MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 9, 2001

FROM: Joyce Weaver, Pharm.D., Safety Evaluator
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THROUGH: Julie Beitz, M.D., Director
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TO: Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD-540

SUBJECT: Postmarketing Safety Review—PID D010141
Drugs: Topical Corticosteroids

Alclometasone dipropionate	Flurandrenolide
Amcinonide	Fluticasone propionate
Betamethasone dipropionate	Halcinonide
Betamethasone valerate	Halobetasol propionate
Clobetasol propionate	Hydrocortisone
Clocortolone pivalate	Hydrocortisone butyrate
Desonide	Hydrocortisone probutate
Desoximetasone	Hydrocortisone valerate
Dexamethasone	Methylprednisolone acetate
Diflorasone diacetate	Mometasone furoate monohydrate
Fluocinolone acetonide	Prednicarbate
Fluocinonide	Triamcinolone acetonide

Reaction: Summary of Adverse Events in Pediatric Patients

INTRODUCTION/ EXECUTIVE SUMMARY

We reviewed 202 AERS adverse event reports for the topical corticosteroids reported for pediatric patients age 0 to 18 years of age. Local irritation and application site reactions were the most frequently reported events in pediatric patients. Numerous systemic adverse events were reported, including striae, Cushing's syndrome, growth retardation, hyperglycemia, hirsutism, glaucoma, and adrenal insufficiency. Some cases resulted in serious outcomes, including hospitalization and death. Long-term application of topical corticosteroids in high-risk settings (for example, application to the genital and groin area in very young patients) resulted in numerous adverse events. In some cases topical corticosteroids were continued despite the failure of the dermatoses to improve.

We recommend that the systemic adverse events in the AERS database be included in the labeling for these products. Additionally, we recommend information be included on the appropriate duration of use of the products, including the appropriate duration of use for dermatoses that prove to be unresponsive to topical corticosteroids.

DRUG INFORMATION/LABELING

The topical corticosteroids are indicated for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Clotrimazole and betamethasone dipropionate cream and lotion are indicated for the topical treatment of symptomatic inflammatory tinea pedis, tinea cruris and tinea corporis due to *Epidermophyton floccosum, Trichophyton metagrophytes,* and *Trichophyton rubrum*. Neomycin and polymixin B sufates, bacitracin zinc and hydrocortisone cream and ointment are indicated for the treatment of corticosteroid-responsive dermatoses with secondary infection.

Many of the topical corticosteroid products are not labeled for use in pediatric patients. Alclometasone dipropionate cream and ointment and prednicarbate emollient cream are approved for use in children 1 year of age and older. Mometasone furoate monohydrate cream and ointment are approved for use in children 2 years of age and older. Fluocinolone acetonide topical oil is approved for pediatric patients 6 years of age and older for up to 4 weeks to treat atopic dermatitis. Fluticasone propionate cream is approved for pediatric patients 3 months of age and older for up to 4 weeks. Some products (betamethasone dipropionate ointment, betamethasone dipropionate cream, betamethasone dipropionate gel, betamethasone dipropionate lotion, betamethasone dipropionate and clotrimazole cream and betamethasone dipropionate and clotrimazole lotion, betamethasone dipropionate and clotrimazole cream, betamethasone dipropionate and clotrimazole lotion, clobetasol propionate cream, clobetasol propionate ointment, clobetasol propionate solution, clobetasol propionate gel, and clobetasol propionate foam) are approved in pediatric patients 12 years of age and older.

All of the products include general information regarding the potential for systemic corticosteroid effects in pediatric patients in the *Warnings, Precautions*, or *Adverse Reactions* sections of the labeling.

Attachment 1 contains a listing of the topical corticosteroids by generic name, tradename, NDA number, and approval date.

MEDICAL LITERATURE SUMMARY

There are published reports of systemic adverse events from the topical use of corticosteroids in pediatric patients. Hypothalamic-pituitary-adrenal (HPA) axis suppression has been observed in infants and children with both high potency and low potency topical corticosteroids.[1,2,3]

Shaffer et al used data from the National Ambulatory Medical Care Survey to determine the demographic characteristics and diagnoses of patients who were prescribed betamethasone dipropionate and clotrimazole cream by family physicians. The study

found that family physicians frequently prescribed betamethasone dipropionate and clotrimazole to children younger than 5 years of age and for use on genital skin disorders.[4]

SELECTION OF CASE SERIES

We searched AERS on May 16, 2001 for adverse event reports for topical corticosteroids in patients age 0 to 18 years of age. We retrieved 234 unique reports from AERS. Thirty-two reports were excluded because the patient had not used topical corticosteroids prior to experiencing the adverse event, the topical corticosteroid used was ophthalmic or otic, the report described a congenital anomaly in a neonate born to an adult woman who had used topical corticosteroids during pregnancy, the report described obvious misuse of a topical corticosteroid (e.g., a 3-year-old child using Lotrisone cream as toothpaste), or a legible copy of the report was not available. We included the 202 remaining reports in this review.

SUMMARY OF CASES

The characteristics of the 202 cases in the series are presented below.

Age: (n=199)	Mean 7.7 yrs, median 7 yrs (range, 8 days to 18 years)
Gender:	Male-78, female-111, not specified-13
Time to onset: (n=147)	Mean 169.3 days, median 30 days (range, 1 day to 7 years)
Location:	US-184, non-US-14, unk-4

Report year:				
	1970-2	1980-3	1990-26	2000-3
	1971-5	1982-1	1991-4	2001-1
	1973-1	1983-6	1992-16	
	1975-3	1984-5	1993-15	
	1976-1	1985-8	1994-12	
	1977-2	1986-6	1995-18	
	1978-1	1987-14	1996-10	
	1979-1	1988-11	1997-13	
		1989-5	1998-6	
			1999-3	

Event:	Local irritation, application site reaction-66
	Lack of effect-32
	Skin depigmentation or discoloration-30
	Striae or skin atrophy-30
	Cushing's syndrome-6

Growth retardation-5
Hyperglycemia, diabetes-5
Scarring or disfigurement-5
Staphylococcal infection (new or worsened), folliculitis, furunculosis, staph scalded skin syndrome-5
Genital hypertrichosis-4
Hirsutism-4
Rosacea-4
Acne-3
Glaucoma-3
Immediate hypersensitivity-3
Adrenal insufficiency-2
Bruising-2
Fungal infection-2
Gynecomastia-2
Lesions, unspecified-2
Immunodeficiency and PCP-2
Mental status or mood change-2
Perioral dermatitis-2
Seizure-2
Others (1 case each):
alopecia, amenorrhea, asthenia, asthma exacerbation, deafness, delayed puberty, dizziness, dyspepsia, granulomatous lesion, hypertonia, idiopathic thrombocytopenic purpura, myasthenia, obesity, perforated duodenal ulcer, pseudotumor cerebri, shortness of breath, skin cancer, underdeveloped breasts, underdeveloped penis, urinary tract infection, vaginal bleeding
(more than 1 event per case possible)

Indication:

Eczema-36
Tinea-24
Diaper rash-21
Unspecified rash-19
Atopic dermatitis-12
Psoriasis-12
Dermatitis-9
Unspecified fungal infection-6
Poison ivy-5
Alopecia-4
Seborrhea-4
Others (reported in fewer than 4 cases)-
Abrasions, acne, allergic contact dermatitis, anal fissure, chemical burn, dry red scale, eosinophilia pustular folliculitis, erythema, granuloma annulare, heat rash, hypertrophic scars, icthyosis, inflammation of finger, insect bite, keloids, keratosis pilaris,

Leiner's disease, mastocytosis, mosquito bite, necrobiasis lipoidica dibeticorum, patches of red skin, red scaly plaque, saliva rash, scabies pruritus, staph infection, scar from laceration, vitiligo
(indication for use of topical steroid not stated in 21 cases)

Drugs and dosage forms implicated More than one product was implicated in some cases; the strength of the product used was not reported in most cases.	
Alclometasone dipropionate cream—5 ointment—1 dosage form not stated—1 Amcinonide cream—3 dosage form not stated—2 Betamethasone dipropionate cream—6 cream, augmented—7 gel—1 lotion—1 ointment—5 Betamethasone and neomycin cream—1 Betamethasone valerate cream—2 ointment—1 Betamethasone valerate and gentamicin ointment—3 Betamethasone dipropionate and clotrimazole cream—52 Clobetasol propionate cream—7 ointment—4 lotion—1 Clocortolone pivalate cream—1 Desonide cream—1 Desoximetasone cream—6 gel—1 dosage form not stated—3 Dexamethasone and neomycin cream—1	Diflorasone diacetate ointment—2 Fluocinolone acetonide cream—8 solution—1 dosage form not stated—2 Fluocinonide cream—3 ointment—1 Flurandrenolide cream—1 tape—2 Fluticasone propionate cream—4 ointment—1 Halcinonide cream—2 Halobetasol propionate cream—1 Hydrocortisone cream—5 lotion—1 ointment—2 Hydrocortisone valerate cream—11 ointment—1 Hydrocortisone and clioquinol—2 Mometasone furoate monohydrate cream—15 lotion—6 ointment—5 Triamcinolone acetonide cream—3 ointment—1 Triamcinolone acetonide and nystatin cream—18

Site of application: Face/neck-40
Buttocks/groin/genitals (including "diaper area")-32
Legs/feet-22
Arms/hands-19
Head/scalp-12
Trunk-8

"Entire body"-4
Axilla-2
Periocular-2
Not stated-79
(more than one site of application per case possible)

Outcome: Death-1
Disability-5
Hospitalization-14
Life threatening-1
(outcome not stated in most cases)

Seventy-eight male children, 111 female children, and 13 children of unspecified gender experienced adverse events after receiving topical corticosteroids. The patients ranged in age from 8 days to 18 years with a mean age of 7.7 years. Sixty-five (32.2%) of the adverse events occurred in pediatric patients younger than 3 years of age, and 32 (15.8%) events occurred in infants. One hundred forty (69.3%) of the adverse events occurred in patients younger than 12 years of age. The patients in the case series had received topical corticosteroids for 1 day to 7 years before experiencing the adverse event. The median time to onset was 30 days. In 40 cases, application of topical corticosteroids continued for 90 days or longer, and in 17 cases application of topical corticosteroids continued for over a year.

Betamethasone-containing products were the most frequently implicated in reports of adverse reactions (79, 39%). Betamethasone dipropionate and clotrimazole cream was implicated in 52 (25.7%) reports, more than any other product. The most commonly reported events were local irritation and application site reactions (66), lack of effect (32), skin depigmentation or discoloration (30), and skin striae or atrophy (30). Outcome was not reported in most cases; however, serious outcomes (death-1, disability-5, hospitalization-14, life threatening-1) were reported. The most common indications for use were eczema (36), tinea infections (24), diaper rash (21), unspecified rash (19), atopic dermatitis (12), and psoriasis (12). The products were applied most often to the face and/or neck (40) or to the buttocks, groin, and/or genital area (32). Positive dechallenge was reported in 21 cases and positive rechallenge was reported in three cases. The area of application was occluded in five cases, and covering (but not occlusion) with "Kling wrap" was reported in one case. In many cases in which occlusion was not reported, partial occlusion might have occurred with clothing or a diaper.

In some cases topical corticosteroids were continued for extended periods of time in high-risk settings. Twenty-two patients younger than 4 years of age received topical corticosteroids for longer than 4 weeks. Seven of these patients received the drugs for longer than 6 months. Fifteen patients had topical corticosteroids applied to their groin/genitals (including "diaper area") longer than 4 weeks. Four of these patients received the drugs for longer than 6 months.

Sometimes topical corticosteroids were continued despite the failure of the treatment. The reports do not explain why the topical corticosteroids were continued when they were not effective. In twelve of the cases in the series, topical corticosteroids were continued for longer than 4 weeks even though the dermatoses did not improve. In one case the topical corticosteroid was continued for one year despite "lack of effect."

Two cases from the series are presented below.

AERS 5209109, MFR A0006921, US (NY) 1995
A registered nurse reported that her 9-year-old daughter received fluticasone cream for several weeks to treat an unspecified rash. After several weeks, the child developed fatigue, polydipsia, polyuria, glycosuria, and hypergylcemia. She was diagnosed with insulin-dependent diabetes. Fluticasone was discontinued and the child was treated with insulin.

AERS 1000000771, MFR 97100307, US (CO) 1997
A dermatologist reported that a 21-month-old girl received betamethasone dipropionate and clotrimazole cream twice daily almost since birth to treat diaper rash. Examination by the dermatologist noted folliculitis around the neck, and epidermal atrophy, hypopigmentation and telangiectasis in the perineal area, mons pubis, and inguinal creases. Betamethasone dipropionate and clotrimazole cream was discontinued, and the diaper rash was treated with a cream not containing corticosteroid (Desitin®). The folliculitis was treated with ketoconazole. The child's condition was improving at the time of the report.

Cases of Adrenal Insufficiency, Cushing's Syndrome, and Growth Retardation

A subset of eleven pediatric patients experienced adrenal insufficiency (2), Cushing's syndrome (7), and/or growth retardation (5) after receiving topical corticosteroids. A listing of these cases is presented in Attachment 2. These patients ranged from 5 months to 15 years of age. Two patients each used betamethasone valerate cream, clobetasol propionate cream, and mometasone ointment. The following other topical corticosteroids were cited in one report each:

betamethasone ointment;
betamethasone dipropionate and clotrimazole cream;
betamethasone and neomycin cream;
clobetasol propionate scalp lotion;
flumetasone pivalate;
fluocinonide cream;
flurandrenolide tape;
mometasone cream; and
triamcinolone cream.

In four cases the patients used more than one topical corticosteroid product. The topical corticosteroid was used for a median of 300 (range, 22 to 1825) days. In two cases each

the children received topical corticosteroids to treat diaper rash and eczema. Other diagnoses for the use of topical corticosteroids included alopecia, icthyosis, Leiner's disease, psoriasis, treatment of a scar, and unspecified patches of red skin. Five patients were hospitalized, and one patient with Cushing's syndrome died of a respiratory infection.

Two cases are presented below.

AERS 4918014, MFR 9207239, Maylasia 1992 (literature report)
A 6-week-old infant with icthyosis was treated intermittently with betamethasone cream for 4 weeks. The product used was not specified. The baby was hospitalized with severe dyspnea, generalized edema, Cushingoid features, and heart failure. The infant initially responded to unspecified treatment, but eventually died of a respiratory system infection.

AERS 5231157, MFR 9409043, US (FL) 1994
A 2-year-old girl with atopic dermatitis was prescribed mometasone furoate ointment. Treatment with the ointment continued for the next 4 years. A physician reported the 6-year-old child experienced growth retardation.

CONCLUSION/RECOMMENDATION

We reviewed 202 AERS adverse events for the topical corticosteroids reported for pediatric patients age 0 to 18 years of age. Local irritation and application site reactions were the most frequently reported events in pediatric patients. Numerous systemic adverse events were reported, including striae, Cushing's syndrome, growth retardation, hyperglycemia, hirsutism, glaucoma, and adrenal insufficiency. Some cases resulted in serious outcomes, including hospitalization and death. Long-term application of topical corticosteroids in high-risk settings (for example, application to the genital and groin area in very young patients) resulted in numerous adverse events. In some cases topical corticosteroids were continued despite treatment failure.

We recommend that the systemic adverse events in the AERS database be included in the labeling for these products. Additionally, the labeling of each product should advise practitioners of the appropriate duration of use of the product. The labeling should give information regarding how quickly improvement in dermatoses should occur after therapy with a topical corticosteroid is started, and practitioners should be advised to discontinue the product if improvement does not occur within this timeframe.

References

1. Ellison, JA, Patel L, Ray D, et al. Hypothalamic-pituitary-adrenal function and glucocorticoid sensitivity in atopic dermatitis. Pediatrics 2000; 105(4): 794-799.

2. Turpeinen M. Adrenocortical response to adrenocorticotropic hormone in relation to duration of topical therapy and percutaneous absorption of hydrocortisone in children with dermatitis. Eur J Pediatr 1989; 148(8): 729-31.

3. Turpeinen M, Salo OP, Leisti S. Effect of percutaneous absorption of hydrocortisone on adrenocortical responsiveness in infants with severe skin disease. Br J Dermatol 1986; 115(4): 475-84.

4. Shaffer MP, Feldman SR, Fleischer AB Jr. Use of clotrimazole/betamethasone diproprionate by family physicians. Fam Med 2000; 32(8): 561-5.
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Concur:

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Attachment 1—
Products by Generic name, tradename, NDA number, and approval date

Alclometasone dipropionate products:
(Aclovate ointment; NDA 018702—12/14/1982)
(Aclovate cream; NDA 018707—12/14/1982)
Amcinonide products:
(Cyclocort cream; NDA 018116—10/18/1979)
(Cyclocort ointment; NDA 018498—11/13/1981)
(Cyclocort lotion; NDA 019729—6/13/1988)
Betamethasone dipropionate products:
(Diprosone cream; NDA 017536—1/29/1975)
(Diprosone ointment; NDA 017691—4/15/1976)
(Diprosone lotion; NDA 017781—2/1/1977)
(Diprosone aerosol; NDA 017829—5/24/1977)
(Diprolene ointment; NDA 018741—7/27/1983)
(Diprolene cream; NDA 019408—1/31/1986)
(Diprolene AF cream; NDA 019555—4/27/1987)
(Diprolene gel; NDA 019408—11/22/91)
(Diprolene lotion; NDA 019716—8/1/1988)
Betamethasone dipropionate and clotrimazole products:
(Lotrisone cream; NDA 018827—7/10/1984)
(Lotrisone lotion; NDA 020010—12/8/2000)
Betamethasone valerate products:
(Luxiq aerosol; NDA 020934—2/28/1999)
Clobetasol propionate products:
(Temovate cream; NDA 019322—12/27/1985)
(Temovate ointment; NDA 019323—12/27/1985)
(Temovate solution; NDA 019966—2/22/1990)
(Temovate gel; NDA 020337—4/29/1994)
(Temovate E cream; NDA 020340—6/17/1994)
(Olux foam; NDA 021142—5/26/2000)
Clocortolone pivalate products:
(Cloderm cream; NDA 017765—8/22/1977)
Desonide products:
(Tridesilon cream; NDA 017010—1/04/1972)
(Tridesilon ointment; NDA 017426—11/1/1974)
(Desowen cream; NDA 019048—12/14/1984)
(Desowen lotion; NDA 072354—1/24/1992)
(Desowen ointment; NDA 071425—6/15/1988)
Desoximetasone products:
(Topicort cream; NDA 017856—2/28/1977)
(Topicort LP cream; NDA 018309—3/28/1980)
(Topicort gel; NDA 018586—3/29/1982)
(Topicort ointment; NDA 018594—10/3/1983)
(Topicort ointment; NDA 018763—9/30/1983)
Dexamethasone products:

(Decaspray aerosol; NDA 012731—3/29/1961)

Diflorasone diacetate products:

(Florone cream; NDA 017741—9/14/1977)

(Florone ointment; NDA 017994—3/1/1978)

(Florone E cream; NDA 019259—8/28/1985)

(Psorcon E ointment; NDA 019260—8/28/1985)

(Psorcon E cream; NDA 020205—11/20/1992)

Fluocinolone acetonide products:

(FS Shampoo; NDA 020001—8/27/1990)

(Synalar cream; NDA 012787—2/15/1963)

(Synalar ointment; NDA 013960—6/19/1963)

(Synalar solution; NDA 015296—5/27/1964)

(Synalar-HP cream; NDA 016161—7/25/1967)

(Derma-smoothe FS oil; NDA 019452—2/3/1988)

Fluocinonide products:

(Lidex cream; NDA 016908—6/30/1971)

(Lidex ointment; NDA 016909—9/22/1971)

(Lidex gel; NDA 017373—5/15/1973)

(Lidex solution; NDA 018849—4/8/1984)

Flurandrenolide products:

(Cordran ointment; NDA 012806—10/18/1965)

(Cordran lotion; NDA 013790—3/19/1963)

(Cordran tape; NDA 016455—7/29/1969)

Fluticasone propionate products:

(Cutivate ointment; NDA 019957—12/14/1990)

(Cutivate cream; NDA 019958—12/18/1990)

Halcinonide products:

(Halog cream; NDA 017556—11/27/1974)

(Halog solution; NDA 017823—5/4/1977)

(Halog ointment; NDA 017824—6/15/1977)

(Halog-E cream; NDA 018234—1/24/1980)

Halobetasol propionate products:

(Ultravate cream; NDA 019967—12/27/1990)

(Ultravate ointment; NDA 019968—12/17/1990)

Hydrocortisone products:

(Cortef cream; NDA 009460—8/20/1954)

(Cortef ointment; NDA 008917—7/28/1953)

(Cortril ointment; NDA 009176—5/24/1972)

Hydrocortisone butyrate products:

(Locoid cream; NDA 018514—3/31/1982)

(Locoid ointment; NDA 018652—10/29/1982)

(Locoid solution; NDA 019116—2/25/1987)

(Locoid lipocream; NDA 020769—9/8/1997)

Hydrocortisone buteprate product:

(Pandel cream; NDA 020453—2/28/1997)

Hydrocortisone valerate products:

(Westcort cream; NDA 017950—before 1/1/1982)
(Westcort ointment; NDA 018726—8/8/1983)

Methylprednisolone acetate products:

(Medrol acetate ointment; NDA 012421—6/21/1960)

Mometasone furoate monohydrate

(Elocon cream; NDA 019625—5/6/1987)
(Elocon lotion; NDA 019796—3/30/1989)
(Elocon ointment; NDA 019543—4/30/1987)

Prednicarbate products:

(Dermatop cream; NDA 019568—9/23/1991)
(Dermatop emollient cream; NDA 020279—10/29/1993)

Triamcinolone acetonide products:

(Kenalog ointment; NDA 011600—6/17/1977)
(Kenalog cream; NDA 011601—11/13/1978)
(Kenalog spray; NDA 012104—10/11/1974)
(Kenalog orabase ointment; NDA 012097—3/4/1960)

Attachment 2—AERS cases of growth retardation, adrenal insufficiency, or Cushing's Syndrome a/w use of topical corticosteroids in pediatric patients

Mfr report #	Loca-tion	yr	Age (yrs)	Gender	Drug and dose	application site	duration (days)	indication	AE	Outcome	comment
B0104663A	France	2001	15	M	clobetasol propionate cream (Dermaval) 10 - 20 mg/d		45	psoriasis	Depigmentation, striae, possible adrenal insufficiency	HO	Positive dechallenge
97-10-8020	AUS	1997	14	M	mometasone ointment (Elocon) 15 g Q2-3 days & betamethasone ointment 30 g Q 7-10 days	entire body		eczema	adrenal insufficiency, delayed puberty, growth suppression		bone scan showed 2-3 yr growth delay; prednisolone cc med
B0042474	Japan	1996	10	F	flumetasone pivalate clobetasol, propionate (Dermovate)	Scalp	180		Cushing's syndrome, obesity, inc hair growth, acne	HO	
95-08-0174	US (NJ)	1995	3	M	fluocinonide, triamcinolone, mometasone cream (Elocon)		455	patches of red skin	growth retardation, leukoderma		Digoxon and furosemide cc meds
94-10-0184	US (CO)	1994	1.25	M	betamethasone and clotrimazole cream (Lotrisone)	diaper area	120	diaper rash	growth retardation		
94-09-043	US (FL)	1994	6	F	mometasone furoate ointment (Elocon)		1460	atopic dermatitis	growth retardation		
92-09-024	US (MD)	1992	9	F	betamethasone valerate cream (Valisone)		1825	eczema	growth retardation		
92-07-239	May-lasia	1992	0.12	M	betamethasone valerate cream		28	icthyosis	Cushing's syndrome	DE	1 m/o infant; DE due to respiratory infection
92-05-178	France	1992	0.67	M	neomycin & betamethasone cream (Diprosone) 1.5 mg betamethasone/day	scalp, diaper area	180	Leiner's disease	Cushing's syndrome	DS, HO	8 m/o baby; residual retardation
US91070727A	US (TX)	1991	14	F	flurandrenolide tape (Cordran tape)	inner thigh	22	Tx scar from repair of laceration	Disfigurement, Cushing's syndrome	HO	
G0003711	Hong Kong	1990	0.42	M	clobetasol propionate cream (Temovate) 1.78 g/ day	diaper area	300	diaper rash	Cushing's syndrome	HO	5 m/o baby given 1 tube (25 g) every 2 weeks for 10 months; positive dechallenge