PRODUCT MONOGRAPH

Taro-Clindamycin

Clindamycin Phosphate Topical Solution USP

1%

Antibiotic

Taro Pharmaceuticals Inc.  Preparation Date:
130 East Drive  April 11, 2005
Brampton, Ontario, L6T 1C1

Control # 092055
PRODUCT MONOGRAPH

Taro-Clindamycin

Clindamycin Phosphate Topical Solution USP

1%

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTIONS

Clindamycin phosphate is inactive in vitro but in vivo hydrolysis converts this compound to the antibacterially active clindamycin. Clindamycin has been shown to have in vitro activity against isolates of Propionibacterium acnes which may account for its usefulness in acne. Clindamycin activity has been demonstrated in serum, urine and in comedonal extracts from acne patients.

The mean concentration of antibiotic activity in extracted comedones after application of clindamycin phosphate for 4 weeks was 597 µg/gram of comedonal material (range 60-1490). Clindamycin in vitro inhibits Propionibacterium acnes cultures tested.

INDICATIONS AND CLINICAL USE

Taro-Clindamycin 1% (clindamycin phosphate) is indicated for the treatment of acne vulgaris.
CONTRAINDICATIONS

Taro-Clindamycin 1% (clindamycin phosphate) is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis. Safety in pregnancy has not been established.

WARNINGS

As with most antibiotics, oral and parenteral clindamycin have been associated with severe diarrhea and pseudomembranous colitis. Diarrhea and colitis including pseudomembranous colitis have been reported infrequently with clindamycin phosphate. Symptoms can occur after a few days, weeks or months following initiation of clindamycin therapy. They have also been observed to begin up to several weeks after cessation of therapy with clindamycin. Therefore, the physician should be alert to the possible development of antibiotic-associated diarrhea or colitis. If significant or prolonged diarrhea occurs, the drug should be discontinued.

Studies indicate that a toxin produced by Clostridium difficile is the major cause of antibiotic-associated colitis which is characterized by severe persistent diarrhea, severe abdominal cramps and in some cases with passage of blood and mucus in the stool. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for C. difficile and assay for C. difficile toxin may be helpful diagnostically,

Mild cases of colitis may respond to simple drug discontinuance. Vancomycin is effective in the treatment of antibiotic-associated colitis produced by C. difficile. The usual dose is 125 mg to 500 mg orally, every 6 to 8 hours for 7 -10 days. Additional supportive medical care may be necessary.

Cholestyramine and colestipol resins have been shown to bind C. difficile toxin in vitro and cholestyramine has been effective in the treatment of some mild cases of antibiotic-associated
colitis. Cholestyramine resins have been shown to bind vancomycin; therefore, when both cholestyramine and vancomycin are used concurrently, their administration should be separated by at least two hours.

Anticholinergics and antiperistaltic agents may worsen colitis.

**PRECAUTIONS**

Taro-Clindamycin 1% (clindamycin phosphate) contains an alcohol base which will cause burning and irritation of the eye. In the event of accidental contact with sensitive surfaces (eye, abraded skin, mucous membranes), bathe with copious amounts of cool tap water.

The solution has an unpleasant taste and caution should be exercised when applying medication around the mouth.

Taro-Clindamycin 1% (clindamycin phosphate) should be prescribed with caution in atopic individuals.

**Use in Pregnancy:**
Safety for use in pregnancy has not been established.

**Use by Nursing Mothers:**
It is not known whether Taro-Clindamycin 1% (clindamycin phosphate) when topically applied is excreted in human milk. However, oral and parenteral clindamycin have been reported to appear in breast milk and therefore nursing should not be undertaken while a patient is on the drug.
ADVERSE REACTIONS

In a large U.S. postmarketing surveillance study among 1298 patients treated only with topical clindamycin phosphate solution, skin dryness/irritation, diarrhea or gastrointestinal symptoms were the most commonly reported medical events. Of those, 258 (19.9%) reported one or more of the following dermatological events. Among patients treated with oral antibiotics only, or no antibiotics, the percentage of patients reporting dermatologic event(s) was 20.8% and 25.4% respectively.

<table>
<thead>
<tr>
<th>Dermatological Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry skin</td>
</tr>
<tr>
<td>Acne worse</td>
</tr>
<tr>
<td>Rash/redness</td>
</tr>
<tr>
<td>Peeling</td>
</tr>
<tr>
<td>Discolouration</td>
</tr>
<tr>
<td>Irritation</td>
</tr>
<tr>
<td>Itching</td>
</tr>
<tr>
<td>New Acne</td>
</tr>
<tr>
<td>Sunburn</td>
</tr>
<tr>
<td>Contact Dermatitis</td>
</tr>
</tbody>
</table>

The following new gastrointestinal problems were reported in this surveillance study by 18.7% of the Clindamycin phosphate treated patients, 22.9% of the oral antibiotic treated patients, and 18.4% of the patients with no antibiotic exposure.

<table>
<thead>
<tr>
<th>Gastrointestinal Event</th>
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</thead>
<tbody>
<tr>
<td>Abdominal Pain/cramps</td>
</tr>
<tr>
<td>&quot;Nervous&quot; stomach</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Ulcers</td>
</tr>
<tr>
<td>Flu/Virus</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Indigestion</td>
</tr>
<tr>
<td>Colon problems</td>
</tr>
<tr>
<td>Gas/Bloating</td>
</tr>
<tr>
<td>(not colitis)</td>
</tr>
</tbody>
</table>

Cases of diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with topical formulations of clindamycin. Diarrhea was reported by 55 of the 1298 (5%) Clindamycin phosphate patients, compared to 3.9% of control patients.
In addition to the above, the following side effects have also been occasionally reported during drug treatment with Clindamycin phosphate: oily skin, and gram-negative folliculitis.

**DOSAGE AND ADMINISTRATION**

Apply a thin film of Taro-Clindamycin 1% (clindamycin phosphate) twice daily to the clean and dry skin in the area to be treated. Patients responding to Taro-Clindamycin 1% (clindamycin phosphate) should show improvement in 8 weeks. Treatment beyond 12 weeks may call for evaluation by the physician.
PHARMACEUTICAL INFORMATION

**Drug Substance:**

**Proper Name:** Clindamycin phosphate

**Chemical name:** (1) L-threo-α-D-galacto-Octopyranoside, methyl
7-chloro-6,7,8-trideoxy-6-[(1-methyl-4-propyl-L-2-pyrrolidinyl)carbonyl]
amino]-1-thio-2-(dihydrogen phosphate), (2,S-trans);

(2) Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-
pyrrolidinecarboxamido)-1-thio- L-threo- α -D-galacto- octopyranoside
2-(dihydrogen phosphate);

(3) 7 -(S)-Chloro- 7 -deoxylincomycin 2-phosphate.

**Structural formula:**

**Molecular Formula:** $C_{18}H_{34}ClN_2O_8PS$

**Molecular Weight:** 504.96

**Description:** Clindamycin phosphate is a water soluble ester of clindamycin and phosphoric acid. The intact ester is essentially inactive as an antibacterial agent. Chemical or
enzymatic hydrolysis of clindamycin phosphate is necessary to obtain the antibiotic activity of the clindamycin base.

Clindamycin phosphate is a white to off-white, hygroscopic, crystalline powder which melts at about 175°C with decomposition. It has two acidic protons with $pK_1 = 0.964$ and $pK_2 = 6.081$. The partition co-efficient is 0.03. The pH of a solution of 10 mg/mL in water is between 3.5 and 4.5.

**Composition:** Each ml contains clindamycin phosphate equivalent to 10 mg clindamycin. The solution also contains isopropyl alcohol 50% v/v, propylene glycol and purified water. When needed, the pH of the solution is adjusted with sodium hydroxide.

**Stability and Storage Recommendations:** Store at controlled room temperature (15°C-30°C)

**AVAILABILITY OF DOSAGE FORMS**

Taro-Clindamycin 1% is available in 30 and 60 mL bottles. A dab-o-matic applicator and cap is provided external to each bottle for placement into the bottle.

To assist the patient, the pharmacist may assemble the bottle upon dispensing as follows:
1) remove cap from bottle and discard,
2) firmly press applicator into bottle,
3) seal firmly by tightening domed-cap.
INFORMATION FOR THE CONSUMER

Taro-Clindamycin 1%
(clindamycin phosphate topical solution USP)

Taro-Clindamycin 1% (clindamycin phosphate) belongs to the family of antibiotics. When applied to the skin in a solution it helps to control acne (pimples commonly seen in teenagers and young adults). This medicine is available on a doctor's prescription only. With any questions concerning this medicine consult your doctor, or pharmacist.

Proper Use of this Medicine

Before applying this medicine, the area to be treated should be washed thoroughly but gently with warm water and bland soap, rinsed well and patted dry. Unless skin is oily, washing 2 or 3 times a day is enough. The face should not be washed for at least two hours after applying this medicine.

The medicine should be used for the full time of treatment recommended by your doctor even if the symptoms clear up after a few days. If the medicine is stopped too soon, the symptoms may return.

After shaving, it is best to wait 30 minutes before applying the medicine because the alcohol in it may irritate freshly shaven skin.

The medicine comes in a bottle with a separate applicator and cap. To use the applicator: 1) remove cap from bottle and discard, 2) firmly press applicator into bottle, 3) seal firmly by tightening domed-cap.

The pharmacist may have assembled the bottle for you, in which case the applicator top will already be attached to the bottle. The applicator top may then be used to apply the medicine directly to the
skin. The bottle should be tilted and pressed firmly against the skin using a dabbing rather than a rolling motion. Reducing the pressure will decrease the flow.

A thin film of the medicine is to be applied to the whole area affected by acne, not just to the pimples themselves.

In order to prevent this medicine from getting in the eyes, nose, or mouth, it should be spread away from these areas on application. If the medicine does get in the eyes, they must be washed out immediately but carefully using large amounts of cool tap water. If the eyes still burn or are painful, a doctor should be consulted.

This medicine should not be used more often than prescribed by your doctor because it may cause dryness or irritation of the skin.

The bottle contains approximately a 4 week (30 mL size) or an 8 week supply (60 mL).

**How to Store this Medicine**
Keep out of the reach of children.
Store away from heat and direct light.
Keep medicine from freezing.
Store the bottle in an upright fashion.

**Precautions While Using this Medicine**
Taro-Clindamycin 1% (clindamycin phosphate) should not be used by individuals with a history of hypersensitivity (allergies) to preparations containing clindamycin or lincomycin. If you experience stomach upset, nausea or diarrhea while using Taro-Clindamycin 1%, check with your doctor.

Safety in pregnancy has not been established.
This medicine may cause the skin to become unusually dry even with normal use. If this occurs check with your doctor.

If frequent diarrhea occurs it should not be treated without first checking with your doctor.

**Use in Pregnancy:**
Safety for use in pregnancy has not been established. If you are pregnant (or become pregnant), check with your doctor before using Taro-Clindamycin 1% (clindamycin phosphate).

**Use by Nursing Mothers:**
It is not known whether Taro-Clindamycin 1% (clindamycin phosphate) when topically applied is excreted in breast milk. If you are currently nursing (or planning on nursing), check with your doctor before using Taro-Clindamycin 1% (clindamycin phosphate).

**Side effects of this Medicine**
Check with your doctor immediately if any of the following very rare side effects occur:
- Abdominal or stomach cramps, pain or bloating is severe
- Diarrhea (watery and severe) which may also be bloody
- Nausea or vomiting

Also check with your doctor as soon as possible if any of the following side effects occur: Skin rash, itching, redness or other signs or irritation not present before using this medicine.

Other side effects that do not normally require medical attention may occur. These include the following:
- Dry or scaly skin
- Peeling of skin
- Stinging or burning feeling

If any other unusual or unexpected effects occur, check with your doctor.
PHARMACOLOGY AND TOXICOLOGY

Human Studies
In vitro studies using human skin from leg amputations indicated that approximately 5 to 10% of a single application of 1% 3H-clindamycin solution penetrated the epidermis. Twice daily applications increased the total amount of clindamycin penetrating the skin but three times a day applications did not.

Clindamycin plasma concentrations were detectable (≥0.5 ng/mL) in 5 of 6 patients when 1% clindamycin phosphate was applied to approximately 300 cm² of the face every 12 hours for 6 doses. Peak concentrations in plasma ranged from a to 3.0 ng/mL which represent levels 1000 times lower than peak levels after 600 mg clindamycin phosphate given intravenously or 300 mg of clindamycin hydrochloride given orally.

Clindamycin phosphate was detected in the urine of all 6 patients in amounts from less than 1 ng/mL to 53 ng/mL. Since the total cumulative dose of clindamycin phosphate applied to the skin was 60 mg, the percent of dose recovered in the urine was 0.156% (range 0.08 to 0.34%).

The penetration of clindamycin into comedones has been demonstrated. When 9 patients were treated with topical 1% clindamycin phosphate twice daily for 16 weeks, all patients had one or more comedones containing clindamycin bioactivity. In addition, quantitative cultures of acne comedones were performed on 5 clindamycin and 8 vehicle-treated patients. Clindamycin produced significantly reduced P. acnes colony counts at weeks 6, 12 and 14. Thirty-five P. acnes isolates from the clindamycin-treated patients were tested for their clindamycin susceptibility. No stepwise increases in MIC were encountered in specimens collected over the observation period (16 weeks treatment, 12 weeks post-treatment). The largest MIC observed was 0.39 µg/mL.

Four patients treated with topical clindamycin phosphate developed resistant strains of Staphylococcus aureus and enterococci during treatment. Two thirds of these strains had disappeared
8 weeks after treatment. All strains of Propionibacteria acnes were sensitive to clindamycin and remained so through an 8 week treatment period.

There were no changes in the colonic flora when patients received topical clindamycin phosphate treatment. No increased resistance to clindamycin was detected in the colon.

A comparative irritancy study showed retinoic acid most irritating, followed by 1% clindamycin hydrochloride and benzoyl peroxide. No irritancy was found for clindamycin phosphate or a 3% sulfur cream.

An evaluation for potential to cause allergic contact dermatitis was performed in 102 patients using 1% and 3% clindamycin phosphate. On rechallenge all were negative.

Clindamycin phosphate 1% solution was tested for sensitization potential by the Draize test with the addition of ultraviolet irradiation. No evidence of photoallergic or allergic contact sensitization was found in any subject.

**Animal Studies**

A 1% solution of clindamycin phosphate was applied once a day and a 3% solution was applied three times a day to rats for 21 days. No inflammation, hyperplasia, parakeratosis, hemorrhage or edema was noted in the treated area of the skin. In the 3% solution study, females grew in weight slightly more, had slightly lower leukocyte and heterophil counts, and had a lower proportion of liver: body weight (21 day) when compared to control animals. Bioactivity was present in serum immediately after last application in the 1% and 3% studies, however in the 3% study, bioactivity was present in the skin, urine and trace amounts in the long bones 5 days after the last application. There was no difference in absorption between animals with intact or abraded skin.

A 1% clindamycin hydrochloride topical solution was applied daily to dogs for 21 days. There was no skin damage and no evidence of absorption in the dog.
A 3% clindamycin hydrochloride solution was applied three-times-a-day to pigs for 21 days. There was no skin irritation and five days post-therapy, there was residual bioactivity present in the treated skin, which was largely confined to the epidermis.

**Ocular Application**
Rats were administered 1% clindamycin hydrochloride or phosphate formulations to the eyes for 20 days. There was no evidence of ocular irritation or inflammation. A single administration of 1% clindamycin hydrochloride to the eyes of rabbit produced mild to moderate irritation similar to that for the vehicle control.
REFERENCES

8) Puhvel SM. Effects of treatment with erythromycin 1.5% topical solution or clindamycin phosphate 1% topical solution on P. acnes counts and free fatty acid levels. Cutis 1983;31:339-42.
10) Product Monograph for Dalacin® T Topical Solution, September 24, 2003, Pfizer Canada Inc.