Application Number 50-769

FINAL PRINTED LABELING
Benzamycin® Pak (erythromycin 3% benzoyl peroxide 5% topical gel)

For Dermatological Use Only – Not for Ophthalmic Use

DESCRIPTION
Benzamycin® Pak contains erythromycin [3S,4S]-6,7-dihydroxy-8-[(4S)-4-methyl-3-oxo-3-oxo-2-(4-ethyl-5-methyl-1H-imidazol-2-yl)-1-benzopyran-2-yl]methyl (44-ethyl-7,12,13-hydroxybenzyl)-3,5,7,9,13,13-a-tetra-methyldiene-3,6-diphenyl-2,6-dioxo-3,6-dihydro-4H-pyran-4-one. Erythromycin is a macrolide antibiotic isolated from a strain of Saccharopolyspora erythraea (formerly Streptomyces erythreus). It is a basic and readily forms salts with acids.

Chemically, erythromycin is (C_{93}H_{122}N_{2}O_{14}). It has the following structural formula:

![Erythromycin Structure](image)

Erythromycin has the molecular weight of 733.94. It is a white crystalline powder and has a solubility of approximately 1 mg/ml in water and is soluble in alcohol at 25°C.

Benzamycin® Pak also contains benzoyl peroxide for topical use. Benzoyl peroxide is an oxidizing agent demonstrating antimicrobial activity.

Chemically, benzoyl peroxide is (C_{9}H_{8}O_{4}). It has the following structural formula:

![Benzoyl Peroxide Structure](image)

Benzoyl peroxide has the molecular weight of 242.23. It is a white granular powder and is sparingly soluble in water and absolutely insoluble in acetone, chloroform, and ether.

Each gram of product contains 30 mg of erythromycin and 30 mg of benzoyl peroxide in a base of 50% Alcohol-40% purified water, hydroxypropyl cellulose, carboxymethyl cellulose, sodium hydroxide, diacetate sodium sulfate sodium chloride 75%. Each Benzamycin® Pak contains 0.8 grams of oil product.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoyl peroxide. A single dose pharmacokinetic study involving the application of either one or three units of Benzamycin® Pak, was performed in 16 adult acne patients to determine systemic absorption of erythromycin. Erythromycin (with a plasma lower limit of quantification of 2 ng/ml) was not detectable, except in one patient who was in the one unit application group.

Pharmacodynamics: The exact mechanism by which erythromycin and benzoyl peroxide reduce lesions of acne vulgaris is not fully known.

CLINICAL STUDIES

In two adequate and well controlled clinical studies 228 patients used Benzamycin® Pak. 113 patients used the currently marketed Benzamycin® topical gel, and 115 patients used vehicle. Benzamycin® Pak applied twice daily for 3 weeks was significantly more effective than vehicle and comparable to Benzamycin® Topical Gel in the treatment of moderate to moderately severe facial acne vulgaris. Patients enrolling in the studies had a minimum of 15 and a maximum of 50 facial inflammatory lesions (papules and pustules) and a minimum of 20 and a maximum of 50 facial non-inflammatory lesions (erosions and closed comedones). The primary efficacy measures evaluated at week 6 were the lesion counts and the investigator's global assessment.

Patients were instructed to wash their face twice daily (morning and evening) with warm water and a mild cleanser provided by sponsor. No abrasive cloths or sponges, alcoholic toners, astringents or medicated solutions were used. The medication was to be applied 15 minutes after washing in a thin film over the entire facial area. A moisturizer (supplied by the sponsor) or non-medicated make-up could be applied one hour after application, as needed. All medications were to be kept away from the eye. Sun exposure to the face was to be limited.

Outcomes for mean percent reductions in lesion counts and investigators global assessment after 6 weeks of treatment are shown below:

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Benzamycin® Topical Gel</th>
<th>Benzamycin® Pak</th>
<th>Benzamycin® Pak Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 119</td>
<td>N = 113</td>
<td>N = 115</td>
<td></td>
</tr>
<tr>
<td>Mean % Lesion Counts Reduction</td>
<td>48%</td>
<td>45%</td>
<td>17%</td>
</tr>
<tr>
<td>Inflammatory*</td>
<td>48%</td>
<td>45%</td>
<td>17%</td>
</tr>
<tr>
<td>Non Inflammatory*</td>
<td>48%</td>
<td>45%</td>
<td>17%</td>
</tr>
<tr>
<td>Total*</td>
<td>48%</td>
<td>45%</td>
<td>17%</td>
</tr>
<tr>
<td>Investigator’s Global</td>
<td>48%</td>
<td>45%</td>
<td>17%</td>
</tr>
<tr>
<td>Global Success*</td>
<td>28%</td>
<td>27%</td>
<td>3%</td>
</tr>
</tbody>
</table>

* p-value < 0.05 for the comparison between Benzamycin® Pak and Benzamycin® Pak vehicle

<table>
<thead>
<tr>
<th>Study 2</th>
<th>Benzamycin® Pak</th>
<th>Benzamycin® Pak Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 119</td>
<td>N = 115</td>
<td></td>
</tr>
<tr>
<td>Mean % Lesion Counts Reduction</td>
<td>57%</td>
<td>34%</td>
</tr>
<tr>
<td>Inflammatory*</td>
<td>36%</td>
<td>30%</td>
</tr>
<tr>
<td>Non Inflammatory</td>
<td>45%</td>
<td>31%</td>
</tr>
<tr>
<td>Total*</td>
<td>57%</td>
<td>34%</td>
</tr>
<tr>
<td>Investigator’s Global</td>
<td>36%</td>
<td>12%</td>
</tr>
</tbody>
</table>

* p-value < 0.05

MISCELLANEOUS

Erythromycin acts by inhibition of protein synthesis in susceptible organisms by reversible binding to 50 S ribosomal subunits, thereby inhibiting translation of aminoacyl transfer-RNA and inhibiting polypeptide synthesis. Antagonism has been demonstrated in vitro between erythromycin, lincomycin, clindamycin and clindamycin.

Benzoyl peroxide has been shown to be effective in vitro against Propionibacterium acne, an anaerobe found in sebaceous follicles and comedones. Benzoyl peroxide is believed to act by releasing active oxygen.

* p-value < 0.05
INDICATIONS AND USAGE
Dexpramipexole is indicated for the treatment of primary hemochromatosis.

CONTRAINDICATIONS
Dexpramipexole is contraindicated in the following conditions:

- Hypersensitivity to dexpramipexole

PRECAUTIONS
General: The use of chelating agents and other iron chelating agents should be avoided in patients with severe liver disease, as these agents may exacerbate liver disease.

- Hepatotoxicity: Patients with liver disease may experience worsening of liver function tests, including increased liver enzymes and bilirubin levels. Close monitoring of liver function tests is recommended.

- Hematologic effects: Patients may experience hematologic side effects, such as anemia, neutropenia, and thrombocytopenia. Close monitoring of hematologic parameters is recommended.

- Nephrotoxicity: Patients may experience renal impairment, including azotemia and hyperkalemia. Close monitoring of renal function tests is recommended.

- Gastrointestinal effects: Patients may experience gastrointestinal side effects, such as nausea, vomiting, and diarrhea. Close monitoring of these parameters is recommended.

- Endocrine effects: Patients may experience endocrine side effects, such as hypothyroidism and hyperparathyroidism. Close monitoring of these parameters is recommended.

- Cardiac effects: Patients may experience cardiac side effects, such as congestive heart failure and atrial fibrillation. Close monitoring of cardiac function tests is recommended.

- Allergic reactions: Patients may experience allergic reactions, including anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Close monitoring of these parameters is recommended.

- Interactions: Dexpramipexole may interact with other medications, including warfarin, digoxin, and corticosteroids. Close monitoring of these parameters is recommended.

INFO FOR PATIENTS
Avoid exposure to sunlight or ultraviolet light, as this may worsen skin reactions. Avoid use of sunscreens and protective clothing to minimize photosensitivity.

Adverse Reactions:
Nausea, vomiting, diarrhea, abdominal pain, and flatulence are common gastrointestinal side effects. Patients should be advised to eat small, frequent meals and to avoid spicy or fatty foods. In addition, patients should be advised to consult their healthcare provider if they experience severe or persistent nausea, vomiting, or diarrhea.

HOW SUPPLIED
Dexpramipexole is supplied as 500 mg and 1000 mg tablets. Each tablet contains 500 mg or 1000 mg of dexpramipexole. The tablets are available in bottles of 100 and 500 tablets.

Dexpramipexole tablets are formulated to be taken with meals to minimize gastrointestinal side effects. The tablets should be swallowed whole and should not be broken, crushed, or chewed.

Prescribing Information:
Dexpramipexole tablets should be taken with meals to minimize gastrointestinal side effects. The tablets should be swallowed whole and should not be broken, crushed, or chewed. The tablets should be stored at room temperature (15°C to 30°C) and protected from moisture. The tablets should be dispensed in a well-closed container.

HOW SUPPLIED
The tablets should be taken once daily, preferably with a meal, and should be swallowed whole. The tablets should be stored at room temperature (15°C to 30°C) and protected from moisture. The tablets should be dispensed in a well-closed container.