Bezafibrate is an off-white to white powder with a molecular weight of 546.48 and a molecular formula of C35H53O5. It is slightly soluble in water and slightly soluble in vegetable oil and ethanol. USP.

Targen® bezafibrate ( Bezafibrate) is a clear gel solution containing 1.0% (w/v) or 1.5% (w/v) bezafibrate in water. Targen® bezafibrate is a bis-ureido derivative distinct from that of niacin-like reductase inhibitors (FAR/tazarotene).

The molecular formula of Targen® bezafibrate is C35H53O5. It has the structural formula as follows:

Bezafibrate is a lipophilic drug that may potentially affect the degradation of bezafibrate. Concomitant gemfribrozil was associated with increased bezafibrate concentrations following oral administration of bezafibrate.

Clinical Studies Targen® bezafibrate was evaluated for the treatment of patients with early stage [IA-IIA CT1] in multiple, open-label, clinical trial programs as a Phase II program (dosage trials with different response criteria than the multivariate trial). These clinical trials enrolled a total of 117 patients. In the multivariate, open-label clinical trials, bezafibrate was evaluated for treatment in early stage breast cancer (IA-IIA CT1) for at least six months on at least two prior therapies. The study was conducted in Europe, and the trial enrolled a total of 50 patients; 46 of these patients were male, 80% Caucassian, and the median age was 64 years (range 30 to 87).

Targen® bezafibrate was also evaluated for the treatment of patients with recurrent primary breast cancer (malignant disease involving patients with stage IIA CT1). This program enrolled a total of 61 patients; 51% of the patients were male, 78% Caucassian, and the median age was 61 years (range 30 to 87).

In the multivariate, open-label clinical trial, considering prior systemic therapies and the patient's response to previous treatments, pazopanib was 19% of the patients (6). For the Phase I/II patients, the response rate was 0% (8). Two percent of patients’ (150) has a clinical complete response. The best response in the Complete Tumor Response Evaluation of bezafibrate (n=14) was 85 days (range: 30 to 87).

The risk of relapse in responding patients by the Complete Tumor Response Evaluation of bezafibrate was 21% (95% CI) over a median follow-up period of 6 months (range 56 to 95 days). Four patients developed clinically abnormal lymph nodes (2.1% of patients). One patient developed a cutaneous tumor (1.50%; 2%).

The Phase I-II program (dose-seeking trials with different response criteria than the multivariate trial) was supported of the multicenter study results.

INDICATIONS AND USAGE Targen® bezafibrate is indicated in patients with known hyperlipidemia to bezafibrate or other components of the bezafibrate family.

Pregnancy: Category X Targen® bezafibrate may cause fetal harm when administered to a pregnant woman. Targen® bezafibrate must not be given to a pregnant woman or a woman who intends to become pregnant, if a woman becomes pregnant while taking Targen® bezafibrate, Targen® bezafibrate must be stopped immediately and the woman given appropriate counseling.

Bezafibrate caused malformations when administered orally to pregnant rats during days 7-11 of gestation. Developmental abnormalities included incomplete ossification at 4 mg/kg/day and cholecalciferol, depressed eye bauxite/micrometaphyseal, and small ears at 20 mg/kg/day. In studies conducted at 10 mg/kg/day bezafibrate caused a decrease in fertility and early pregnancy loss.

Renal Insufficiency: No clinical trials have been conducted with Targen® bezafibrate in patients with renal insufficiency. In the study of bezafibrate's metabolism, there is in vitro evidence of existence of hepatic contribution to bezafibrate elimination, hepatic insufficiency may result in increased amounts of significantly decreased clearance (see PRECAUTIONS: Hepatic Insufficiency).

Dosage and Administration

No formal studies to evaluate drug interactions with bezafibrate, gemfibrozil, or other drugs used to treat hyperlipidemia. Some animal metabolites appear to be formed through cytochrome P450 3A4. Patients on concurrent therapy with drugs that induce cytochrome P450 3A4 may potentially affect the degradation of bezafibrate. Concomitant
Targetrin® (hexobaritone) 1% gel

Patient’s Instructions for Use

For Topical Use Only

To help you get the full benefits from this medicine, you should read this leaflet carefully and ask your doctor to explain anything you do not understand.

What are the most important things I should know about Targetrin® gel?

Do not use Targetrin® gel if you are pregnant or if you believe you are becoming pregnant.

Targetrin® gel may harm your fetus (unborn baby). You should contact your doctor immediately if you believe you are or suspect you are pregnant while you are using Targetrin® gel and until one month after you stop using Targetrin® gel.

If you are capable of becoming pregnant, you must have a pregnancy test, within one week before you start Targetrin® gel therapy and monthly while you are using Targetrin® gel, to confirm you are not pregnant.

You must use effective contraception (birth control) continuously starting one month before beginning treatment with Targetrin® gel until one month after you stop using Targetrin® gel. It is recommended that two reliable forms of contraception be used together.

If you are male and your partner is pregnant or capable of becoming pregnant, you should consult with your doctor the precautions you should take.

What is Targetrin® gel?

Targetrin (bar-GRET-in) gel contains hexobaritone (hexobaritone). Targetrin® gel belongs to a class of medicines known as retinoids.

What are the uses for Targetrin® gel?

This medicine is used to treat the skin problems arising from a disease called cutaneous T-cell lymphoma, or CTCL. Your health care provider has prescribed Targetrin® gel for the topical treatment of the cutaneous T-cell lymphomas (CTCL), or mycosis fungoides (MF), lesions (sometimes referred to as patches or plaques) on your skin. You must strictly instruct you on the proper use of Targetrin® gel. The following instructions will help you successfully begin and continue your treatment.

Do not use Targetrin® gel if you are allergic to this medicine.

Do not use Targetrin® gel if you are pregnant or believe you may be pregnant.

If you have any of the following conditions, make sure you have discussed them with your doctor before you start to take this medicine.

If you are breast feeding.

If you are allergic to retinoid medications (for example: Accutane®; [isotretinoin]; Sarotane® [acenocumarol]; Legran® [etretinate]; Visoren® [isotretinoin]).

When should you be extra careful while using Targetrin® gel?

Because vitamin A in large doses may cause some side effects which are similar to those seen in patients using a disposable Targetrin® gel, do not take more than the recommended daily dietary allowance of vitamin A (4000 to 5000 International Units). If you take vitamins, check the label to see how much vitamin A they contain. If you are not sure, ask your doctor or pharmacist.

Your skin may become more sensitive to sunlight while using this medicine. Minimize exposure to sunlight and do not use a suntan lamp.

WARNINGS

For adults only.

DO NOT apply the gel on or near mucosal surfaces of the body.

DO NOT apply the gel on or near mucosal surfaces of the body such as eyes, nostrils, mouth, lips, vagina, tip of the penis, rectum, or anus.

DO NOT use insect repellents containing DEET (N,N-diethyl-m-toluamide) or other products containing DEET while using Targetrin® gel.

Keep out of reach of children.

Product contains alcohol and should be kept away from open flame.

DO NOT use Targetrin® gel if you are pregnant or breastfeeding. Speak to your health care provider if you are not sure you do not need more information about possible side effects.

HOW TO APPLY

Apply a thin coat of gel to your CTCL lesions using a clean washed finger. Place a generous coating of gel over the entire lesion surface of each lesion. You should not apply gel to the healthy skin around the lesion. The extra effort you take in carefully applying the gel only to the area of the CTCL lesions will help to lessen any irritation or redness that may occur. Proper application should leave some gel visible on the surface of the lesion when you are finished with the application.

Immediately following application, wipe the finger(s) you have used to apply the gel with a disposable tissue and wash your hands using soap and water.

Allow five (5) to ten (10) minutes for the gel to dry before covering a treated area with clothing.

A mild non-deodorant soap is recommended when bathing or showering. If you apply Targetrin® gel after your shower or bath, you should wait 20 minutes before application.

WHEN TO APPLY

Targetrin® gel should be applied at an initial frequency of once every other day for the first week. The frequency of application should then be increased as tolerated at weekly intervals to once daily, twice daily, then three times daily, and finally four times daily. Your health care provider may instruct you to apply Targetrin® gel at a different frequency.

YOU SHOULD AVOID...

You should avoid applying Targetrin® gel to areas of healthy skin around a CTCL lesion. Exposure of healthy skin to Targetrin® gel may cause unnecessary irritation or redness.

You should avoid shaving, bathing, or swimming until at least three (3) hours after any application, if possible.

You should avoid covering the CTCL lesions treated with Targetrin® gel with any bandage or material other than the gel application.

You should avoid prolonging exposure of the treated area to sunlight or other ultraviolet (UV) light (such as tanning lamps).

You should avoid the use of other topical products on your treated CTCL lesions.

You should avoid scratching the treated areas.

WHAT SIDE EFFECTS DOES TARGETRIN® GEL HAVE?

When using Targetrin® gel, you may experience some local effects such as redness, itching, burning, irritation, and scaling at the application site. In clinical trials, the majority of these effects were mild or moderate, but some patients did experience more severe rash, itching, irritation, and inflammation. A few patients discontinued treatment due to these types of effects. Should these or other effects become troublesome to you, consult your health care provider. He or she can provide information on how to manage these effects.

All medications have side effects. You should call your physician regarding any questions or concerns you may have when using Targetrin® gel.

HOW QUICKLY CAN I EXPECT TARGETRIN® GEL TO WORK?

Be patient. Targetrin® gel takes time to work. In clinical trials, some patients began to respond as early as 4 weeks, but most patients did not experience their best response until 46 to 62 weeks of treatment. Do not stop treatment at the first sign of improvement. You should Continue to use Targetrin® gel as instructed by your health care provider.

OTHER INFORMATION

The opening of the Targetrin® gel tube is covered by a metal safety seal. If this seal has been punctured or is not visible when you first open the package, DO NOT USE this tube and promptly return the product to your pharmacy or place of purchase.

To open, use the pointed portion of the cap to puncture the metal safety seal. Always use the cap to close the tube lightly after each use.

Store at room temperature. Keep away from heat or flame.

The gel should not be used after the expiration date printed on the tube.

Keep this medicine out of the reach and sight of children.

IF YOU HAVE QUESTIONS…

If you have any questions about your treatment, talk with your health care provider.

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Table 1. Incidence of All Adverse Events and Application Site Adverse Events with Incidence ≥5% for All Application Formulations of Targetrin® gel in Multicenter CTCL Study

<table>
<thead>
<tr>
<th>All Adverse Events</th>
<th>Application Site Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>COSTART 5</td>
<td>Body System/PREFERRED Term</td>
</tr>
<tr>
<td>N = 50</td>
<td>N = 50</td>
</tr>
<tr>
<td>h (%)</td>
<td>h (%)</td>
</tr>
</tbody>
</table>

Skin and Appendages

Contact dermatitis* | 7 (14) |
| 4 (8) |

Exfoliative dermatitis* | 3 (6) |

Pruritus | 14 (28) |
| 9 (18) |

Rash* | 36 (72) |
| 28 (56) |

Maculopapular rash | 3 (6) |

Skin Disorder (NOS)* | 13 (26) |
| 9 (18) |

Sweating | 5 (10) |

Body as a Whole

Asthma | 3 (6) |

Headache | 7 (14) |

Infection | 9 (18) |

Pain | 15 (30) |
| 9 (18) |

Cardiovascular System

Dizziness | 5 (10) |

Peripheral Edema | 3 (6) |

Hemic and Lymphatic System

Leukopenia | 3 (6) |

Lymphocytopenia | 3 (6) |

WBC Abnormal | 3 (6) |

Metabolic and Nutritional System

Hypertriglyceridemia | 5 (10) |

Nervous System

Paresthesia | 3 (6) |

Psychiatric | 3 (6) |

Respiratory System

Cough Increased | 3 (6) |

Pharyngitis | 3 (6) |

* Regardless of association with treatment

Includes Investigator terms such as:

1. Contact dermatitis, irritant contact dermatitis, irritant dermatitis
2. Pruritus, itching, itching of face
3. Edema, swelling, irritation, redness, rash, dermatitis

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