

EXECUTIVE SUMMARY: LOTRISONE ADVERSE EVENTS

March 9, 1999.

Lois LaGrenade, M.D., M.P.H.
Amarilys Vega, M.D., M.P.H.

Office of Postmarketing Drug Risk Assessment

**This memorandum contains IMS trade secret data.
Released with permission from IMS HEALTH**

Introduction

This is a summary of all reported adverse events to Lotrisone cream since its approval. We were asked to include information on whether the adverse events coincided with length of use beyond the label indicated usage and on adverse events in the pediatric age groups.

Lotrisone cream is marketed by Schering and was approved in July 1984. It contains a combination of clotrimazole, USP, a synthetic antifungal agent, and betamethasone dipropionate, USP, a synthetic corticosteroid, for dermatologic use (1). It is labeled for twice daily use for two weeks in tinea cruris and tinea corporis and four weeks in tinea pedis (2). Foreign brand names for this combination of clotrimazole and betamethasone dipropionate cream include Clotrasone, Lotricomb, Lotriderm, and Sinium.

Methods

We searched the Adverse Event Reporting System (AERS) database for all adverse events to Lotrisone reported to FDA since July 1984 when the cream was approved. In addition we requested a search of the World Health Organization (WHO) adverse events database for foreign reports of adverse events to Lotrisone cream and clotrimazole/betamethasone dipropionate combination creams by any other foreign brand names. Because AERS summary results reports do not include information on indication for use nor duration of use we printed images of original report forms for all reported adverse events and manually abstracted the relevant information from each form. The data were then entered into an Excel spreadsheet, which was used for subsequent analysis.

A comprehensive literature search was done including the following databases: Medline , Toxline, IPA (International Pharmaceutical Abstracts), Dialog databases, Physicians Desk Reference On-line (PDR 1999) , STAT!REF (database used by CDER medical library), and Pharmaprojects.

Drug use data were obtained from the IMS HEALTH National Disease and Therapeutic Index (NDTI™) [National Disease and Therapeutic Index is an ongoing survey of treatment patterns and diseases encountered during patient visits at office-base medical practices in the continental United States], and the National Prescription Audit database (NPA Plus™) [National Prescription Audit Plus measures both what is prescribed by the physician and what is dispensed by the pharmacist to the consumer (continental United States only). (IMS HEALTH, LTD. Plymouth Meeting, PA)]

Results

AERS Results

AERS identified a total of 344 cases of adverse events to Lotrisone, many of which reported more than one event, leading to a total of 761 adverse events. Figure 1 displays the total adverse events reported by year. Figure 2 summarizes the major reported Lotrisone adverse events in order of frequency. The commonest reported adverse event was that the drug was ineffective (19%). Application site reactions (10%) and aggravation of the original condition (8.5%) were next.

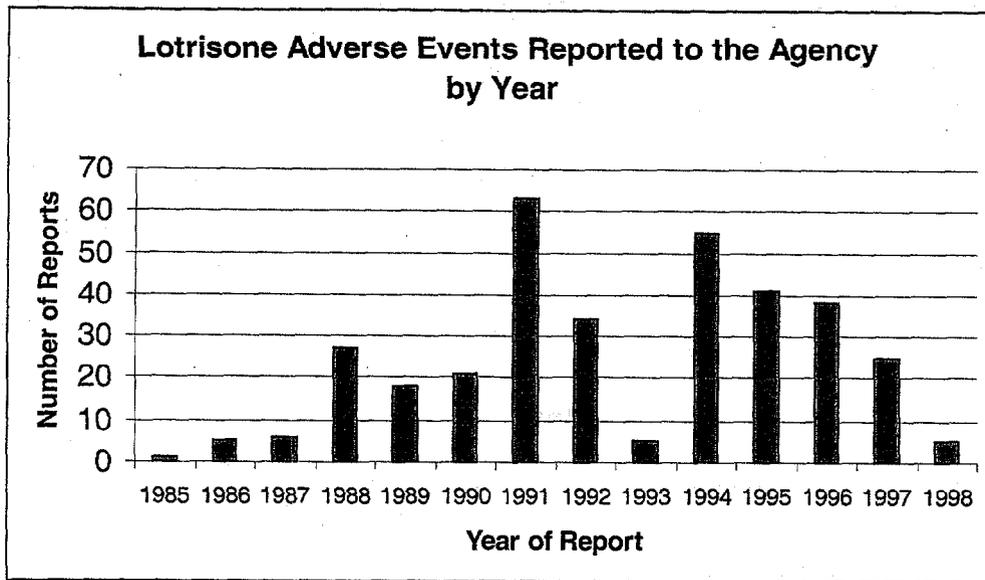


Figure 1

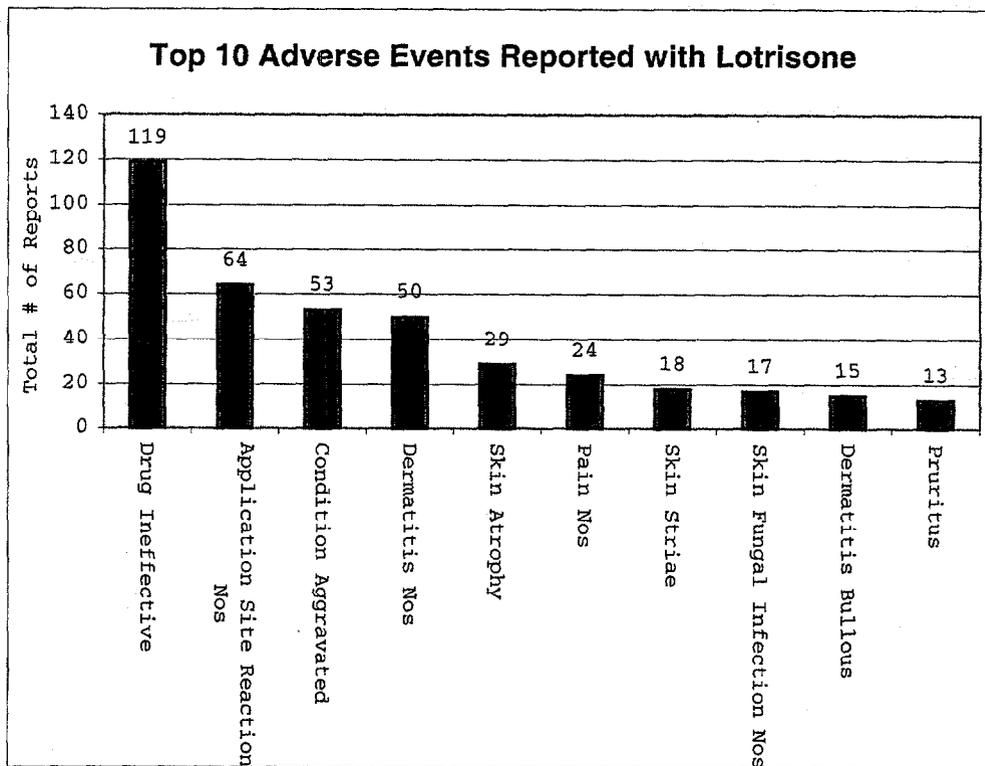


Figure 2

We included in our analysis a total of 315 unduplicated reports. Ages were recorded for 143 cases, 53 (37%) of which were pediatric. Table 1 summarizes data on age distribution and proportion treated for more than two weeks. When we excluded cases with a diagnosis of tinea pedis, the proportion of all cases treated for more than two weeks was 70%.

Table 1. Distribution of Cases by age, gender and proportion treated > 2 weeks

Age Distribution of Cases					
Age Group	Number of Cases	Females	Males	Unknown	Treated >2 Weeks N (%)
0 to <2	12	7	3	2	11 (64%)
≥2 to 6	12	8	4		10 (50%)
7 to 12	19	8	11		18 (44%)
13 to 18	10	9	1	1	10 (60%)
19 to 91	118	67	50	49	104 (47%)
Unknown	144	46	49	52	----
TOTAL	315	145	118	102	

Information on gender was available for 276 cases, 149 (54%) females and 127 (46%) males. Duration of therapy was recorded in 133 cases. The mean duration of therapy was 42 weeks with a median of 4 weeks and a range of one application to 2346 weeks. Four cases were classified as being disabled and 4 were hospitalized.

The total number of cases with data on indication was 153. The three most common indications were tinea corporis (21), tinea cruris (13) and tinea pedis (13). Non-specific 'rash' (11), tinea faciei (10) and diaper dermatitis - all synonyms combined - (10)

Pediatric Subset

In the infant age group (0-2) nine (75%) of the 12 cases had diaper dermatitis as the indication for treatment, nine had information on duration of therapy and in seven of them duration exceeded two weeks. The mean duration of therapy for the infant group was 16.5 weeks, with a median of six and range one to 80 weeks.

Growth Retardation

The single report of growth retardation occurred in a male infant aged 1.3 years (case number 5288123), who was treated for diaper dermatitis for 27 weeks .

WHO Results

There were 297 reported cases of adverse events to Lotrisone or Clotrasone, all but two of which were from the USA. The two non-USA reports were an erythematous rash from Spain and exfoliative dermatitis from the United Kingdom. Only summary figures are available in the WHO database, but it is likely that their case reports overlap with those reported to AERS.

Drug Use Data

For the past 6 years, there have been over 4 million prescriptions for lotrisone per year (see Table 2). The male:female use ratio is about 1:1 (see Table 3). The use of Lotrisone is uniform between the specified pediatric age groups (see Table 4). Table 5 shows the top 5 ICD-9 codes for which Lotrisone is recommended by age group.

Table 2 .Total Number of Prescriptions of Lotrisone Prescriptions by Year*

Total Number of Prescriptions of Lotrisone Prescriptions by Year					
<i>(numbers in thousands)</i>					
1993	1994	1995	1996	1997	1998
4,315	4,359	4,434	4,578	4,700	4,954

*National Prescription Audit, On-Line, IMS HEALTH

Table 3. Lotrisone Total Number of Drug Appearances by Sex and Year*

Lotrisone Total Number of Drug Appearances by Sex and Year								
<i>(numbers in thousands)</i>								
	% from Total	Total	1992	1993	1994	1995	1996	1997
Lotrisone (All)	100 %	9101	1673	1518	1585	1530	1498	1296
Female	49.6%	4517	757	678	826	754	820	681
Male	46.7%	4252	848	774	695	733	634	568
Unspecified	3.6%	332	68	66	65	42	44	47

* National Disease and Therapeutic Index, IMS HEALTH

Table 4. Lotrisone Total Number of Drug Appearances by Age and Year*

	Total	% from Total	1992	1993	1994	1995	1996	1997
Lotrisone (All)	9101	100	1673	1518	1585	1530	1498	1296
000-001 years	651	7.2	134	137	125	123	92	40
002-006 years	620	6.8	99	100	122	105	128	67
007-012 years	562	6.2	106	85	81	91	98	101
013-018 years	645	7.1	101	105	110	121	120	88
019+ years	6205	68.2	1202	1015	1053	996	990	949
Unspecified	417	4.6	31	76	95	95	70	51

* National Disease and Therapeutic Index, IMS HEALTH. Numbers in thousands

Table 5. Drug Uses for the Top 5 ICD-9 Codes for which Lotrisone is Being Recommended by Age Group*

(in thousands)								
	Total	% from Total	199 2	199 3	199 4	199 5	199 6	199 7
LOTRISONE (All)	9222	100	1695	1535	1601	1560	1513	1319
0-1 years	658	7.1	134	137	131	123	92	40
1123 CANDIDIASIS SKIN+NAILS	248	37.7	62	44	50	21	48	23
6910 DIAPER OR NAPKIN RASH	192	29.3	43	53	26	27	27	17
1100 DERMATO SCALP+BEARD	9	1.4	---	---	---	9	---	---
1103 DERMATO GROIN+PERIANAL	1	0.2	---	---	1	---	---	---
1105 DERMATOPHYTOSIS OF BODY	46	7	11	6	8	15	6	---
2-6 years	634	6.9	103	100	122	110	128	70
1105 DERMATOPHYTOSIS OF BODY	182	28.7	13	31	58	24	38	18
1119 UNSPEC DERMATOMYCOSIS	20	3.2	5	---	---	---	---	15
1100 DERMATO SCALP+BEARD	43	6.8	12	4	7	5	6	9
6929 DERM+ECZ UNSPEC CAUSE	86	13.5	17	4	8	15	33	9
6910 DIAPER OR NAPKIN RASH	21	3.4	---	6	3	---	6	6
7-12 years	569	6.2	106	87	81	97	98	101
1105 DERMATOPHYTOSIS OF BODY	167	29.4	30	22	17	36	23	41
6929 DERM+ECZ UNSPEC CAUSE	67	11.9	12	21	2	7	4	23
1119 UNSPEC DERMATOMYCOSIS	22	3.9	---	5	---	4	---	13
7040 ALOPECIA	7	1.2	---	---	---	---	---	7
6963 PITYRIASIS ROSEA	6	1	---	---	---	---	---	6
13-18 years	647	7	101	107	110	121	120	88
6929 DERM+ECZ UNSPEC CAUSE	58	9	10	2	4	9	16	18
1104 DERMATOPHYTOSIS OF FOOT	77	11.9	12	10	21	15	6	13
7821 RASH+OTH NONSP SKIN ERUP	48	7.3	11	4	11	5	5	11
1105 DERMATOPHYTOSIS OF BODY	89	13.7	4	8	17	21	29	9
1103 DERMATO GROIN+PERIANAL	117	18.1	21	28	24	21	17	6
19+ years	6288	68.2	1219	1020	1062	1014	1005	969
1105 DERMATOPHYTOSIS OF BODY	573	9.1	100	95	72	68	103	135
6929 DERM+ECZ UNSPEC CAUSE	950	15.1	199	135	149	187	157	123
7821 RASH+OTH NONSP SKIN ERUP	545	8.7	43	77	116	102	109	99
1103 DERMATO GROIN+PERIANAL	608	9.7	162	120	53	111	80	83
6161 VAGINITIS+VULVOVAGINITIS	527	8.4	61	64	121	82	131	69
Unspecified	426	4.6	31	84	95	95	70	51
6929 DERM+ECZ UNSPEC CAUSE	57	13.5	11	17	4	7	4	15
1119 UNSPEC DERMATOMYCOSIS	15	3.5	---	---	5	---	---	10
7821 RASH+OTH NONSP SKIN ERUP	57	13.3	---	---	26	18	4	8
1105 DERMATOPHYTOSIS OF BODY	34	8.1	---	6	13	---	7	8
1179 MYCOSES OTHER & UNSPEC	6	1.3	---	---	---	---	---	6

* National Disease and Therapeutic Index, IMS HEALTH

Literature Review

The following adverse events to Lotrisone or combination creams consisting of clotrimazole and betamethasone dipropionate were reported in the literature: treatment failure in tinea corporis caused by *Microsporum canis* (3), exacerbation of tinea corporis (4), striae (5), perioral dermatitis (6). The article on perioral dermatitis reported a series of 14 cases seen in a 16 month period by a single dermatologist. Their ages ranged from 9 months to 6.5 years and 5 of the 14 had been treated with clotrimazole/betamethasone dipropionate cream prior to the appearance of the perioral dermatitis. Other reports make reference to the potential development of side effects of topical steroids with prolonged use of Lotrisone (7,8). Yet others reported on side effects observed during the course of clinical trials (9).

Discussion

These data indicate that Lotrisone is widely used in the USA (> 4 million prescriptions per year consistently), and has a broad array of reported adverse events, in keeping with the observation that the longer a drug is on the market the greater the variety of adverse event seen. We must note also that AERS is a passive surveillance system and there is thus the likelihood of substantial underreporting of adverse events. It is therefore highly probable that there are many more cases of adverse events to Lotrisone. This is supported by the fact that at least three physicians wrote letters stating that the drug had been ineffective in several of their patients.

Of the 10 most commonly reported adverse events, most are labeled. However if we combine the most commonly reported adverse event, that the drug was ineffective, with the third most common adverse event, that it aggravated the condition, we realize that the drug failed to achieve the desired effect in 23% of reported cases.

The drug use data indicate that about 30% of the use of Lotrisone is in the pediatric age group (Table 4). Drug use data (Table 5) also show that much of this is off label for age and indication.

We sought additional information from the WHO database because all the AERS cases were domestic. However the vast majority of the WHO cases were also US cases with only two non – USA reports. It is not possible to determine to what extent this represents differences in prescribing practices, true differences in adverse events experience or spurious differences due to underreporting.

Conclusion

The results show that Lotrisone is widely used in the USA, and that adverse events are not rare. The data suggest that adverse events are associated with off label use of the drug, in terms of age, indication for use and length of use. This is particularly so in the pediatric age group. The commonest overall adverse event was that the drug was ineffective. There was a single case of growth retardation associated with prolonged use of the drug for an off label indication.

References

1. Lotrisone. Mosby's GenRx – Stat!Ref On-line Medical Reference, Winter 1999 CD-Rom
2. Lotrisone. Schering. Physicians' Desk Reference On-line, 1999
3. Rosen T and Elewski BE. (1995): Failure of clotrimazole-betamethasone dipropionate cream in treatment of *Microsporum canis* infections. *Journal of the American Academy of Dermatology*. 32 (6): 1050-1
4. Reynolds RD, Boiko S and Lucky AW. (1991): Exacerbation of tinea corporis during treatment with 1% clotrimazole/0.5% betamethasone dipropionate. *American Journal of Diseases of Children*. 145 (11): 1224-5
5. Barkey WF. (1987): Striae and persistent tinea corporis related to prolonged use of betamethasone dipropionate 0.05 % cream/clotrimazole 1% cream. *Journal of the American Academy of Dermatology*. 17 (3): 518-9
6. Manders SM and Lucky AW. (1992): Perioral dermatitis in childhood. *Journal of the American Academy of Dermatology*. 27 (5) I: 688-92.
7. Fisher DA. (1995): Adverse Effects of Topical Steroids. *Western Journal of Medicine*. 162 (2): 123-6
8. Hanson SG and Nigro JF. (1998): Pediatric Dermatology. *Medical Clinics of North America*. 82 (6): 1381-1403
9. Smith EB, Breneman DL, Griffith RF, Hebert AA, Hickman JG, Maloney JM, Millikan LE, Sulica VI, Dromgoole SH, et al. (1992): Double-blind comparison of naftifine cream and clotrimazole/betamethasone dipropionate cream in the treatment of tinea pedis. *Journal of the American Academy of Dermatology*. 26 (1): 125-7