



some patients treated with a topical corticosteroid may have been treated earlier with a systemic steroid.

## **SELECTION OF CASE SERIES**

### **Adverse Event Reporting System**

We searched AERS on September 11, 2003 for adverse adrenal events and growth retardation in children 0 to 18 years of age using the following terms and active ingredients:

#### **MedDRA terms :**

Adrenal gland disorders (HLGT)  
Hypothalamus and pituitary gland disorders (HLGT)  
Growth retardation (PT)  
Blood growth hormone decreased (PT)  
Blood growth hormone abnormal (PT)

#### **Active Ingredients**

|                            |                                |
|----------------------------|--------------------------------|
| 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        |

We retrieved 21 unique reports from AERS using the criteria above. Two cases were excluded. One was excluded because the consumer reported an event unrelated to adrenal suppression or growth retardation. A second case was excluded because it involved the use of topical corticosteroid drops used either for an otic or ophthalmic indication. One report contained two cases.

### **Medical Literature**

We searched the medical literature for published articles of adrenal suppression and growth retardation in children following exposure to topical corticosteroids. Are search was limited to published case reports. This search resulted in two additional cases found in the literature not already in AERS.<sup>6, 7</sup>

We included a total of 22 cases from AERS and/or the medical literature<sup>2-7</sup> in this review.

## **SUMMARY OF CASE SERIES**

Twenty-two pediatric patients experienced adrenal insufficiency (7), Cushing’s syndrome (13), and/or growth retardation (10) after receiving topical corticosteroids. Six of the cases are published in English-language or foreign medical literature. The characteristics of the 22 cases in the series are presented below. Narrative summaries of all cases are provided in attachment 1 and a listing of all cases is presented in attachment 2.

| Table 1. Characteristics of Case Series |   |  |
|---|---|--|
| Age: (n=21)                             | Mean 5.3 yrs, median 3 yrs (range, 44 days to 15 years)   |  |
| Gender:                                 | Male-14, female-6, not reported-2   |  |
| Duration of use (n=17)                  | Mean 21 months, median 6 months (range, 22 days to 7 years)                                       |  |
| Location:                               | US-10, Foreign-12   |  |
| *Outcome:                               | Death-2<br>Disability-1<br>Hospitalization-10   | Medically significant-5<br>None reported-6   |
| *Indication:                            | Atopic dermatitis-4<br>Eczema-3<br>Diaper rash-6<br>Alopecia areata/Hair loss-2<br>Not reported-2 | Ichthyosis-1<br>Leiner’s disease-1<br>Patches of red skin-1<br>Psoriasis-1<br>Scar from laceration-1<br>Second-degree burn-1 |
| *Site of application:                   | Diaper area-7<br>Scalp-4<br>Entire body-2   | Inner thigh-1<br>Neck, pectoral, upper arm-1<br>Not reported-9   |

\*more than one possible per case

### Drugs and dosage forms implicated:

#### Betamethasone

dipropionate ointment—1  
dipropionate/clotrimazole cream—1  
dipropionate/neomycin cream—1  
valerate/gentamicin ointment—1  
valerate/gentamicin/tolnaftate/iodochlorhydroxyquin cream—1  
valerate cream—2  
valerate ointment—1

Clobetasol propionate  
cream—4  
unknown—3

Mometasone furoate monohydrate  
cream—4  
ointment—2  
lotion—1

Flurandrenolide tape—2

Fluocinonide—1

Triamcinolone—1

Hydrocortisone butyrate—1  
(More than one product was implicated in some cases)

The patients ranged from 6 weeks to 15 years of age. Nine (41%) of the adverse events occurred in pediatric patients younger than 3 years of age, and five (24%) occurred in infants. The patients in the case series received topical corticosteroids for 22 days to 7 years. Eleven were receiving the product for 3 months or longer, and in seven cases application of topical corticosteroids continued for over a year.

Seven children were being treated with topical corticosteroids for atopic dermatitis (4) or eczema (3). In six cases the children received topical corticosteroids to treat diaper rash, and two were being treated for hair loss or alopecia. Betamethasone-containing, mometasone, and clobetasol products were the most frequently implicated in reports of adverse reactions.

In four cases the patient was treated with more than one topical corticosteroid product, one of which was also being treated with oral prednisolone for asthma. An additional case mentioned the use of oral betamethasone, however the dates of administration in relation to the onset of the event was unknown. One case of growth retardation was possibly due to underlying endocrinopathy or pituitary failure however an endocrine workup had not performed at the time of reporting and follow-up was not provided.

In eight cases, there was indication that the topical corticosteroid was misused. In six cases, parents applied large amounts of potent topical corticosteroids to treat diaper rash (5) or second-degree burns (1). In 4 of the 6, treatment occurred without medical supervision because the product was obtained over-the-counter and continued for prolonged periods of time. Two adolescent males appeared to be misusing topical corticosteroids. The cases described the application of the topical steroid to the entire body or self-medicating with large quantities of the topical corticosteroid product. It is unknown whether misuse occurred because the treatment was ineffective. The treatment course of therapy of the eight cases is described below.

- ?? 8 to 10 clobetasol 25g tubes applied over two months for diaper rash
- ?? Seven clobetasol tubes applied over two months for diaper rash
- ?? One clobetasol 25g tube applied every 2 weeks for 10 months for diaper rash
- ?? Three betamethasone/neomycin tubes every 2 weeks for 6 months for diaper rash
- ?? 30g betamethasone every 7-10 days and 15g mometasone every 2-3 days over entire body for eczema
- ?? 1 to 2 clobetasol tubes per day for one to two months
- ?? Eight tubes of hydrocortisone cream and 6 tubes of clobetasol for diaper dermatitis
- ?? 30g of betamethasone combination cream applied to burn areas every week for 17 months

Ten patients were hospitalized, and two patients with Cushing's syndrome died. One death was secondary to a respiratory infection. The circumstances in the other case were not provided.

The most profound case was published over 20 years ago and involves an infant who was treated with topical betamethasone for six months in the diaper area and scalp. Several days prior to admission, she developed vomiting, anorexia, and a cough. She was hospitalized in the infant intensive care unit with a temperature of 104<sup>o</sup>F, in shock and comatose. Her immediate care in the ICU lasted 14 days and she eventually recovered however she was followed and maintained on oral hydrocortisone for 14 months and suffered residual mental retardation.<sup>2</sup>

Clinical laboratory evidence of adrenal suppression was provided in some cases (attachment 1 cases 1, 2, 3, 9, and 20). In several other cases, there was mention that the diagnosis of adrenal suppression or growth retardation was supported by laboratory or other objective evidence, however the actual data was not provided (attachment 1, cases 12, 13, 21, and 22).

## **DISCUSSION**

The factors affecting penetration or absorption of topical corticosteroids into the skin are multifactorial and include (but may not be limited to) the potency of the corticosteroid, the size of the area being treated, the duration of treatment, the use of occlusive dressing, and the skin site. Penetration of the steroid is related to thickness of the stratum corneum and the vascular supply to the area. Additionally, infants may be at increased risk for systemic events of topical corticosteroids because they have a higher ratio of skin surface area to weight.<sup>8</sup>

One or more of these factors were present the cases we reviewed. Five of the 22 patients were infants. Fifteen of the 22 cases reported the use of "very high" or "high" potency corticosteroids (attachment 3 includes the relative potency of topical corticosteroids). Two reported the use of the topical corticosteroid on the entire body and three reported the use in more than one location. The duration of use was for 3 months or longer in 11 cases, and over a year in seven cases. Although the use of occlusive dressings was not specifically stated in the cases, application of the topical corticosteroid to the diaper area in seven cases resulted in occlusion of the steroid by the diaper. The site of application may have been a factor in some cases. It is unknown if the specific sites of application in some of the cases such as the diaper area are associated with greater absorption of the topical corticosteroids. However, there was one case where the product was applied to second degree burns which were devoid of epidermis.

## **CONCLUSION**

We reviewed 22 cases of adrenal suppression/insufficiency, Cushing's syndrome, and growth retardation in children aged 6 weeks to 15 years. 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 children) resulted in numerous adverse events. It is important to keep in mind that the degree of HP suppression is unknown. Most adverse event reports do not contain complete laboratory data and if present, interpretation is difficult because standard laboratory measurements to determine the degree of HP suppression are often lacking. It is unknown whether the sequential use of different corticosteroid formulations resulted in possible subsequent additive suppressive effects on the HP axis. For example, some patients treated with a topical corticosteroid may have been treated earlier with a systemic steroid.

## **References**

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## Attachment 1—Narrative Summaries of all Cases

### 1. Literature Case, Foreign, 2003

A 4-month-old boy was hospitalized with a one month history of accelerated weight gain, obesity, and diaper dermatitis which was unresponsive to topical corticosteroid therapy. At about 2 months of age, he developed skin lesions on his bottom. He was prescribed hydrocortisone 0.1% cream 3 to 4 times per day for a week. In addition the mother also used clobetasol propionate due to persisting lesions. A total of 8 tubes of hydrocortisone and 6 tubes of clobetasol were used in a two-month time frame. On physical exam, he appeared cushingoid with mild hypertrichosis. He had a weight gain of 2.2 kg in the prior month. Laboratory evaluation included the following: ACTH < 5pg/ml (normal 10-42pg/ml), cortisol 1µg/dL (normal 8-25µg/dL), and 24 hour urinary free cortisol 15µg/day (normal < 90 µg/day). A low-dose (1µg) corticotrophin test showed no increase in cortisol level which confirmed a clinical suspicion of adrenal suppression. The parents were instructed to reduce the frequency of the applications to prevent adrenal crisis. After 1 month the child appeared less cushingoid and his ACTH level was still below 5pg/ml but his cortisol was within normal limits. Two months later, a low dose ACTH test was repeated and showed a significant cortisol response.<sup>6</sup>

### 2. MFR B0133418A, AERS 3906438-0, Foreign, 2002 (Case 1)

A 4 ½ month old male infant presented with a history of sudden increase in weight and body fat since 2 months of age. It was discovered that the mother had been applying clobetasol propionate 0.05% (available OTC in country of origin) for diaper rash for over 2 months, (approximately 8 to 10 25g tubes). The infant had cushingoid features with unequal distribution of body fat, ‘buffalo hump’, double chin, and thick subcutaneous collection of fat on the scalp. He also had hypertrichosis mainly on the forehead. The skin in the diaper area was hypopigmented and atrophied. His morning serum cortisol was 0.5 mcg/dL (normal being 5-18mcg/dL) and in the evening was 0.8mcg/dL (normal being 2-13mcg/dL). He also had biochemical evidence of vitamin D deficiency. The infant was discharged on physiological oral replacement with hydrocortisone and vitamin D drops. On two subsequent physician visits 2 months apart the child had evidence of adrenal suppression. A normal response was seen after 6 months of observation at which time his hydrocortisone was tapered and eventually discontinued. During the 6 months, his weight also reduced and there was an increase in linear growth.<sup>3</sup>

|                     | Serum Cortisol Level (mcg/dL) |                  |                  |
|---------------------|-------------------------------|------------------|------------------|
|                     | Pre ACTH                      | 30 min post ACTH | 60 min post ACTH |
| 2mos after hosp dc  | 5.4                           | 4.3              | 2.8              |
| 4 mos after hosp dc | NR                            | NR               | NR               |
| 6 mos after hosp dc | 14.6                          | 18.4             | 19.4             |

### 3. MFR B0133418A, AERS 3906438-0, Foreign, 2002 (Case 2)

A 1 year old male infant was brought in to the baby clinic with a history of sudden increase in weight (2.2kg in 10 weeks) and increasing fat deposits all over his body. It was discovered that the mother used approximately 7 tubes of clobetasol propionate 0.05% (available OTC in country of origin) for diaper rash for over 2 months. He

exhibited cushingoid features with ‘moon face’ and extensive fat deposits in the abdominal wall and thighs. He also had hypertrichosis of the forehead, upper lip and extremities as well as hyperpigmentation of the skin. The skin in the diaper area was hypopigmented and atrophied. His serum cortisol was 0.5 mcg/dL. The infant was placed on physiological oral replacement with hydrocortisone. Adrenocorticotrophic hormone stimulation tests 2 months later showed a serum cortisol of 2.8mcg/dL, 20mcg/dL, and 23mcg/dL before, and 30 and 60 minutes after ACTH injection. Hydrocortisone was tapered and stopped. On subsequent visits, his cushingoid features gradually improved and his weight decreased to a normal range.<sup>3</sup>

4. MFR 2002-07-2888, AERS 3970267-2, US, 2002

A 4-year-old boy was treated with mometasone furoate cream 0.01% for atopic dermatitis. He had been prescribed the therapy as an infant by a dermatologist and it was continued on and off by the pediatrician for about 3 ½ years. The boy experienced growth suppression which was being treated with growth hormone injections.

5. MFR 2001-05-1933, AERS 3860727-7, US, 2001

A 4-year-old female initiated betamethasone dipropionate ointment for eczema. Treatment was continued for approximately five years. During this time frame “serious medical problems and metabolic dysfunctions” were noted. The patient began to show signs of growth retardation, hypertension, and Cushing’s syndrome. The patient had a history of eczema since the age of 2 months, mild atopic dermatitis, multiple food allergies, reactive airway disease, and multiple hospital admission during early childhood. In addition to being treated with betamethasone ointment she was concomitantly treated with flurandrenolide topical for an unknown period of time.

6. MFR B0104663A, AERS 375083-1, Foreign, 2001

A 15-year-old was receiving clobetasol propionate cream for psoriasis. It was noted that he self-medicated and had used 1 to 2 tubes of clobetasol per day for 1 to 2 months. He developed severe depigmentation on his face, arm, and trunk with skin striae. Clobetasol was discontinued and he was hospitalized for possible adrenal insufficiency. No additional information provided.

7. MFR 2000-10-0055, AERS 3592691-2, US, 2000

A 9-year-old child was treated with mometasone furoate cream for an unknown indication and duration and developed Cushing’s syndrome “symptoms”. No additional information provided.

8. MFR 1999-03-0240, AERS 3219210-4, US, 1999

A 2-year-old child was treated with mometasone furoate lotion for alopecia areata on the scalp. A flattened growth curve was reported. The reporting dermatologist did not believe the mometasone was related to the patient’s condition. He felt the patient had multiple organ endocrinopathy/pituitary failure and that the growth suppression preceded the use to mometasone. The endocrinologist wanted to rule out other causes prior to a full endocrine workup. It is unknown if the mometasone was discontinued.

9. MFR 1999-12-0738, AERS 3434995-X, Foreign, 1999

An 11-year-old male with a history of atopic dermatitis (8 years) developed Cushing's syndrome secondary to long term use of topical betamethasone valerate/gentamicin sulfate. He presented with amnesia and somnolence and with hospitalized with moon face, "low height", and obesity (42kg). His ACTH was 9.6pg/dL and serum cortisol level was noted to be 0.9mcg/dL (ref 5-15 mcg/dL). He was diagnosed with Cushing's syndrome. Betamethasone ointment was discontinued Decreased adrenal cortical was noted. A rapid ACTH test was 1.1 pre-test, 4.3 at 30 minutes, and 2.8 at 60 minutes. He had concomitantly receive betamethasone tablets and betamethasone/dexchlorphenirame maleate tablets at some point in his treatment, however the actual date of administration and duration were not reported.

10. MFR 1998-07-1081, AERS 3113532-3, US, 1998

A 3-year-old male was treated with mometasone furoate cream for an atopic dermatitis. A few months later, linear growth retardation was noted. The boy had not responded to ACTH stimulation at the time of the report. No additional information provided.

11. MFR B0058504, AERS 3112510-8, Foreign, 1998

A physician reported that a female child (age unknown) died from Cushing's syndrome while receiving clobetasol propionate. No additional information provided.

12. MFR 97-10-8020, AERS 3000375-4, Foreign, 1997

A 14-year-old male receiving prednisolone for asthma, applied 30g of betamethasone valerate 0.02% every 7-10 days and 15g of mometasone furoate ointment every 2 to 3 days for eczema. Adrenal suppression and delay in puberty was noted. A bone scan indicated that there was a 2-3 year growth delay and a synthen stimulation test showed a flat plasma cortisol curve. It was suspected that the patient was self-medicating and applied both products over his whole body.

13. MFR B0042474, AERS 1872624, Foreign, 1996

A 10 year old girl with a history of atopic dermatitis since infancy received clobetasol propionate scalp lotion for loss of hair. After one month of treatment she developed Cushing's syndrome with obesity, hypertrichosis on her back and legs, red cutaneous striae on her thighs, moon face, erythema on her cheeks, and facial acne. The clobetasol was discontinued after three months of treatment and she was hospitalized three weeks later for adrenocortical suppression. Blood and urine cortisol and ACTH were below the limit of detection. A dexamethasone suppression test revealed complete suppression of cortisols. Cortisol function recovered after three weeks. The patient had previously been receiving flumetasone pivalate for 5 months for the same condition with no effect. (foreign literature report, citation not provided)

14. MFR 95-08-0174, AERS 1733286, US, 1995

A 3-year-old boy who was being treated with mometasone furoate cream for about 15 months for "patches of red skin", experienced growth retardation (height and weight) and leukoderma. He was also on two other corticosteroid creams, triamcinolone and

fluocinolnide on the head and for diaper rash. An MRI of the brain, bone and many blood tests were performed which the reporter states were normal.

15. MFR 9409043, AERS 5231157, US, 1994

A 6-year-old girl who was being treated with mometasone furoate ointment for four years experienced growth retardation. No additional information provided.

16. MFR 94-10-0184, AERS 1652362, US, 1994

A 15 month old boy was treated with betamethasone/clotrimazole for approximately six months for a monilial diaper rash. Growth retardation was noted by the infants parents, however the reporting physician considered this event to be unrelated to the mometasone therapy.

17. AERS 4918014, MFR 9207239, Foreign, 1992

A 6-week-old infant with ichthyosis 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.<sup>5</sup>

18. MFR 92-09-024 AERS 1443792, US, 1992

A 9-year-old girl who was being treated with betamethasone valerate cream for five years for eczema experienced growth retardation. No additional information provided.

19. MFR US91070727A, AERS 840618, US, 1991

A 14-year-old female was involved in a bicycle accident and lacerated her right inner thigh. The laceration was closed surgically and plastically reconstructed about 11 days after the accident. About 6 weeks later she was placed on flurandrenolide tape for 22 days at which time she was noted to have Cushing's syndrome. No additional information provided.

20. MFR G0003711, AERS 687092, Foreign, 1990

A 15-month-old boy was admitted to the hospital because of suspected Cushing's syndrome. He developed a napkin rash at the age of 5 months and was prescribed clobetasol propionate cream. Treatment was continued without medical supervision for the next 10 months. The product was available without prescription and one 25g tube was applied every 2 weeks. The parents noticed an increase in weight and hypertrichosis for 3 months before admission. On exam he was found to be cushingoid with plethoric moon facies, generalized obesity, hypertrichosis and buffalo hump. He had an erythematous napkin rash with raised patches and satellite lesion suggestive of candidiasis. The morning cortisol was 15 nmol/L and the evening cortisol was 13 nmol/L. A diagnosis of Cushing's syndrome resulting from the prolonged use of a potent topical steroid was made. Following discontinuation of clobetasol, the morning cortisol rose to 79 nmol/L after 12 days and 394 nmol/L after 17 days. A synacthen test was performed 3 weeks after his presentation. The morning cortisol was 177, rising to 778nmol/L and 501 nmol/L at 30 and 60 minutes after 250mcg synacthen IM. Two months after initial

presentation, he was well with a decrease in body weight and examination was unremarkable except for very mild cushingoid features.<sup>4</sup>

21. MFR 92-05-178, AERS 869652, Foreign, 1992

An 8-month-old girl was hospitalized with coma, adrenal insufficiency, and Cushing's syndrome. She had been treated with betamethasone propionate/neomycin ointment twice daily for 6 months for nonpruriginous diaper rash with scalp involvement. The rate of application was 3 tubes every 2 weeks or 1.5mg/day of betamethasone. Three days prior to admission, she developed vomiting, anorexia and a cough. She was admitted to the intensive care unit comatose, with temperature of 104F, and was in a preagonal state. She was cushingoid with a puffy and erythrotic face, pilosity of the forehead and interscapular area, adiposity of the neck and trunk and atrophic muscle mass. She was intubated, rehydrated, and administered hydrocortisone IV. She eventually improved over the next 3 weeks. After transfer from the ICU, she underwent a metopirone test with confirmed adrenal insufficiency. Hormone replacement therapy was continued for additional 6 months at 10mg/day. Another metopirone test performed 9 months after hospitalization confirmed the persistence of corticotropin deficiency with low blood levels of cortisol (3mcg/dL). Eventually all hormone therapy was discontinued after 14 months.<sup>2</sup>

22. Literature Case, Foreign, 1982

A 2-year-old boy was hospitalized with Cushing's syndrome following prolonged topical corticosteroid treatment. At the age of 11 months, he suffered accidental second-degree burns caused by boiling water, on the neck, pectoral area, and right upper arm. The burned areas were treated with topical application of a cream containing a mixture of 0.06% betamethasone valerate, 1% tolnaftate, 1%iodochlorhydroxyquin, and 1% gentamicin. The mother applied 30g of the cream to the burned areas every week for 17 months. After six months she noticed physical changes suggestive of Cushing's syndrome. At the time of examination, he was 50<sup>th</sup> percentile for weight and less than 3<sup>rd</sup> percentile for height. He had a moon face, facial and body hypertrichosis, and atrophic striae on the abdomen and thighs. There were deep ulcerations with exposed muscles and fat tissue on upper half of the anterior thoracic wall. Bone roentgenogram showed generalized osteoporosis and retarded bone growth. On admission the topical corticosteroid was discontinued. The ulcers were gently cleaned and proteolytic enzyme ointment was applied twice a day. Twenty-five units of corticotropin was given every other day during the first four weeks and once a week during the next two months. The ulcers healed after 83 days and the Cushing's syndrome regressed.

| Attachment 2—AERS cases of growth retardation, adrenal insufficiency, or Cushing's Syndrome a/w use of topical corticosteroids in pediatric patients |                     |          |            |          |           |     |   |                      |                 |  |   |      |   |
|--|---------------------|----------|------------|----------|-----------|-----|---|----------------------|-----------------|--|---|------|---|
|  | Mfr #               | Location | Event year | Rpt year | Age (yrs) | Sex | Topical Corticosteroid Product  | Application site     | Duration (days) | Indication                             | AE  | OT*  | Comment   |
| 1  | Literature          | Foreign  | NR         | 2003     | .33       | M   | -Hydrocortisone 17-butyrate cream (Locoid)<br>-Clobetasol propionate (Dermovate)        | Diaper area          | 60              | Diaper dermatitis                      | Cushing's syndrome<br>Adrenal suppression   | HO   | A total of 8 tubes of hydrocortisone and 6 tubes of clobetasol used in 2 months.  |
| 2  | B0133418A<br>Case a | Foreign  | NR         | 2002     | .33       | M   | Clobetasol propionate cream (Temovate)  | Diaper area          | 60              | Diaper rash                            | Cushing's syndrome<br>Adrenal suppression   | HO   | Approximately 8 to 10 tubes used during the 2 mo treatment  |
| 3  | Literature          | Foreign  | NR         | 2002     | 1         | M   | Clobetasol propionate cream (Temovate)  | Diaper area          | 60              | Diaper rash                            | Cushing's syndrome<br>Adrenal suppression   | None | Approximately 7 tubes used during the 2 mo treatment  |
| 4  | 2002-07-2888        | US       | NR         | 2002     | 4         | M   | Mometasone furoate cream (Elocon)   | NR                   | 1278            | Atopic dermatitis                      | Growth retardation                          | MS   | Was being treated with growth hormone injections  |
| 5  | 2001-05-1933        | US       | 1985       | 2001     | 4         | F   | -Betamethasone dipropionate ointment (Diprolene)<br>-flurandrenolide tape (Cordran)     | NR                   | 1825            | Atopic eczema                          | Cushing's syndrome<br>Growth retardation    | MS   | Used numerous topical corticosteroids over the years and IM celestone   |
| 6  | B0104663A           | Foreign  | NR         | 2001     | 15        | M   | Clobetasol propionate cream (Dermoval)  | NR                   | 45              | Psoriasis                              | Possible adrenal insufficiency              | HO   | Positive dechallenge. Pt self medicated with 1 to 2 tubes per day equivalent to 10-20mg of clobetasol per day)  |
| 7  | 2000-10-0055        | US       | NR         | 2000     | 9         | NR  | Mometasone furoate cream (Elocon)   | NR                   | NR              | NR                                     | Cushing's syndrome symptoms                 | MS   | Poorly documented with no follow up provided.   |
| 8  | 1999-12-0738        | Foreign  | 1999       | 1999     | 11        | M   | Betamethasone valerate/gentamicin ointment (Rinderon -VG)                               | Entire body          | 2555            | Atopic dermatitis                      | Cushing's syndrome                          | HO   | Also on concomitant betamethasone tablets and betamethasone/chlorpheniramine tablets (sometime in 1996, dates of administration and duration unknown) |
| 9  | 1999-03-0240        | US       | NR         | 1999     | 2         | NR  | Mometasone furoate lotion (Elocon)  | Scalp                | NR              | Alopecia areata                        | Growth retardation                          | MS   | Possible underlying multiple organ endocrinopathy/pituitary failure.  |
| 10   | 1998-07-1081        | US       | NR         | 1998     | 3         | M   | Mometasone furoate cream (Elocon)   | NR                   | Few months      | Atopic dermatitis                      | Growth retardation                          | MS   | Reporter stated child had not responded to ACTH stimulation.  |
| 11   | B0058504            | Foreign  | NR         | 1998     | Unk child | F   | Clobetasol propionate (Dermovate)   | NR                   | NR              | NR                                     | Cushing's syndrome                          | DE   | Poorly documented with no follow up provided.   |
| 12   | 97-10-8020          | Foreign  | NR         | 1997     | 14        | M   | -Mometasone furoate ointment (Elocon)<br>-Betamethasone valerate ointment (Celestone-M) | entire body          | NR              | eczema                                 | Sdrenal insufficiency<br>Growth suppression | None | bone scan showed 2-3 yr growth delay; prednisolone cc med; applied 30g of betamethasone q 7-10 days & 15g of mometasone furoate q 2 to 3 days         |
| 13   | B0042474            | Foreign  | 1994       | 1996     | 10        | F   | Clobetasol propionate 14(Dermovate)   | Scalp                | 90              | Hair loss (? due to atopic dermatitis) | Cushing's syndrome<br>Adrenal insufficiency | HO   | Previously received flumetasone pivalate for 5 months for the same condition with no effect.  |
| 14   | 95-08-0174          | US       | NR         | 1995     | 3         | M   | -Fluocinonide<br>-Triamcinolone<br>-Mometasone furoate cream (Elocon)                   | Head and diaper area | 455             | patches of red skin<br>Diaper rash     | Growth retardation                          | None | Digoxon and furosemide cc meds  |

|    | Mfr #        | Location | Event year | Rpt year | Age (yrs) | Sex | Topical Corticosteroid Product   | Application site          | Duration (days) | Indication                        | AE  | OT*    | Comment  |
|----|--------------|----------|------------|----------|-----------|-----|--|---------------------------|-----------------|-----------------------------------|---|--------|--|
| 15 | 94-10-0184   | US       | 1994       | 1994     | 1.25      | M   | Betamethasone dipropionate/clotrimazole cream (Lotrisone)                            | diaper area               | 120             | diaper rash                       | Growth retardation                          | None   |  |
| 16 | 94-09-043    | US       | 1994       | 1994     | 6         | F   | Mometasone furoate ointment (Elocon)   | NR                        | 1460            | atopic dermatitis                 | Growth retardation                          | None   |  |
| 17 | 92-09-024    | US       | 1992       | 1992     | 9         | F   | Betamethasone valerate cream (Valisone)  | NR                        | 1825            | eczema                            | Growth retardation                          | None   |  |
| 18 | 92-07-239    | Foreign  | NR         | 1992     | 0.12      | M   | Betamethasone valerate cream   | NR                        | 28              | ichthyosis                        | Cushing's syndrome                          | DE, HO | 1 m/o infant; death due to respiratory infection   |
| 19 | 92-05-178    | Foreign  | 1975       | 1992     | 0.67      | M   | Betamethasone dipropionate/neomycin cream (Diprosone)                                | scalp, diaper area        | 180             | Leiner's disease                  | Adrenal insufficiency<br>Cushing's syndrome | DS, HO | -8 m/o baby; residual retardation<br>-Used 3 tubes every 2 weeks for 6 months equivalent to 1.5mg/day of betamethasone |
| 20 | US91070727 A | US       | 1989       | 1991     | 14        | F   | Flurandrenolide tape (Cordran tape)  | inner thigh               | 22              | Tx scar from repair of laceration | Cushing's syndrome                          | HO     |  |
| 21 | G0003711     | Foreign  | NR         | 1990     | 1.25      | M   | Clobetasol propionate cream (Temovate)   | 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                                       |
| 22 | Literature   | Foreign  | NR         | 1982     | 2.33      | M   | Betamethasone valerate/tolnaftate/iodochlorhydroxyquin/gentamicin cream (QuadriDerm) | Neck, pectoris, upper arm | 510             | Second degree burns               | Cushing's syndrome<br>Growth retardation    | HO     | Was given product 30g every week for 17 months   |

\*Reported outcomes (OT): DE=death; HO=hospitalization; DS=disability; MS=medically significant; None=none reported

### Attachment 3—Potency Ranking of Some Topical Corticosteroids

The relative potency of a product depends on several factors including the characteristics and concentration of the drug and the vehicle used. Vasoconstrictor assays are used to measure the relative potency of the commercially available products. Ranking is based on vasoconstrictor assays of brand name products.

**Estimated Relative Potency of Selected Topical Corticosteroid Products**

|                               | <b>CORTICOSTEROID INGREDIENT</b>     | <b>DOSAGE FORM</b>   | <b>STRENGTH</b>             |
|-------------------------------|--------------------------------------|--|-----------------------------|
| <b>I</b><br>Very High Potency | Augmented betamethasone dipropionate | Ointment   | 0.05%                       |
|                               | Clobetasol propionate                | Cream, Ointment  | 0.05%                       |
| <b>II</b><br>High Potency     | Augmented betamethasone dipropionate | Cream  | 0.05%                       |
|                               | Betamethasone dipropionate           | Cream, Ointment  | 0.05%                       |
|                               | Betamethasone valerate               | Ointment   | 0.1%                        |
|                               | Desoximetasone                       | Cream, Ointment,<br>Gel  | 0.25%<br>0.05%              |
|                               | Fluocinolone acetonide               | Cream  | 0.2%                        |
|                               | Fluocinonide                         | Cream, Ointment, Gel   | 0.05%                       |
|                               | Triamcinolone acetonide              | Cream, Ointment  | 0.5%                        |
| <b>III</b><br>Medium Potency  | Betamethasone dipropionate           | Lotion   | 0.05%                       |
|                               | Betamethasone valerate               | Cream  | 0.1%                        |
|                               | Desoximetasone                       | Cream  | 0.05%                       |
|                               | Fluocinolone acetonide               | Cream, Ointment  | 0.025%                      |
|                               | Hydrocortisone valerate              | Cream, Ointment  | 0.2%                        |
|                               | Mometasone furoate                   | Cream, Ointment, Lotion  | 0.1%                        |
| Triamcinolone acetonide       | Cream, Lotion, Ointment              | 0.025%, 0.1%   |                             |
| <b>IV</b><br>Low Potency      | Aclometasone dipropionate            | Cream, Ointment  | 0.05%                       |
|                               | Desonide                             | Cream  | 0.05%                       |
|                               | Dexamethasone                        | Aerosol  | 0.01%, 0.04%                |
|                               | Dexamethasone sodium phosphate       | Cream  | 0.1%                        |
|                               | Fluocinolone acetonide               | Cream, Solution  | 0.01%                       |
|                               | Hydrocortisone                       | Lotion<br>Cream, Ointment, Lotion, Aerosol<br>Cream, Ointment, Lotion, Solution<br>Cream, Lotion, Ointment | 0.01%<br>0.5%<br>1%<br>2.5% |
|                               | Hydrocortisone acetate               | Cream, Lotion  | 0.5%                        |