

FDA, European Agencies Extend Cooperation Pact

BY JONATHAN GARDNER
Contributing Writer

Drug regulators in the United States and Europe have announced "intensified" information sharing and dialogue aimed at increasing cooperation in drug approval and surveillance activities in the world's two largest pharmaceutical markets.

At a March review meeting in Brussels, representatives from the Food and Drug

Administration, the European Medicines Agency, and the European Commission judged as a success the implementation of a confidentiality agreement that has enabled greater transatlantic information sharing and dialogue on pharmaceutical regulations protecting 753 million people in 26 countries.

The three agencies hope to particularly strengthen joint activities on vaccines in preparation for potential pandemic flu outbreaks, as well as cancer, children's, and

orphan drugs, and pharmacogenomics. Future activities will address counterfeit medicines.

The original agreement, signed in September 2003, paved the way for quarterly exchanges on information on new drug applications, regulatory guidance, and inspections of manufacturing plants, which began in 2004. The agreement also authorized ad hoc exchanges of information on drug safety and public health, including advance notice of significant regula-

tory actions such as pulling drugs from the market.

Such an exchange prevents other agencies from issuing contradictory advice when one agency takes significant regulatory action.

The ad hoc exchanges also have enabled "parallel" scientific guidance for drug applicants seeking the advice of the three agencies on how to proceed with research at such milestones as the conclusion of clinical trials. The first such parallel scientific meeting occurred in September 2003, and as part of the initial confidentiality arrangement a 1-year pilot project was initiated in 2005.

The focus of those parallel meetings is breakthrough drugs, those for rare conditions, medication for children, or other new medicines considered important.

The three agencies agreed to extend the pilot project, although the document released by the agencies did not give a time period. A spokesman for the European Commission said the meetings do not guarantee joint scientific advice from the three agencies but give applicants better guidance on how to proceed if they are seeking international drug approvals. ■

Topicort® (Desoximetasone)

LP Cream 0.05%, Gel 0.05%, and Cream and Ointment 0.25%

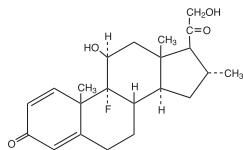
For topical use only. Not for ophthalmic use.

Rx only

DESCRIPTION

Topicort® LP (desoximetasone) Cream 0.05%; Topicort® (desoximetasone) Cream 0.25%; Topicort® (desoximetasone) Gel 0.05%; and Topicort® (desoximetasone) Ointment 0.25% contain the active synthetic corticosteroid desoximetasone. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. Each gram of Topicort® LP Cream 0.05% contains 0.5 mg of desoximetasone in an emollient cream base consisting of white petrolatum, purified water, isopropyl myristate, lanolin alcohols, mineral oil, cetostearyl alcohol, and edetate disodium. Each gram of Topicort® Cream 0.25% contains 2.5 mg of desoximetasone in an emollient cream base consisting of white petrolatum, purified water, isopropyl myristate, lanolin alcohols, mineral oil, and cetostearyl alcohol. Each gram of Topicort® Gel 0.05% contains 0.5 mg of desoximetasone in a gel base consisting of purified water, docusate sodium, edetate disodium, isopropyl myristate, carbomer 940, triethylamine, and SDAG-3 95% alcohol. Each gram of Topicort® Ointment 0.25% contains 2.5 mg of desoximetasone in an ointment base consisting of white petrolatum and fractionated coconut oil. The chemical name of desoximetasone is Pregna-1, 4-diene-3, 20-dione, 9-fluoro-11, 21-dihydroxy-16-methyl-, (11 β ,16 α)-. Desoximetasone has the molecular formula C₂₂H₂₉FO₄ and a molecular weight of 376.47. The CAS Registry Number is 382-67-2.

The structural formula is:



CLINICAL PHARMACOLOGY

Topical corticosteroids share anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Pharmacokinetic studies in men with Topicort® (desoximetasone) Cream 0.25% with tagged desoximetasone showed a total of 5.2% ± 2.9% excretion in urine (4.1% ± 2.3%) and feces (1.1% ± 0.6%) and no detectable level (limit of sensitivity: 0.005 µg/mL) in the blood when it was applied topically on the back followed by occlusion for 24 hours. Seven days after application, no further radioactivity was detected in urine or feces. The half-life of the material was 15 ± 2 hours (for urine) and 17 ± 2 hours (for feces) between the third and fifth trial day.

Pharmacokinetic studies in men with Topicort® (desoximetasone) Ointment 0.25% with tagged desoximetasone showed no detectable level (limit of sensitivity: 0.003 µg/mL) in 1 subject and 0.004 and 0.006 µg/mL in the remaining 2 subjects in the blood when it was applied topically on the back followed by occlusion for 24 hours. The extent of absorption for the ointment was 7% based on radioactivity recovered from urine and feces. Seven days after application, no further radioactivity was detected in urine or feces. Studies with other similarly structured steroids have shown that predominant metabolite reaction occurs through conjugation to form the glucuronide and sulfate ester.

INDICATIONS AND USAGE

Topicort® LP (desoximetasone) Cream 0.05%; Topicort® (desoximetasone) Cream 0.25%; Topicort® (desoximetasone) Gel 0.05%; and Topicort® (desoximetasone) Ointment 0.25% are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

WARNINGS

Topicort® LP (desoximetasone) Cream 0.05%; Topicort® (desoximetasone) Cream 0.25%; Topicort® (desoximetasone) Gel 0.05%; and Topicort® (desoximetasone) Ointment 0.25% are not for ophthalmic use. **Keep out of reach of children.**

PRECAUTIONS

General

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Pediatric patients may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (See **PRECAUTIONS - Pediatric Use**). If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
- Patients should report any signs of local adverse reactions, especially under occlusive dressings.
- Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests

The following tests may be helpful in evaluating the hypothalamic-pituitary-adrenal (HPA) axis suppression: Urinary free cortisol test
ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results. Desoximetasone did not show potential for mutagenic activity *in vitro* in the Ames microbial mutagen test with or without metabolic activation.

Pregnancy, Teratogenic Effects, Pregnancy Category C

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Desoximetasone has been shown to be teratogenic and embryotoxic in mice, rats, and rabbits when given by subcutaneous or dermal routes of administration in doses 3 to 30 times the human dose of Topicort® (desoximetasone) Cream 0.25% or Topicort® (desoximetasone) Ointment 0.25% and 15 to 150 times the human dose of Topicort® LP (desoximetasone) Cream 0.05% or Topicort® (desoximetasone) Gel 0.05%. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, Topicort® LP Cream 0.05%, Topicort® Cream 0.25%, Topicort® Gel 0.05%, and Topicort® Ointment 0.25% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to pediatric patients should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients. Safety and effectiveness of Topicort® Ointment in pediatric patients below the age of 10 have not been established.

ADVERSE REACTIONS

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence:

Burning	Hypertrophicosis	Maceration of the skin
Itching	Acneiform eruptions	Secondary infection
Irritation	Hypopigmentation	Skin atrophy
Dryness	Perioral dermatitis	Striae
Folliculitis	Allergic contact dermatitis	Miliaria

In controlled clinical studies the incidence of adverse reactions was low (0.8%) for Topicort® (desoximetasone) Cream 0.25% and included burning, folliculitis, and folliculo-pustular lesions. The incidence of adverse reactions was also 0.8% for Topicort® LP (desoximetasone) Cream 0.05% and included pruritus, erythema, vesiculation, and burning sensation. The incidence of adverse reactions was low (0.3%) for Topicort® (desoximetasone) Ointment 0.25% and consisted of development of comedones at the site of application.

OVERDOSAGE

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Apply a thin film of Topicort® LP (desoximetasone) Cream 0.05%, Topicort® (desoximetasone) Cream 0.25%, Topicort® (desoximetasone) Gel 0.05%, and Topicort® (desoximetasone) Ointment 0.25% to the affected skin areas twice daily. Rub in gently.

HOW SUPPLIED

Topicort® LP (desoximetasone) Cream 0.05% is supplied in 5 gram tubes for physician samples, 15 gram and 60 gram tubes.
Topicort® (desoximetasone) Cream 0.25% is supplied in 5 gram tubes for physician samples, 15 gram and 60 gram tubes.
Topicort® (desoximetasone) Gel 0.05% is supplied in 5 gram tubes for physician samples, 15 gram and 60 gram tubes.
Topicort® (desoximetasone) Ointment 0.25% is supplied in 5 gram tubes for physician samples, 15 gram and 60 gram tubes.
Store at controlled room temperature 15° - 30°C (59° - 86°F).

Mfd. by: Taro Pharmaceuticals Inc., Brampton, Ontario, Canada L6T 1C1
Dist. by: **TaroPharma** a division of Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532
Topicort® and TaroPharma® are trademarks of Taro Pharmaceuticals U.S.A., Inc. and/or its affiliates.

Revised: November, 2004

TaroPharma®

a division of Taro Pharmaceuticals U.S.A., Inc.
3 Skyline Drive, Hawthorne, NY 10532
1-888-TARO-USA (827-6872)
Fax: 1-800-329-TARO (8276)
www.taropharma.com

AD 100-0002-R1

INDEX OF ADVERTISERS

Abbott Laboratories	
Humira	44a-44h
Astellas Pharma US, Inc.	
Protopic	35-36
Barrier Therapeutics, Inc.	
Vusion	19
Solagé	48a-48b
Centocor, Inc.	
Remicade	28a-28d, 29
Chester Valley Pharmaceuticals, Inc.	
Atopiclair	10
CollaGenex Pharmaceuticals, Inc.	
Corporate	20
Connetics Corporation	
Olux	27-28
CORIA Laboratories, Ltd.	
Salex	5-6
Corporate	18
Dermik Laboratories	
BenzaClin	7-8
Galderma Laboratories, L.P.	
Cetaphil	36a-36b
Clobex	51-52
Genentech, Inc.	
Raptiva	20a-20b
Intendis, Inc.	
Corporate	17
Finacea	43-44
Neutrogena Corp.	
Ultra Sheer	41
OrthoNeutrogena	
Ertaczo	3
Physician's Choice of Arizona, Inc.	
Perfecting Body Hydrator	23
PhotoMedex	
XTRAC	25
Stiefel Laboratories, Inc.	
Zeasorb	11, 39
Sarna	15
Rosac	31-32
Brevoxyl	55-56
Taro Pharmaceuticals U.S.A., Inc.	
Topicort	53-54
Travel Tech Mohs Services, Inc.	
Corporate	42
Wyeth Pharmaceuticals Inc.	
Enbrel	12a-12d, 13-14