

FDA Issues Conflict of Interest Rules for Advisers

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Experts serving on the Food and Drug Administration's advisory committees are now subject to new rules aimed at ensuring that they do not have conflicts of interest that could bias their decisions.

In early August, the FDA issued four final guidance documents and a draft guidance outlining how it plans to handle con-

licts of interest among members of advisory committees, which review the safety and efficacy of drugs, medical devices, diagnostic tests, and other products and ingredients that the agency regulates.

In a separate move, the agency said that it plans to make it easier to find documents before and after advisory committee meetings by improving how it posts meeting information on its Web site.

Guidance documents represent the agency's current thinking on a topic, but

carry less weight than does a regulation. The FDA has no power to enforce guidance documents, which manufacturers and the agency generally use as rules of thumb.

The newest guidance documents will help ensure that the FDA "is getting the highest quality scientific advice, while at the same time preserving public trust in our decisions," Randall Lutter, Ph.D., the FDA's deputy commissioner for policy, said in a teleconference briefing with reporters.

In the past, the agency has asked advis-

ers to disclose potential conflicts of interest, but there was no monetary limit. Each potential conflict was weighed individually, and waivers were granted based on whether the adviser's expertise was considered necessary for a particular meeting.

With the new guidance, the agency sets a dollar limit on advisers' financial interests. If an adviser—or his or her spouse or minor child—has interests of at least \$50,000 in an entity that would be directly or indirectly affected by the outcome of a particular meeting, the adviser would be barred from participating. Advisers with interests less than \$50,000 will be allowed to participate and vote, unless they are found to have a significant conflict of interest.

An advocate who has been critical of the FDA's conflict of interest policy for advisers said that the \$50,000 cap is too high.

"The FDA wants us to believe that an advisory committee member can receive \$49,999 from a company and still make an

unbiased decision. I don't buy it and the research doesn't support it," said Diana Zuckerman, Ph.D., president of the National Research Center for Women and Families, an advocacy organization in Washington.

Advisers would be barred from participating in a meeting if they had interests of at least \$50,000 in an entity that would be affected by the outcome of the meeting.

She and another agency critic, Dr. Sidney Wolfe, director of Public Citizen's Health Research Group, both expressed concern that the new guidance would still allow advisers with conflicts to vote. Those advisers will be granted waivers if they are determined to provide essential expertise. This is not much of a change from current policy, according to Dr. Wolfe and Dr. Zuckerman.

But the FDA said that the Food and Drug Administration Amendments Act of 2007, which was signed into law last year, limits the number of waivers it is allowed to grant.

In another guidance, the agency said that it will require simultaneous voting by all committee members. Advisers at some meetings have begun using an electronic voting system to ensure that panel members don't influence the votes of those who succeed them in voting; the votes are conducted privately, and then broadcast immediately afterward on a screen. Dr. Wolfe said that when he has seen the voting system in action, "it worked well and served the stated purpose."

He also praised the agency's proposed guidance to set out a more definitive policy on when a product should be referred to an advisory committee for review.

The FDA also is changing the administrative process for advisory committee meetings. The agency will formally notify a sponsoring company 55 days in advance that a meeting has been scheduled. Also, the FDA will post materials relating to the meeting on its Web site no later than 2 full days in advance of the meeting. ■

ClindaReach™

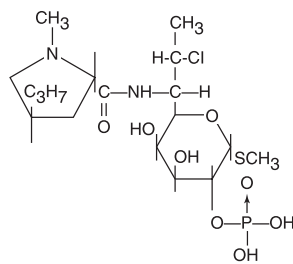
(Clindamycin Phosphate Topical Solution USP, 1%) Pledgets
For External Use Only

DESCRIPTION

ClindaReach™ (Clindamycin Phosphate Topical Solution USP, 1%), Pledgets (ClindaReach™) contain clindamycin phosphate, USP at a concentration equivalent to 10 mg clindamycin per milliliter. Each ClindaReach™ pledget applicator contains approximately 1 mL of topical solution.

Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

The solution contains isopropyl alcohol 50% v/v, propylene glycol, sodium hydroxide (to adjust the pH to between 4.0–7.0) and purified water. The structural formula is represented below:



The chemical name for clindamycin phosphate is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-4-propyl-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galactooctopyranoside 2- (dihydrogen phosphate). It has a molecular weight of 504.96, and the molecular formula is C₁₈H₃₄ClN₂O₈PS. Flash point 75°F.

CLINICAL PHARMACOLOGY

Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

Following multiple topical applications of clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per mL in an isopropyl alcohol and water solution, very low levels of clindamycin are present in the serum (0-3 ng/mL) and less than 0.2% of the dose is recovered in urine as clindamycin.

Clindamycin activity has been demonstrated in comedones from acne patients. The mean concentration of antibiotic activity in extracted comedones after application of Clindamycin Phosphate Topical Solution for 4 weeks was 597 mcg/g of comedonal material (range 0-1490). Clindamycin *in vitro* inhibits all *Propionibacterium acnes* cultures tested (MICs 0.4 mcg/mL). Free fatty acids on the skin surface have been decreased from approximately 14% to 2% following application of clindamycin.

INDICATIONS AND USAGE

ClindaReach™ is indicated in the treatment of acne vulgaris. In view of the potential for diarrhea, bloody diarrhea and pseudomembranous colitis, the physician should consider whether other agents are more appropriate. (See CONTRAINDICATIONS, WARNINGS and ADVERSE REACTIONS.)

CONTRAINDICATIONS

ClindaReach™ 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.

WARNINGS

Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin.

Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea.

Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 milligrams to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parenteral therapy with clindamycin.

PRECAUTIONS

General

ClindaReach™ contains an alcohol base that 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.

ClindaReach™ should be prescribed with caution in atopic individuals.

Drug Interactions

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore it should be used with caution in patients receiving such agents.

Pregnancy: Teratogenic Effects—Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin ranging from 100 to 600 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to clindamycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of ClindaReach™. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients under the age of 12 have not been established.

ADVERSE REACTIONS

In 18 clinical studies of various formulations of topical Clindamycin Phosphate using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events [see table below].

Treatment Emergent Adverse Event	Number of Patients Reporting Events		
	Solution n=553 (%)	Gel n=148 (%)	Lotion n=160 (%)
Burning	62 (11)	15 (10)	17 (11)
Itching	36 (7)	15 (10)	17 (11)
Burning/Itching	60 (11)	# (—)	# (—)
Dryness	105 (19)	34 (23)	29 (18)
Erythema	86 (16)	10 (7)	22 (14)
Oiliness/Oily Skin	8 (1)	26 (18)	12* (10)
Peeling	61 (11)	# (—)	11 (7)

not recorded

* of 126 subjects

Orally and parenterally administered clindamycin has been associated with severe colitis which may end fatally.

Cases of diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulations of clindamycin and rarely with topical clindamycin (see WARNINGS).

Abdominal pain and gastrointestinal disturbances as well as gram-negative folliculitis have also been reported in association with the use of topical formulations of clindamycin.

OVERDOSAGE

Topically applied ClindaReach™ can be absorbed in sufficient amounts to produce systemic effects. (See WARNINGS.)

DOSAGE AND ADMINISTRATION

Apply a thin film of ClindaReach™ twice daily to affected area. More than one pledget may be used. Each pledget should be used only once and then be discarded.

Pledget: Remove pledget from jar just before use. Do not use if the seal under the cap is broken. Discard after single use.

Keep all liquid dosage forms in containers tightly closed.

HOW SUPPLIED

ClindaReach™ Pledgets contain Clindamycin Phosphate Topical Solution. The solution contains Clindamycin Phosphate equivalent to 10 mg clindamycin per milliliter.

ClindaReach™ is supplied as 120 single use pledgets, packaged as two jars of 60 single use pledgets each.

Store at controlled room temperature 15° to 30°C (59° to 86°F) [See USP]. Protect from freezing. Flash Point 75°F.

R only

Manufactured for: Sirius Laboratories, a wholly owned subsidiary of DUSA Pharmaceuticals, Inc., 25 Upton Dr, Wilmington, MA 01887

DUSA®

Manufactured by:
PERRIGO, Bronx, NY 10457
Patent pending

MKT-1402 Rev A