GYNAZOLE-1® Butacizone Nitrate Vaginal Cream USP, 2% contains butacizone nitrate 2%, an imidazoline derivative with anti-inflammatory and analgesic properties. It is a white to off-white crystalline powder with a molecular weight of 474.79. It is sparingly soluble in ethanol, slightly soluble in ether, benzene, methyl chloride, acetone, and ethyl acetate; very slightly soluble in ethyl acetate; and practically insoluble in water. It melts at about 159°C with decomposition.

GYNAZOLE-1® Butacizone Nitrate Vaginal Cream USP, 2% contains 2% butacizone nitrate in a cream of edetate disodium, glycerol monostearate, mephylparaben, mineral oil, poloxamer-338, propylene glycol, propanediol, colloidal silicon dioxide, sorbitol solution, purified water, and microcrystalline wax.

CLINICAL PHARMACOLOGY
Following vaginal administration of butacizone nitrate vaginal cream, 2% to 3 women, 1.7% (range 1.3-2.2%) of the dose was absorbed on average. Peak plasma levels (13.6-14.6 ng/mL) were reached 30 min after drug administration of the cream, and its metabolites are attained between 12 and 24 hours after vaginal administration.

Microbiology - The exact mechanism of the anti-inflammatory effect of butacizone nitrate is unknown; however, it is presumed to function as another imidazoline derivatives via inhibition of aldosterone synthesis. Imidazolates generally inhibit the conversion of lanosterol to ergosterol, resulting in a change in fungal cell membrane lipid composition. This structural change alters cell permeability and, ultimately, results in the osmotic disruption or growth inhibition of the fungal cell.

Butacizone nitrate is an imidazoline derivative that has fungicidal activity in vitro against Candida spp, and has been demonstrated to be clinically effective against vaginal infections due to Candida albicans. Candida albicans has been identified as the predominant species responsible for vulvovaginal candidiasis.

INDICATIONS AND USAGE
GYNAZOLE-1® Butacizone Nitrate Vaginal Cream USP, 2% is indicated for the local treatment of vulvovaginal candidiasis (infections caused by Candida). The diagnosis should be confirmed by KOH smear or cultures (see CLINICAL STUDIES). Note: GYNAZOLE-1® Butacizone Nitrate Vaginal Cream USP, 2% is safe and effective in non-pregnant women, however, the safety and effectiveness of this product in pregnant women has not been established. (REAGATIONS - Pregnancy.)

CONTRAINDICATIONS
GYNAZOLE-1® Butacizone Nitrate Vaginal Cream USP, 2% is contraindicated in patients with a history of hypersensitivity to any of the components of the product.

CLINICAL STUDIES
Vulvovaginal Candidiasis: Two studies were conducted that compared 2% butacizone nitrate cream with clotrimazole tablets. There were 322 enrolled patients. 161 received 2.0% butacizone nitrate vaginal cream and 161 patients inserted the 500-mg clotrimazole vaginal tablet. At the second follow-up visit 30 days post-treatment, 129 patients (81%) in the butacizone nitrate group and 116 in the clotrimazole group were evaluable for efficacy analysis, respectively. All of these patients had infection caused by Candida albicans. The efficacy of the study drugs was assessed by evaluating clinical, mycologic and therapeutic cure rates, which are summarized in Table 1.

The therapeutic cure was defined as complete resolution of symptoms and signs of vulvovaginal candidiasis (vulvovaginal candidiasis) along with a negative KOH examination and negative culture for Candida spp. (microbiologic eradication) at the long term follow-up (360 days). The therapeutic cure rate was 67% in the butacizone group and 61% in the clotrimazole group.

Table 1
<table>
<thead>
<tr>
<th>Butacizone Nitrate Cream</th>
<th>Clotrimazole Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>161</td>
</tr>
<tr>
<td>Discontinued</td>
<td>100</td>
</tr>
<tr>
<td>Evaluated at 30 Days</td>
<td>95/118 (81%)</td>
</tr>
<tr>
<td>Cure Rate</td>
<td>93/116 (80%)</td>
</tr>
</tbody>
</table>

*Note: 87/117 (74%) and 77/116 (66%) were evaluated at 90 and 180 days, respectively.

Therapeutic Cure 79/116 (67%) 71/116 (61%)

C. albicans in the vaginal culture was proven at admission in all of these patients, 2% butacizone nitrate cream 500-mg clotrimazole vaginal tablet

WARNINGS
This cream contains mineral oil. Mineral oil may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragm. Therefore, use of these products within 72 hours following treatment with GYNAZOLE-1® Butacizone Nitrate Vaginal Cream USP, 2% is not recommended. Recurrent vaginitis infections, especially those that are difficult to eradicate, may be an early sign of infection with the human immunodeficiency virus (HIV) in women who are considered at risk for HIV infection.

PRECAUTIONS
General - It clinical symptoms persist, tests should be repeated to rule out other pathogens, to confirm the original diagnosis, and to rule out other conditions that may predispose a patient to recurrent vaginitis.

Carcinogenesis, Mutagenesis, Impairment of Fertility - Carcinogenesis - Long term studies in animals have not been performed to evaluate the carcinogenic potential of this drug. Mutagenicity - Butacizone nitrate was not mutagenic when tested in the Ames bacterial test, yeast, chromosomal aberration assay in CHO cells, CH0/HGPRT point mutation assay, mouse micronucleus, and rat dominant lethal assays.

Impairment of Fertility - No impairment of fertility was seen in rabbits or rats administered butacizone nitrate in oral doses up to 30 mg/kg/day (5 times the human dose based on mg/m²) or 100 mg/kg/day (10 times the human dose based on mg/kg), respectively.

Pregnancy: Pregnancy Category C - In pregnant rats administered 6 mg/kg/day of butacizone nitrate intravenously during the period of organogenesis, there was an increase in resorptions and stillbirths and a decrease in fetal size, however, no teratogenicity was noted. This dose represents a 130- to 253-fold margin of safety based on serum levels achieved in rats following intravenous administration of the drug levels achieved in humans following intravenous administration of the recommended therapeutic dose of butacizone nitrate.

Butacizone nitrate has no apparent adverse effect when administered orally to pregnant rats throughout organogenesis at doses levels up to 50 mg/kg/day (5 times the human dose based on mg/m²). Daily oral doses of 100, 300, and 750 mg/kg/day (10, 30, or 135 times the human dose based on mg/kg) resulted in fetal malformations (subtle limb defects, cleft palate). However, maternal stress was also evident at these higher dose levels. There were, however, no adverse effects on litter size of rats who received butacizone nitrate orally, even at maternally stressful dose levels (e.g., 150 mg/kg, 24 times the human dose based on mg/kg).

Butacizone nitrate, like other azole antifungal agents, causes dysuria in rats when treatment is extended through parturition. However, this effect was not apparent in rabbits treated with as much as 100 mg/kg/day orally (16 times the human dose based on mg/kg).

There are, however, no adequate and well-controlled studies in pregnant women. GYNAZOLE-1® Butacizone Nitrate Vaginal Cream USP, 2% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers - It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when butacizone nitrate is administered to a nursing woman.

Pediatric Use - Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Of the 314 patients treated with GYNAZOLE-1® Butacizone Nitrate Vaginal Cream USP, 2% for 1 day in controlled clinical trials, 18 patients (5.7%) reported complaints such as vulvar/vaginal burning, itching, soreness and swelling, pelvic or abdominal pain, or cramping, or a combination of two or more of these symptoms. In 3 patients (1%) these complaints were considered treatment-related. Five of the 18 patients reporting adverse events discontinued study because of them.

DOSAGE AND ADMINISTRATION
The recommended dose of GYNAZOLE-1® Butacizone Nitrate Vaginal Cream USP, 2% is 1 applicatorful of cream (approximately 5 g) inserted into the vagina at bedtime. This amount of cream contains approximately 100 mg of butacizone nitrate.

HOW SUPPLIED
GYNAZOLE-1® Butacizone Nitrate Vaginal Cream USP, 2% is available in containers containing one single-dose prefilled disposable applicator (NDC 45820-396-01).

Store at 25°C (77°F); excursions permitted to 15-25°C (59-77°F) [see USP definition of "room temperature". Avoid heat above 30°C (86°F).

Made in Israel
Manufactured by Perrigo
Veinle, Israel
Distributed by Perrigo

ABBOTT, KENILWORTH, N.J. 08821, USA
Rev 11-14
Using the GYNAZOLE-1® Butoconazole Nitrate Vaginal Cream USP, 2%
Prefilled Disposable Applicator

3 Easy Steps:

Step 1: Preparing the Applicator
Peel back the protective foil and remove the prefilled applicator. Applicator is designed to be used with tip in place. Do not remove tip; do not use applicator if tip has been removed.

Do not warm applicator before using. While holding the applicator firmly, pull the ring back to fully extend the plunger (see Figures 1 and 2).

Step 2: Inserting the Applicator
Gently insert the applicator into the vagina as far as it will comfortably go (see Figures 3A and 3B).

Step 3: Applying the Cream
Push the plunger to release the cream (see Figures 4A, 4B and 4C). Remove the empty applicator from the vagina and throw it away.

Important Instructions
• One prefilled applicator of GYNAZOLE-1® Butoconazole Nitrate Vaginal Cream USP, 2% should be administered.
• This cream contains mineral oil. Mineral oil may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms; therefore, use of such products within 72 hours following treatment with GYNAZOLE-1® Butoconazole Nitrate Vaginal Cream USP, 2% is not recommended.
• There are no adequate and well-controlled studies in pregnant women. GYNAZOLE-1® Butoconazole Nitrate Vaginal Cream USP, 2% should be used during pregnancy only under the supervision of a physician.

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