hepatitis has been seen with orally administered ketoconazole (1:10,000 reported incidence). Lowered testosterone and ACTH-induced corticosteroid serum levels have been seen with high doses of orally administered ketoconazole. These effects have not been seen with topical ketoconazole.

6 ADVERSE REACTIONS

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. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be related to drug use and for approximating rates.

The safety data presented in Table 1 reflect exposure to EXTINA Foam in 672 subjects, 12 years and older with seborrheic dermatitis. Subjects applied EXTINA Foam or vehicle foam twice daily for 4 weeks to affected areas on the face, scalp, and/or chest. Adverse reactions occurring in > 1% of subjects are presented in Table 1.

Table 1: Adverse Reactions Reported by > 1% Subjects in Clinical Trials

| Adverse Reactions | EXTINA Foam N = 672 n (%) | Vehicle Foam N = 497 n (%) |
|--|--|---|
| Subjects with an Adverse Reaction | 188 (28%) | 122 (25%) |
| Application site burning | 67 (10%) | 49 (10%) |
| Application site reaction | 41 (6%) | 24 (5%) |

Application site reactions that were reported in < 1% of subjects were dryness, erythema, irritation, paresthesia, pruritus, rash and warmth.

6.2 Dermal Safety Studies

In a photoallergenicity study, 9 of 53 subjects (17%) had reactions during the challenge period at both the irradiated and non-irradiated sites treated with EXTINA Foam. EXTINA Foam may cause contact sensitization.

6.3 Postmarketing Experience

The following adverse events have been identified during postmarketing use of EXTINA Foam:

Gastrointestinal disorders: Cheilitis

General disorders and administration site conditions: Application site pain and application site burn

Skin and subcutaneous tissue disorders: Skin burning sensation and erythema

Because these events 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on EXTINA Foam use in pregnant women to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. No reproductive studies in animals have been performed with EXTINA Foam. In animal reproduction studies with pregnant mice, rats and rabbits both embryotoxic and developmental effects (structural abnormalities) were observed following oral dosing of ketoconazole during organogenesis. Assuming equivalent systemic absorption of topical and oral ketoconazole doses and an EXTINA Foam maximum recommended human dose (MRHD) of 8 grams (equivalent to 160 mg ketoconazole), embryotoxic effects were observed at 0.8 to 2.4 times the MRHD and developmental effects were observed at 4.8 times the MRHD [see Data].

The background risk of major birth defects and miscarriage for the indicated population 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

Animal Data

The animal multiples of human exposure calculations are based on body surface area (BSA) comparisons of oral doses administered to animals and an EXTINA Foam maximum recommended human dose (MRHD) of 8 grams (equivalent to 2.67 mg ketoconazole/kg/day for a 60 kg individual or 98.8 mg ketoconazole/m²/day).

Embryofetal development studies have been conducted in mice, rats and rabbits with orally administered ketoconazole. When orally administered to mice on gestational days 6 through 18 (covering the period of organogenesis), ketoconazole was embryotoxic (25 mg/kg and higher; 0.8 times the MRHD based on BSA comparisons) with a high incidence of resorptions, increased number of stillbirths and delayed parturition. Delays in maturation were also observed. There was no evidence of maternal toxicity or malformations at up to 50 mg/kg (1.5 times the MRHD based on BSA comparisons). No treatment related developmental effects were observed at 10 mg/kg (0.3 times the MRHD based on BSA comparisons).

In the presence of maternal toxicity in rats, orally administered ketoconazole was both embryotoxic (40 mg/kg and higher; 2.4 times the MRHD based on BSA comparisons), including increased resorbed fetuses and stillbirths, and teratogenic (80 mg/kg and higher; 4.8 times the MRHD based on BSA comparisons), including syndactylia, oligodactylia, waved ribs and cleft palate. Additionally, 100 mg/kg (6 times the MRHD based on BSA comparisons) ketoconazole orally administered on a single day during gestation (gestational days 9 through 12) was embryotoxic (increased resorptions). This same oral dose given on gestation day 12, 13, 14 or 15 induced external malformations including cleft palate, micromelia and digital anomalies (brachydactyly, ectrodactyly, syndactyly).

In pregnant rabbits orally administered ketoconazole, evidence of embryotoxicity (increased resorptions) was observed at 10 mg/kg (1.2 times the MRHD based on BSA comparisons) and higher and an increased incidence of skeletal abnormalities was observed at 40 mg/kg (4.8 times the MRHD based on BSA comparisons).

8.2 Lactation

Risk Summary

There is no information available on the presence of ketoconazole in human milk, or the effects on the breastfed child, or the effects on milk production after topical application of EXTINA Foam to women who are breastfeeding. In animal studies ketoconazole was found in milk following oral administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXTINA Foam and any potential adverse effects on the breastfed infant from EXTINA Foam or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

In animal fertility studies in rats and dogs, administration of oral doses of ketoconazole between 3-day and 3-month periods resulted in infertility that was reversible [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of EXTINA Foam in pediatric patients less than 12 years of age have not been established.

Of the 672 subjects treated with EXTINA Foam in the clinical trials, 44 (7%) were from 12 to 17 years of age. [See *Clinical Studies (14)*].

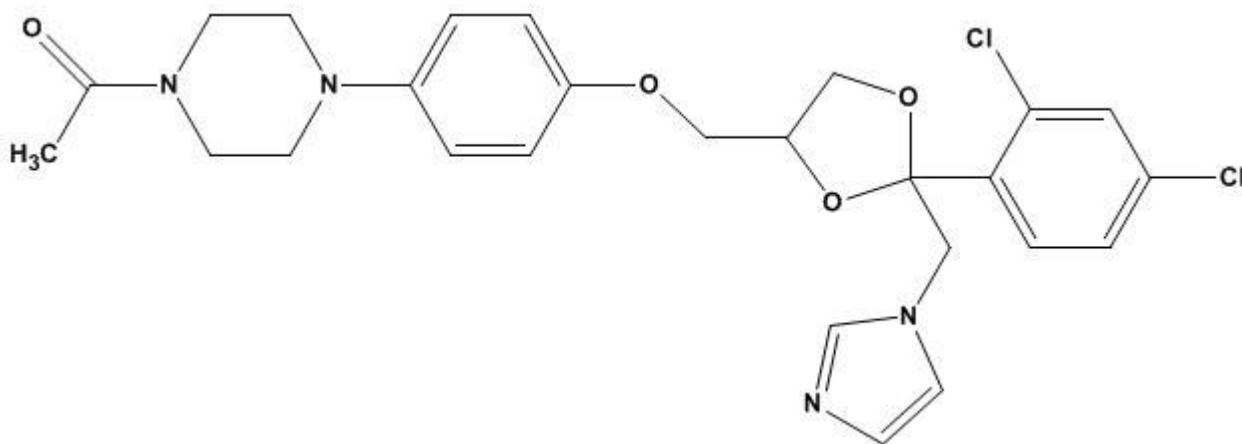
8.5 Geriatric Use

Of the 672 subjects treated with EXTINA Foam in the clinical trials, 107 (16%) were 65 years and over. Clinical trials of EXTINA Foam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.

11 DESCRIPTION

EXTINA Foam contains 2% ketoconazole USP, an antifungal agent, in a thermolabile hydroethanolic foam for topical application.

The chemical name for ketoconazole is piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, *cis*- with the molecular formula $C_{26}H_{28}Cl_2N_4O_4$ and a molecular weight of 531.43. The following is the chemical structure:



EXTINA Foam contains 20 mg ketoconazole per gram in a thermolabile hydroethanolic foam vehicle consisting of cetyl alcohol, citric acid, ethanol (denatured with *tert*-butyl alcohol and brucine sulfate) 58%, polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol pressurized with a hydrocarbon (propane/butane) propellant.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of ketoconazole in the treatment of seborrheic dermatitis is not known.

12.2 Pharmacodynamics

The pharmacodynamics of EXTINA Foam has not been established.

12.3 Pharmacokinetics

In a bioavailability study, 12 subjects with moderate to severe seborrheic dermatitis applied 3 g of EXTINA Foam twice daily for 4 weeks. Circulating plasma levels of ketoconazole were < 6 ng/mL for a majority of subjects (75%), with a maximum level of 11 ng/mL observed in one subject.

12.4 Microbiology

Ketoconazole is an antifungal agent which inhibits the *in vitro* synthesis of ergosterol, a key sterol in the cell membrane of *Malassezia furfur*. The clinical significance of antifungal activity in the treatment of seborrheic dermatitis is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic or photo-carcinogenic potential of EXTINA Foam.

In oral carcinogenicity studies in mice (18-months) and rats (24-months) at dose levels of 5, 20 and 80 mg/kg/day ketoconazole was not carcinogenic. The high dose in these studies was approximately 2.4 to 4.8 times the MRHD based on BSA comparisons. In a bacterial reverse mutation assay, ketoconazole did not express any mutagenic potential. In three *in vivo* assays (sister chromatid exchange in humans, dominant lethal and micronucleus tests in mice), ketoconazole did not exhibit any genotoxic potential.

In animal fertility studies, oral ketoconazole impaired both male and female fertility in rats in a dose and duration dependent manner. In females, oral doses up to 40 mg/kg (2.4 times the MRHD based on BSA comparisons) had no effect on fertility, while doses of 75 mg/kg (4.5 times the MRHD based on BSA comparisons) and higher decreased the pregnancy rate and number of implantation sites. In male rats, oral dosing at 200 mg/kg/day (12 times the MRHD based on BSA comparisons) for three days decreased fertility and 400 mg/kg/day (24 times the MRHD based on BSA comparisons) for three days resulted in a complete loss of fertility. When administered for longer durations (up to 3 months), decreased fertility in male rats was observed at doses as low as 24 mg/kg/day (1.4 times the MRHD based on BSA comparisons). In male beagle dogs, an oral dose of 25 mg/kg/day ketoconazole for up to 4 weeks (5.2 times the MRHD based on BSA comparisons) resulted in decreased sperm motility, decreased sperm count, increased abnormal sperm and atrophy of the testes. These effects were reversed subsequent to withdrawal of treatment.

14 CLINICAL STUDIES

The safety and efficacy of EXTINA Foam were evaluated in a randomized, double-blind, vehicle-controlled trial in subjects 12 years and older with mild to severe seborrheic dermatitis. In the trial, 427 subjects received EXTINA Foam and 420 subjects received vehicle foam. Subjects applied EXTINA Foam or vehicle foam twice daily for 4 weeks to affected areas on the face, scalp, and/or chest. The overall disease severity in terms of erythema, scaling, and induration was assessed at Baseline and week 4 on a 5-point Investigator's Static Global Assessment (ISGA) scale.

Treatment success was defined as achieving a Week 4 (end of treatment) ISGA score of 0 (clear) or 1 (majority of lesions have individual scores for scaling, erythema, and induration that averages 1 [minimal or faint]) and at least two grades of improvement from baseline. The results are presented in Table 2. The database was not large enough to assess whether there were differences in effects in age, gender, or race subgroups.

Table 2: Efficacy Results

| Number of Subjects | EXTINA Foam N = 427 n (%) | Vehicle Foam N = 420 n (%) |
|--------------------------------------|--|---|
| Subjects Achieving Treatment Success | 239 (56%) | 176 (42%) |

16 HOW SUPPLIED/STORAGE AND HANDLING

EXTINA (ketoconazole) Foam, 2% contains 20 mg of ketoconazole, USP per gram. The thermolabile hydroethanolic foam is available as follows:

NDC 0378-8136-50
50 g aluminum can

NDC 0378-8136-01
100 g aluminum can

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

Do not store under refrigerated conditions.

Contents are flammable. Do not expose containers to heat and/or store at temperatures above 49°C (120°F). Do not store in direct sunlight.

Contents under pressure. Do not puncture and/or incinerate container.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Package Insert).

Instruct patients on a proper use of EXTINA Foam

- **Avoid fire, flame and/or smoking during and immediately following application.**
- Do not apply EXTINA Foam directly to hands. Dispense onto a cool surface, and apply to the affected areas using the fingertips.
- Wash their hands after application
- EXTINA Foam may cause skin irritation (application site burning and/or reactions)
- Instruct a patient to contact a health care provider if the area of application shows signs of increased irritation and report any signs of adverse reactions.

PATIENT INFORMATION
EXTINA (ex-TEEN-ah)
(ketoconazole)
Foam, 2%

Important Information: EXTINA Foam is for use on the skin only. Do not use EXTINA Foam in your eyes, mouth or vagina.

What is EXTINA Foam?

EXTINA Foam is a prescription medicine used on the skin (topical) to treat seborrheic dermatitis in people 12 years of age and older with a normal immune system.

It is not known if EXTINA Foam is safe and effective when used to treat fungal infections.

It is not known if EXTINA Foam is safe and effective in children less than 12 years of age.

Before using EXTINA Foam, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if EXTINA Foam will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if EXTINA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with EXTINA Foam.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use EXTINA Foam?

- Use EXTINA Foam exactly as your healthcare provider tells you to use it. See the detailed “Instructions for Use” at the end of this leaflet for directions about how to apply EXTINA Foam the right way.
- Apply EXTINA Foam to the affected skin area(s) 2 times each day for 4 weeks. You should apply enough EXTINA Foam to cover the entire affected area(s).
- Talk to your healthcare provider if your skin does not improve after 4 weeks of treatment with EXTINA Foam.
- Dispense EXTINA Foam directly into the cap. **Do not** dispense EXTINA Foam directly onto your hands, because the foam will begin to melt on contact with warm skin.
- Wash your hands after applying EXTINA Foam.

What should I avoid while using EXTINA Foam?

- **EXTINA Foam is flammable.** Avoid fire, flames, or smoking during and right after you apply EXTINA Foam to your skin.
- Avoid getting EXTINA Foam in or near your eyes, mouth, lips or vagina. If you get EXTINA Foam on your lips or in your eyes, mouth or vagina, rinse well with water.

What are the possible side effects of EXTINA Foam?

EXTINA Foam may cause serious side effects, including:

- **Skin irritation at the application area(s), including skin reactions caused by exposure to light.** Tell your healthcare provider if you develop skin irritation during treatment with EXTINA Foam.

The most common side effects of EXTINA Foam include, burning, dryness, redness, irritation, numbness, itching, rash and warmth at the application site.

These are not all of the possible side effects of EXTINA Foam.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EXTINA Foam?

- Store EXTINA Foam at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not store the EXTINA Foam can in the refrigerator or freezer.
- Keep EXTINA Foam away from heat. Never throw the EXTINA Foam can into a fire, even if the can is empty.
- Do not store EXTINA Foam at temperatures above 120°F (49°C).
- Do not break through (puncture) the EXTINA Foam can.

Keep EXTINA Foam and all medicines out of the reach of children.

General information about the safe and effective use of EXTINA Foam.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EXTINA Foam for a condition for which it was not prescribed. Do not give EXTINA Foam to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about EXTINA Foam that is written for health professionals.

What are the ingredients in EXTINA Foam?

Active ingredient: ketoconazole

Inactive Ingredients: cetyl alcohol, citric acid, ethanol (denatured with *tert*-butyl alcohol and brucine sulfate) 58%, polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol pressurized with a hydrocarbon (propane/butane) propellant



Manufactured for:

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Manufactured by:

DPT Laboratories, Ltd.
San Antonio, TX 78215 U.S.A.

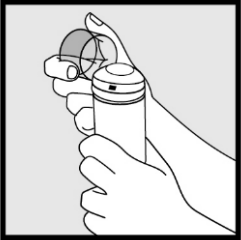
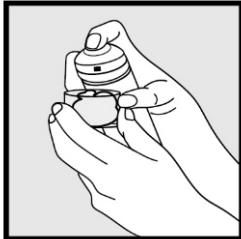

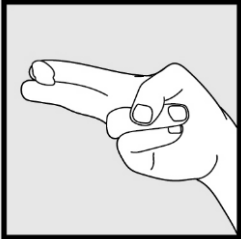

For more information, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or visit www.extina.com.



This Patient Information leaflet has been approved by the U.S. Food and Drug Administration.

Revised: 06/2018

Instructions for Use
EXTINA (ex-TEEN-ah)
(ketoconazole)
Foam, 2%

Important Information: EXTINA Foam is for use on the skin only. Do not use EXTINA Foam in your eyes, mouth or vagina.

| | |
|--|--|
| <p>Step 1: Remove the clear cap from the EXTINA Foam can.</p> |  |
| <p>Step 2: Hold the can upright and firmly press the nozzle to dispense EXTINA Foam into the clear cap.</p> <ul style="list-style-type: none">• Dispense enough EXTINA Foam to cover the entire affected area(s). |  |
| <ul style="list-style-type: none">• If the can seems warm or the foam seems runny, run the can under cold water. |  |
| <p>Step 3: Pick up small amounts of EXTINA Foam with your fingertips and gently rub the foam into the affected area(s) until the foam disappears.</p> |   |

| | |
|--|---|
| <ul style="list-style-type: none"> If you are treating areas such as your scalp, part the hair so that EXTINA Foam may be applied directly to the skin. |  |
| <p>Step 4: Wash your hands after applying EXTINA Foam.</p> <ul style="list-style-type: none"> Throw away any of the unused medicine that is left in the cap. |  |

How should I store EXTINA Foam?

- Store EXTINA Foam at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not store the EXTINA Foam can in the refrigerator or freezer.
- Keep EXTINA Foam away from heat. Never throw the can into a fire, even if the can is empty.
- Do not store EXTINA Foam at temperatures above 120°F (49°C).
- Do not break through (puncture) the EXTINA Foam can.

Keep EXTINA Foam and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 06/2018



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Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Manufactured by:
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