

4. Since the human exposure in psoriasis patients (for use on up to 20% of body surface area) may be in the same order of magnitude as that in pregnant animals that developed teratogenic effects, Pregnancy Category X is recommended for tazarotene. The labeling is to be rewritten to be consistent with the requirements given in 21CFR201.57. In addition, adequate birth control should be used in females of child-bearing potential who are to be treated with tazarotene and physicians are to consider the possibility of pregnancy at the time of institution of therapy.

5. The precautions regarding irritation due to retinoid use, sun exposure and concomitant use of photosensitizers are to be stated.

6. Changes are to be made in the INFORMATION FOR PATIENTS section with respect to pregnancy, irritation due to retinoid use, sun exposure and concomitant use of photosensitizers to reflect those in the prescribing information section.

5. Risk benefit analysis

Tazarotene is a new molecular entity which has shown efficacy in the once-a-day topical treatment of stable plaque psoriasis covering less than 20% of body surface area and of mild to moderate facial acne vulgaris. Theoretically tazarotene is able to act on these disease states through multiple mechanisms; whereas in practice, it holds little advantage over existing marketed products for these indications. As with other retinoids, there is a risk of teratogenicity, although this is hard to estimate because of the lack of human data. It also poses certain local safety concerns, particularly when used to treat mild cases of these conditions but may be considered to have acceptable safety if properly labeled so that physicians may prescribe and patients may use it with due precautions.

6. Recommendations

6.1 Regulatory Recommendations:

1. It is recommended that tazarotene 0.05% gel be approvable for the daily topical treatment of stable plaque psoriasis covering not more than 20% of body surface area.
2. It is recommended that tazarotene 0.1% gel be approvable for the daily topical treatment of stable plaque psoriasis covering not more than 20% of body surface area and in the treatment of mild to moderate facial acne vulgaris.

6.2 Phase 4 Recommendations:

6.3 Labeling: Labeling should be modified as per comments given in Section 4.

6.4 Other: Deficiencies listed in the comments in this review should be addressed.

1. Study R168-146-8606, a phase 3 trial being conducted in the U.K., has not been included in the safety update. Although it has not been unblinded, available safety data should be submitted.

2. The Study Report for R168-722-8606 has been submitted previously. The only additional information in this submission was addition of a Table of ALL adverse events shown in the Safety Update (Safety Update Table 2c from 6/27/96 submission, p. 1-050). This Table does not agree with that in the study report (Table 8 of study report, p. 4-069 of 6/27/96 submission). The differences should be explained.

3. In R168-128-8606, the Applicant is unable to document an allergic component and has conceded that the reactions represent local irritation produced by tazarotene gel. However, the Applicant still classifies them as allergic contact dermatitis in their data analysis. This needs to be corrected.

4. The Applicant could have analyzed age subsets within those <45 of age in acne studies.

5. Information on follow-up of the three babies born of mothers who became pregnant while being treated with tazarotene in the clinical trials is needed. In addition, plasma drug levels from subject in Study R168-221-8606 taken when pregnancy was discovered should be presented.

H. S. Ko 12-14-96

Hon-Sum Ko, M.D.

M. Katz, MD 12/16/96

cc: Original NDA 20-600

HFD-540

HFD-340

HFD-540/CSO/Cross

HFD-540/CHEM/Gilman

HFD-540/PHARM/Nostrandt

HFD-715/BIOMETRICS/Thomson

HFD-880/BIOPHARM/Lee

HFD-540/MO/Ko

**Medical Officer's Review of NDA 20-600
Amendment**

MAY 9 1997

**NDA #20-600
AZ**

**Submission dates: 1/17/97
Received date: 1/21/97
Review completed: 4/3/97
Review revised: 4/14/97**

Drug name: tazarotene

Generic name: tazarotene

Proposed trade name: Tazorac™

Chemical name : Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate

**Applicant: Allergan, Inc.
P.O. Box 19534
2525 Dupont Drive
Irvine, CA 92713-9534**

Pharmacologic Category: Retinoid

**Proposed Indication(s): 1. for the topical treatment of plaque psoriasis and
2. for the topical treatment of acne vulgaris**

Dosage Form(s) and Route(s) of Administration: topical gel 0.1% and 0.05%.

NDA Drug Classification: 1 S

Related NDAs: none. Studies in NDA 20-600 were conducted under IND

**Related Reviews: Pharm/Tox Review dated: 4/13/97
Biopharm Review dated: 3/14/97**

Background and Material Reviewed

This review is based on the clinical sections from the Applicant's response dated 1/17/97. This is a response to the Approvable Letter of 12/30/96, which stated that "Tazarotene gel, 0.05%, is approvable for the daily topical treatment of stable plaque psoriasis covering not more than 20% of body surface area. Tazarotene gel, 0.1%, is approvable for the daily topical treatment of stable plaque psoriasis covering not more than 20% of body surface area and in the treatment of mild to moderate facial acne

vulgaris." The following items were requested:

I. Labeling, Additional Information and Commitments

1. Revised draft labeling,
2. Study R168-146-8606 safety data,
3. Explanation for differences in the safety data for Study R168-722-8606 in the Safety Update of 6/27/96 submission and in the study report,
4. Corrections in the analyses of safety data due to misclassification of 3 cases of irritant contact dermatitis as allergic contact dermatitis in Study R168-128-8606,
5. Analysis of age subsets in patients <45 years of age in acne studies,
6. Information on follow-up of the three babies born of mothers who became pregnant while being treated with tazarotene in the clinical trials and plasma drug levels from subject in Study R168-221-8606 taken when pregnancy was discovered,
7. Commitment to conduct the following Phase 4 Study:

8. Commitment to provide the following:

II. Safety Update

An update with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc. and in addition, the following items:

1. Retabulation of safety data including results of trials that were still ongoing at the time of NDA submission.
2. Retabulation of drop-outs with new drop-outs identified.
3. Details of significant changes or findings, if any.
4. Summary of worldwide experience on the safety of this drug.
5. CRFs for each patient who died or who did not complete a study because of an adverse event.

This review will be organized into three sections as follows, the first two corresponding to the above requests and the third a labeling review:

- I. Response to requests,
- II. Safety update and
- III. Proposed label by the Applicant.

I. Response to Requests on Labeling, Additional Information and Commitments

1. Revised draft labeling. See Labeling Review (Section III).

2. Study R168-146-8606 safety data. See Safety Update (Section II).

3. Explanation for differences in the safety data for Study R168-722-8606 in the Safety Update of 6/27/96 submission and in the study report.

The Applicant indicated that the study report has omitted some adverse events such as erythema and mild irritation on the normal skin surrounding a treated psoriatic plaque, which were reported on the Case Record Forms. Upon further review and in consultation with the Investigators, the incidences of adverse events have been corrected in the Safety Update of 6/27/96.

4. Corrections in the analyses of safety data due to misclassification of 3 cases of irritant contact dermatitis as allergic contact dermatitis in Study R168-128-8606. Corrections submitted.

5. Analysis of age subsets in patients <45 years of age in acne studies.

The following two Tables summarize the analyses for efficacy and safety data with age 20 as the cutoff for the two subsets analyzed. Age 20 was chosen because the median age was about 20 so that there might be maximal numbers of subjects on either side for analysis.

Subset Analysis of Adverse Event Data by AGE for Acne Trials Combined*

	<20				20 or Over		
	0.1%*	0.05%	Vehicle	0.1% vs 0.05%	0.1%	0.05%	Vehicle
Total pt no	179	165	172		120	132	123
Pts with AE	106 (59)	83 (50)	52 (30)		71 (59)	78 (59)	59 (48)
p values	<u>0.001</u>	<u>0.001</u>					
Skin	86 (48)	64 (39)	22 (13)		57 (48)	65 (49)	25 (20)
p values	<u>0.001</u>	<u>0.001</u>			<u>0.001</u>	<u>0.001</u>	
Desquamation	52 (29)	26 (16)	2 (1)		32 (27)	35 (27)	4 (3)
p values	<u>0.001</u>	<u>0.001</u>		<u>0.004</u>	<u>0.001</u>	<u>0.001</u>	
Burning	40 (22)	26 (16)	5 (3)		35 (29)	31 (24)	3 (2)
p values	<u>0.001</u>	<u>0.001</u>			<u>0.001</u>	<u>0.001</u>	
Dry skin	38 (21)	30 (18)	9 (5)		21 (18)	30 (23)	6 (5)
p values	<u>0.001</u>	<u>0.001</u>			<u>0.001</u>	<u>0.001</u>	
Erythema	28 (16)	14 (9)	0		27 (23)	19 (14)	0
p values	<u>0.001</u>	<u>0.001</u>		<u>0.048</u>	<u>0.001</u>	<u>0.001</u>	
Irritation	9 (5)	5 (3)	1 (1)				
p values	<u>0.021</u>						
Respiratory System							
Rhinitis					2 (2)	0	9 (7)
p values						<u>0.001</u>	

*Acne trials combined=pooled data from phase 3 acne trials (R168-220-7997 and R168-221-8606). 0.1% and 0.05% represent tazarotene 0.1% and 0.05% gels respectively. Percent incidences given in parentheses, with actual patient numbers preceding them. Only data with significant differences between treatment groups are shown.

*Significant differences in incidence rates between vehicle and tazarotene gels are highlighted (p<0.05).

**Significant differences in incidence rates between tazarotene gels are shown double-underlined (p<0.05).

Subset Analysis of Efficacy Data by AGE for Acne Trials Combined*

	<20			20 or Over		
	Taz 0.1% (N=156)	Taz 0.05% (N=136)	Veh (N=156)	Taz 0.1% (n=99)	Taz 0.05% (N=117)	Veh (N=108)
Inflammatory Lesion Counts						
wk-0	24	24	24	18	17	19
wk-4	22 (9)*	21 (10)	23 (5)	13 (27)	13 (26)	14 (28)
wk-8	17 (29)	17 (27)	19 (23)	10 (45)	10 (43)	12 (37)
wk-12	14 (40)	16 (51)	19 (20)	8 (54)	9 (47)	11 (42)

	(p<0.01)	(p<0.05)				
Noninflammatory Lesion Counts						
wk-0	63	64	60	48	42	47
wk-4	48 (23) (p<0.01)	56 (18) (p<0.05)	56 (6)	34 (29)	30 (29)	38 (20)
wk-8	40 (36) (p<0.01)	46 (28) (p<0.01)	50 (17)	25 (48) (p<0.01)	23 (45) (p=0.04)	30 (36)
wk-12	36 (43) (p<0.01)	42 (28) (p<0.01)	46 (23)	19 (59) (p<0.01)	21 (50)	27 (43)
Total Lesion Counts						
wk-0	86	87	84	65	59	67
wk-4	69 (20) (p<0.01)	76 (12) (p<0.05)	77 (8)	47 (29)	42 (29)	51 (24)
wk-8	56 (35) (p<0.01)	63 (23) (p<0.05)	68 (19)	34 (48) (p=0.01)	33 (45) (p=0.02)	42 (37)
wk-12	50 (43) (p<0.01)	57 (28) (p<0.01)	65 (23)	27 (58) (p<0.01)	30 (50)	39 (42)
"Treatment Success" (Percent of subjects)						
wk-4	17	12	9	26	23	20
wk-8	37 (p<0.01)	22 (p<0.05)	19	51 (p=0.05)	50	35
wk-12	49 (p<0.01)	22 (p<0.05)	25	72 (p<0.01)	53 (p=0.04)	50

*Acne trials combined=pooled data from phase 3 acne trials (R168-220-7997 and R168-221-8606). Taz=tazarotene, veh=vehicle. "Treatment success" defined as global score of "good" or better. Percent reduction in lesion counts is given in parentheses. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05).

Comments

1. These posthoc subset analyses do not necessarily have the power to detect significance, as the studies were not designed to yield subset information.
2. Efficacy. In the ≥20 age group, there was a substantial effect by vehicle, thus lessening the significance of tazarotene effect, such that none of the efficacy parameters showed significant differences between tazarotene 0.05% gel and vehicle at endpoint (12 weeks). Tazarotene 0.1% gel was effective in both age groups.
3. Safety. It appears that for the <20 age group, the incidence of adverse events with use of tazarotene 0.05% gel was lower, with desquamation and erythema showing significant differences between the 0.1% and 0.05% gels. None of the other adverse events showed significant differences between the two formulations in either the <20 or ≥20 age groups.
4. Laboratory (data not presented here). No consistent clinically significant abnormalities in either age subset.

6. **Information on follow-up of the three babies born of mothers who became pregnant while being treated with tazarotene in the clinical trials and plasma drug levels from subject C14 in Study R168-221-8606 taken when pregnancy was discovered** See Safety Update (Section II, item 10.2.8).
7. **Commitment to conduct a phase 4 pharmacokinetic study clarifying the systemic exposure to and distribution of AGN 190299, the active metabolite of tazarotene, following long term use in psoriatic patients**

Report on a study, numbered 190168-004 and entitled "An open-label safety, pharmacokinetics and efficacy study of tazarotene (AGN 190168 0.1% or 0.05% gel applied once daily for twelve weeks in the treatment of plaque psoriasis:

pharmacokinetic analysis) was submitted. See Biopharm Review.

Comment The purpose of this proposed commitment is to find out the systemic exposure and distribution of the active metabolite of tazarotene in patients on stable long-term topical treatment with tazarotene. In this study, a treatment period of 12 weeks may be considered as sufficiently long-term for tazarotene application. Other aspects of the study design will be commented on by the Biopharm Reviewer.

8. Commitment to provide the following:

Comment Although there are no positive human data showing adverse effects on fetus, since the degree of exposure in the treatment of psoriasis covering 20% of body surface area may be in the same order of magnitude as that in animal experiments demonstrating teratogenic effects, a registry documenting the condition and follow-up of babies born of exposed women will certainly help to elucidate the potential of teratogenicity in humans.

II. Safety Update

A. Reports of safety data, including those from studies and usages involving other indications, other dosage forms and other dose levels, etc.

No other dosage forms or indications have been studied. Safety data from three studies have been submitted (see review in Section II B). These studies involved using different dosing regimens of tazarotene or tazarotene in combination with corticosteroids or vehicle in the treatment of psoriasis:

R168-146-8606, AGN 190168 0.05% and 0.1% gels in the long-term (up to 24 weeks) treatment of plaque psoriasis.

190168-001-00, Investigator-masked study of the safety and efficacy of tazarotene (AGN 190168) 0.1% gel (and) plus corticosteroid cream or placebo cream each applied once-daily for 12 weeks in the treatment of plaque psoriasis.

190168-002-00. Safety and efficacy of tazarotene 0.1% gel vs vehicle gel applied once every other day for up to 24 weeks in plaque psoriasis.

<u>Study</u>	<u>Dosing regimen</u>		<u>Enrolled</u>	<u>Dropout</u>		
				<u>AE</u>	<u>LOC</u>	<u>Other</u>
<u>R168-146-8606</u>	Taz* 0.1% qd or less frequently	x 24 wks	93	18	9	12
	Taz 0.05% qd or less frequently	x 24 wks	95	18	20	8
<u>190168-001-00</u>	Taz 0.1% qd + vehicle qd	x 12 wks	75	10	3	10
	Taz 0.1% qd + Synalar 0.01% cream qd	x 12 wks	78	13	1	10
	Taz 0.1% qd + Elocon 0.1% cream qd	x 12 wks	74	4	0	5
	Taz 0.1% qd + Lidex 0.05% cream qd	x 12 wks	73	7	1	5
<u>190168-002-00</u>						
Phase 1	Gp (a) Taz 0.1% q2d	x 12 wks	84	9	0	15
	Gp (b) Vehicle q2d	x 12 wks	82	8	3	8
Phase 2	Gp (a) Taz 0.1% q2d	x 12 wks	60	5	2	4
	Gp (b) Taz 0.1% q2d**	x 12 wks	64	5	1	4

*Taz=tazarotene, AE=adverse event dropouts, LOC=lack of efficacy dropouts and Other=dropouts due to other reasons.
 **Gp (b) patients used vehicle in first 12 weeks and then Taz 0.1% in the remaining 12 weeks of the 24-week study.

B. Integrated Summary of Safety.

The Applicant has not integrated new data with previously submitted safety information. Since the treatment regimens in the new studies were different from those in the pivotal phase 3 trials, it is difficult to compare directly these studies with previous trials. These new data do not have an impact on the proposed label, because this Application only includes dose regimens as used in the phase 3 pivotal studies for psoriasis and acne. This part of the review will be presented in the same format as in Section 10 of the original NDA review.

10. Overview of Safety

Updated information in the current submission includes data from 2 U.S. and one non-U.S. controlled trials with tazarotene in the treatment of plaque psoriasis (see Section IIA for details). There were no additional studies for acne. As stated above, these data were obtained from patients using dose regimens different from those in the phase 3 pivotal trials for psoriasis.

Comment It is not appropriate to pool previous and new data for analysis. In none of the new studies, exposure to tazarotene exceeded that encountered in previously submitted studies. Even in the long-term study, R168-146-8606, exposure (0.1% or 0.05% gel qd or less frequently for up to 24 weeks) was substantially lower than that in the previously reported long-term safety study, R168-128-8606 (0.1% or 0.05% gel qd for one year). Moreover, the recommended dosing regimens in the proposed label are based on those in the previous studies. Thus, in this review, the Safety Update data will be presented alone and reference to previous data will only be made if either (a) there is substantial departure from old information or (b) previous data are needed to put the new information into perspective.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths In this update, there were two deaths in the clinical trials:

<u>Study</u>	<u>Patient Age/Sex</u>	<u>Cause of Death</u>	<u>Relationship to Tazarotene treatment</u>
190168-001-00	37/M	Heart failure, AIDS	not related (Taz 0.1% qd + Synalar 0.01% qd)
190168-002-00	45/F	GI bleeding, cardiac arrest	not related (Taz 0.1% q2d)

10.1.2 Other Significant/Potentially Significant Events The study reports did not specify the incidence of "serious" adverse events. The following Tables show the patients who discontinued treatment on the basis of adverse events in this Safety Update. Case Record forms were only provided for deaths in the submission of 1/17/97 but those for adverse event discontinuations were presented upon request on 3/17/97. Safety data from postmarketing experience are lacking, since tazarotene has just been approved in Germany in December, 1996. Pregnancies encountered in clinical trials involving tazarotene are discussed in Section 10.2.8.

Dropouts due to Adverse Events in R168-146-8606

<u>Tazarotene 0.1% qd or less frequently</u>		<u>Tazarotene 0.05% qd or less frequently</u>	
<u>Patient No</u>	<u>Adverse Event</u>	<u>Patient No</u>	<u>Adverse Event</u>
	burning pruritus/psoriasis worse burning/psoriasis worse/joint disease pruritus burning/erythema pruritus burning erythema erythema irritation irritation burning/erythema/focal edema pruritus/chills burning/erythema/pruritus/edema pruritus burning irritant contact dermatitis irritation		peripheral edema dry skin/desquamation flu syndrome irritation skin pain pruritus pruritus burning liver function abnormal skin fissure psoriasis worse burning/chills erythema burning burning skin pain/erythema atopic dermatitis psoriasis worse

Dropouts due to Adverse Events in 190168-001-00

<u>Taz 0.1% qd + Vehicle qd</u>		<u>Taz 0.1% qd + Synalar qd</u>		<u>Taz 0.1% qd + Elocon qd</u>		<u>Taz 0.1% qd + Lidex qd</u>	
<u>Pt no</u>	<u>AE</u>	<u>Pt no</u>	<u>AE</u>	<u>Pt no</u>	<u>AE</u>	<u>Pt no</u>	<u>AE</u>
I			dermatitis	PW		I/Pa	
I/PW			P/rash	E/P/excoriation/		E/P/De	
P/PW/folliculitis			B/I	folliculitis		arthralgia	
De/B/P			felt skin cold	ICD		E/stinging	
De/PW/headache			AIDS/CHF/death	myocardial infarct		B/P	
B/E/P			ICD/P/headache			felt skin cold & damp	
B			B/De/P			E	
B			E/P				
E/P/tightness/hives			ICD				
P/felt skin cold			PW				
			PW				
			P				
			B/E				

*B=burning, D=dry skin, De=desquamation, E=erythema, I=irritation, ICD=irritant contact dermatitis, P=pruritus, Pa=skin pain, PW=psoriasis worse

Dropouts due to Adverse Events in 190168-002-00

<u>Tazarotene 0.1% q2d</u>		<u>Vehicle q2d</u>	
<u>Pt No</u>	<u>Adverse Event</u>	<u>Pt No</u>	<u>Adverse Event</u>
	skin discharge/psoriasis worse/skin pain burning/pruritus excoriation/pruritus/skin pain/skin hemorrhage chest & foot pain/flu/irritant contact dermatitis lichen dermatitis/desquamation/headache/ psoriasis worse/rhinitis irritation/pruritus/skin pain eczema/irritation erythema/pruritus/burning/dry skin/focal edema psoriasis worse/irritation erythema/pruritus/skin pain psoriasis worse psoriasis worse GI bleed/cardiac arrest/death skin fissure/skin hemorrhage/pruritus/psoriasis worse		psoriasis worse/irritation psoriasis worse psoriasis worse psoriasis worse <u>psoriasis worse/erythema/pruritus*</u> psoriasis worse <u>irritation</u> psoriasis worse desquamation/skin fissure/skin pain <u>pruritus</u> <u>general edema</u> atrial flutter/heart failure/drug interaction (coagulopathy with coumadin) psoriasis worse/irritation

*Dropouts belonging to "vehicle group" in phase 2 (in which they use Taz 0.1% q2d) are underlined.

10.1.3 Overdosage exposure No new information submitted.

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables New adverse event data in the current Safety Update are presented in Appendices I through III of this review. Such data are not pooled with previous data in this review because the dosing regimens were sufficiently different such that combining the datasets would lead to misleading information. Thus, Appendices I to III represent only the individual adverse event data of the 3 psoriasis trials of this Safety Update.

Comments No new pertinent information has been gained from AE data of R168-146-8606. Retabulation of data from 190168-001-00 and 190168-002-00 is being submitted and will be reviewed upon receipt.

10.2.2 Laboratory Findings, Vital Signs, ECGs Laboratory data not presented in the three trials of this Update.

Comment In at least two of the studies, laboratory data were collected but not presented or discussed. These should have been included in the Update.

10.2.3 Special Studies Report of one PK study, #190168-004, entitled "An open-label safety, pharmacokinetics and efficacy study of tazarotene (AGN 190168) 0.1% or 0.05% gel applied once daily for 12 weeks in the treatment of plaque psoriasis: pharmacokinetic analysis" is included in this submission. This is reviewed by Biopharm and the findings incorporated into the new label (see Section III).

10.2.4 Drug-Demographic Interactions Previously submitted safety data have not suggested significant drug-demographic interactions when analyzed according to subsets for age, sex or race. A new analysis has not been made using data from this Update. However, because the number of patients in the subsets would be small, due to the limited numbers enrolled into the various arms using different dosing regimens, it is not anticipated that such an analysis would be helpful in detecting significant interactions.

10.2.5 Drug-Disease Interactions No new information submitted.

10.2.6 Drug-Drug Interactions There is little information on the interaction between tazarotene and other drugs. As with other retinoids, local irritation may become exaggerated if tazarotene is used in conjunction with other skin irritants. In addition, coadministration with photosensitizers should be avoided because of the possibility of augmented phototoxicity. The drying effect of tazarotene gels may also be aggravated by other dermatologic preparations that have a drying effect.

One of the studies in this Update, #190168-001-00, compared the use of tazarotene plus vehicle vs tazarotene plus a topical corticosteroid in the treatment of plaque psoriasis. Tazarotene plus Elocon cream 0.1% appears to reduce the incidence and severity of treatment-related adverse events vs tazarotene plus vehicle:

Drug	N	Patients with Adverse Events			Total
		mild	moderate	severe	
taz*+vehicle	75	11 (15%)	20 (27%)	7 (9%)	38 (51%)
taz+Synalar	78	9 (12%)	27 (35%)	3 (4%)	39 (50%)
taz+Elocon	74	16 (22%)	11 (15%)	2 (3%)	29 (39%)
taz+Lidex	73	11 (15%)	15 (21%)	5 (7%)	31 (42%)

*taz=tazarotene

Comment This study was not powered to detect significant differences between treatment groups for safety parameters, and the Applicant has not presented a statistical analysis (analysis by the Agency's Biometrician, Steve Thomson, showed no significant differences between treatment groups). These data must be regarded as preliminary and require confirmation with trials having more rigorous design.

10.2.7 Withdrawal Phenomena/Abuse Potential No new information.

10.2.8 Human Reproduction Data Pregnant women and those attempting pregnancy were excluded from studies. In the original submission, seven cases of pregnancy were reported in the clinical trials. Three of these patients used vehicle gel and one used Dovonex 0.05% cream. The remainder used tazarotene. In the current Safety Update, the Applicant presented three additional cases but details were given for only one patient. The other two cases included one woman in a bilateral comparison study for psoriasis (tazarotene 0.1% to one lesion and vehicle to a contralateral lesion) in Japan and another in a U.S. trial using tazarotene 0.1% gel plus Synalar 0.01%

cream for psoriasis. At the time of submission of the amendment of 1/17/97, the last patient has not yet given birth.

<u>Study/Pt no</u>	<u>Age</u>	<u>BL-BSA*</u>	<u>Pregnancy detected*</u>	<u>Duration of exposure from last negative pregnancy test</u>	<u>Outcome of baby</u>
<u>Psoriasis Trials</u>					
120-J15	26	8%	63 d	33 d x tazarotene 0.1% qd	FT*/healthy
120-E18	29	3%	121 d (32 d post-Tx)	0	FT/healthy
190168-001-B02	<u>(data being submitted; not received)</u>			? d x tazarotene 0.1% qd + Synalar 0.01% qd	___?___
190168-002-D36	31	6%	86 d	33 d x tazarotene 0.1% q2d	FT/healthy
190168-901-Ha6142	35	N/A*	25 d	? d x tazarotene 0.1% qd <u>(No documentation of negative pregnancy test)</u>	healthy
<u>Acne Trials</u>					
221-C14	20	N/A	37 d	31 d x tazarotene 0.1% qd	FT/healthy

*Race=Japanese; all other patients were white. BL-BSA=Baseline body surface area involvement by psoriasis. N/A=not applicable (in bilateral comparison psoriasis trial or in acne trial). Pregnancy detected=time from start of treatment to detection by pregnancy test. FT=full term.

Comments

1. Patient was found pregnant in the posttreatment period, 32 days after her last dose. It is possible that she did not have exposure in pregnancy.
2. Only patient had LMP information, so that her exposure from the time of conception could be determined (27 d).
3. The other 4 patients might have been exposed for a few days to more than 5 weeks during their pregnancy, depending on the timing and sensitivity of the pregnancy test. As the window of organogenesis in relation to tazarotene exposure is unknown in these patients, it is not appropriate to draw conclusions on the potential for reproductive toxicity in humans from these data.
4. There is limited information on the degree of exposure in relation to the size of the lesions treated.
5. Plasma levels were available for the following patients:
However, was found pregnant in the posttreatment period (see above) and had blood drawn 13 days after her last dose. The blood level data are therefore not helpful in evaluating exposure.
6. For patient data on plasma drug levels were requested by the Agency. The Applicant states that these are no data, as there was difficulty in obtaining blood.

Conclusions for Safety Update

1. Safety data from the three new studies R168-146-806, 190168-001-00 and 190168-002-00 have not sufficiently altered the safety profile as seen in the pivotal studies.
2. Information from the five (possibly six) patients who have used tazarotene gel during pregnancy is of limited value but does suggest that it is possible to give birth to apparently healthy babies despite tazarotene use. Since the extent and exact timing of exposure in these patients is not well documented, a pregnancy registry designed specifically to study the relationship between exposure and fetal risk is warranted.

III. Labeling Review on Proposed Label by Applicant

Two areas of concern have been raised and discussed by the Applicant: efficacy of tazarotene 0.05% gel in the treatment of noninflammatory acne and pregnancy category.

1. Efficacy of Tazarotene 0.05% Gel in the Treatment of Noninflammatory Acne. No new information has been submitted.

Comment Reference is made to my review of November 26, 1996 detailing the reasons why tazarotene 0.05% should not be approved for the treatment of acne. To summarize, the clinical studies were designed to support the indication *mild to moderate facial acne vulgaris* and *not noninflammatory acne*. The 0.05% gel was not approved for acne because neither the investigator's global distribution (including "treatment success" rates, defined as 50% or better improvement vs baseline) nor patient's assessment favored this drug product over vehicle in either of the two studies, despite significant reductions in noninflammatory and total lesion counts at endpoint. No new information has been submitted to support the indication of *noninflammatory acne* for tazarotene 0.05% gel.

2. Pregnancy Category. The Applicant contends that both concentrations of tazarotene gel should be under category C rather than category X for the following reasons:

Psoriasis. To support Pregnancy Category C for plaque psoriasis, the label proposes to limit the use of tazarotene in the treatment of plaque psoriasis to no more than 10% of surface area in women of child-bearing potential and to no more than 30 Gm of gel over any 10 day period.

Comments

1. This limitation is proposed in the WARNINGS section and not the INDICATIONS section.
2. A dose of 30 Gm/10 days gives an average of 3 Gm/d, suggesting about 1500 cm² to be treated, approximately 10% surface area of an adult. This may sound reasonable. However, there may be patients who have a flare of psoriasis in which case most of one tube is used for a few days and most of a second tube is used in the next few days but can still be considered as having used a 30 Gm tube for the first 10 days and the second 30 Gm tube in the next 10 days. Thus, the two conditions (≤ 30 Gm over 10 days and $\leq 10\%$ surface area) must be in combination and not considered as a case of "either" "or".
3. As there is no way to prevent off-label use, it is unclear how effective these restrictions may be in the actual clinical setting.
4. The Pharm/Tox Reviewer notes that at 10% total body surface area, tazarotene 0.1% gel administered to psoriatic patients may still give systemic exposure in the same order of magnitude as that in orally treated rats whose offspring experienced teratogenic or fetotoxic effects (AUC_{0-24 hr} observed in such rats only 1:4 times higher than that extrapolated in psoriatic patients using TAZORAC™ 0.1% gel over 10% of body surface). For patients using tazarotene 0.05% gel, this safety margin (AUC_{0-24 hr}) over the same teratogenic/fetotoxic level in rats may be extrapolated to be 2.8 times, still within the same order of magnitude.
5. There are safer topical drugs for the treatment of stable plaque psoriasis covering up to 20% of body surface area. It appears unwarranted to take the

risk of teratogenicity/fetotoxicity by allowing this indication in pregnant females.

6. In the INFORMATION FOR PATIENTS pamphlet, the Applicant states:

(A) **"BEFORE YOU USE THIS MEDICINE**

You should be aware that:

(a) TAZORAC™ should not be used if you are pregnant, attempting to become pregnant or at high risk of pregnancy. Consult your physician." and

(B) under WARNINGS, "TAZORAC™ should not be used if you are pregnant, attempting to become pregnant or at high risk of pregnancy."

This is defacto Pregnancy Category X.

Acne. To support Pregnancy Category C for acne vulgaris, the Applicant argues that percutaneous absorption in acne subjects may be expected to be similar to that in healthy individuals, who had been shown in previous studies to have lower systemic exposure than in psoriatics upon application of tazarotene ($AUC_{0-24\text{ hr}}$ 17 times lower). As the face constitutes about 2% of surface area, systemic exposure can be expected to be minimal when compared to that in animals given teratogenic/fetotoxic doses.

Comments

1. This argument is based on extrapolation of exposure in healthy subjects. However, those studies were done on normal skin in the back. Facial skin was not studied. As the facial skin has more vasculature and better systemic absorption, systemic exposure upon facial application may be expected to be greater than application on the back.

2. Studies have not been done on skin with acne lesions. As tazarotene is to be used for the treatment of inflammatory as well as noninflammatory acne, absorption through facial skin with such lesions cannot be assumed to be equal to that over normal skin on the back. Documentation of systemic exposure upon application to facial acne would be needed in order to support the Applicant's contention.

3. As there is no way to prevent off-label use, patients who use this drug product over acne sites other than the face may have additional exposure.

4. A drug with teratogenic potential should not be used by pregnant women for facial acne of *mild to moderate* severity.

5. In the INFORMATION FOR PATIENTS pamphlet, the Applicant states:

(A) **"BEFORE YOU USE THIS MEDICINE**

You should be aware that:

(a) TAZORAC™ should not be used if you are pregnant, attempting to become pregnant or at high risk of pregnancy. Consult your physician." and

(B) under WARNINGS, "TAZORAC™ should not be used if you are pregnant, attempting to become pregnant or at high risk of pregnancy."

This is defacto Pregnancy Category X.

The rest of this labeling review is based on the revised proposed label submitted on 1/17/97 and will follow the layout in Section 11 of the standard NDA review format.

11 Labeling Review

11.1 Description acceptable

11.2 Clinical Pharmacology

Pharmacokinetics

see Biopharm Reviewer's review. The Pharmacokinetics section has been revised by the Biopharm Reviewer to include changes arising from the study report of 190168-004-00. The Applicant wishes to also include the data from therapeutic drug monitoring in the clinical trials. This is not acceptable to the Biopharm Reviewer because of the lack of information on the skin surface area involved, dose applied and blood sampling time relative to dosing time. As C_{max} occurred 6 hrs (normals) to 9 hrs (psoriatics) after dosing in previous PK studies, it is likely that the blood taken in therapeutic monitoring had missed the peak plasma levels, since the drug application in the clinical studies were all in the evenings and patient visits were in the day time. Inclusion of these data would be misleading.

Clinical Studies

1. The Applicant wishes to add data at the endpoint of the posttreatment period from Study R168-120-8606 to the Table for clinical signs for the psoriasis studies. This is agreeable. However, the following sentence should be deleted:

Data from Study R168-145-8606 have not shown significant advantage over calcipotriol over the posttreatment period. Such a sentence would be misleading, as Dovonex 0.005% ointment has not been given such a claim. Studies R168-125-8606 and R168-126-8606 showed some advantage over Lidex 0.05% cream in the posttreatment period. However, topical corticosteroids are poor comparators for effects in the posttreatment period because of the problems of possible tachyphylaxis and rebound phenomenon. In addition, the issue of bias introduced by postrandomization selection between different treatment groups of patients entering the posttreatment period is extremely difficult to resolve, in any comparison involving previously treated patients who do enroll in such a posttreatment phase.

2. Data for _____ on acne is to be deleted because this

3. Percentage figures for global scores are to be added: this will be more meaningful to the reader.

11.3 Indications and Usage

1. The sentence

_____ should be eliminated.

2. It is acceptable to limit the use of TAZORAC™ gels to psoriasis covering less than 10% of body surface area in women of child-bearing potential. This restricted indication should be stated in this section.

11.4 Contraindications This section should include the information on Pregnancy Category X in accordance to 21 CFR 201.57. The Pharm/Tox Reviewer has revised this information.

11.5 Warnings

1. The warning in relation to Pregnancy Category X should be reinstated.
2. As retinoids may augment a phototoxic reaction resulting from the use of a photosensitizer, the word _____ should be reinstated.

11.6 Precautions

11.6.1 General

1. The sentence

should be reinstated.

2. The sentence

should be reinstated.

11.6.2 Information for patients no change necessary in the physician's package insert. Apart from minor modifications which are acceptable, the pharmacist-distributed pamphlet should be rewritten to be consistent with the version sent to the Applicant with the Approvable Letter of 12/30/96 and with data seen in the clinical trials (re: onset of effect in psoriasis).

11.6.3 Laboratory tests no such subsection.

11.6.4 Drug interactions no change necessary.

11.6.5 Carcinogenesis, mutagenesis, impairment of fertility
The Pharm/Tox Reviewer does not agree with the changes proposed by the Applicant and wishes to use the version sent to the Applicant on 12/30/96 with the Approvable Letter, except for addition of the following paragraph with modifications:

11.6.6 Pregnancy This subsection should remain as in the version sent to the Applicant on 12/30/96 with the Approvable Letter. The addition of a paragraph on healthy babies born to women who have used tazarotene in pregnancy may be helpful to the prescribing physician:

11.6.7 Labor and delivery no such subsection.

11.6.8 Nursing mothers no change necessary.

11.6.9 Pediatric use no change necessary.

11.7 Adverse Reactions acceptable with elimination of wording for the 0.05% gel in the treatment of acne.

11.8 Drug Abuse and Dependence no such subsection.

11.9 Overdosage no change necessary.

11.10 Dosage and Administration Information on limitation of use in women of child-bearing potential should be added (30 Gm/10 days and use on \leq 10% surface area).

11.11 How Supplied as per Chemistry Reviewer.

A new version of the label will be finalized after the labeling meeting for this NDA on 4/14/97.

Conclusions:

1. The Applicant has responded to the requests of the Action Letter of 12/30/96 but refuses to set up a pregnancy registry after approval for marketing.
2. The Safety Update has not significantly changed the safety profile of tazarotene as presented in the pivotal trials.
3. The labeling requires further revision.

Regulatory Recommendations:

1. This NDA is approvable upon revision of the label.
2. The Applicant should develop measures in the postmarketing phase to follow up patients who have used tazarotene in pregnancy in order to gain better information on the teratogenicity and fetotoxicity potential of tazarotene in humans.
3. The Applicant should be reminded of the the commitment to follow up on the incidence of photosensitivity associated with long-term use of tazarotene.

H-S. Ko 4-14-97
Hon-Sum Ko, M.D.

cc: Original NDA 20-600
HFD-540
HFD-340
HFD-540/CSO/Cross
HFD-540/CHEM/Gilman
HFD-540/PHARM/Nostrandt
HFD-715/BIOMETRICS/Thomson
HFD-880/BIOPHARM/Lee
HFD-540/MO/Ko

Frank W. 5/9/97

Total/Treatment-Related Adverse Events in Study R168-146-8606
Group 1: Dosing QD

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>
	58 (100%)	61 (100%)
ENROLLED		
PATIENTS WITH AE	37 (64%)/28 (48%)	39 (64%)/25 (41%)
BODY	4 (7%)/ 2 (3%)	5 (8%)/ 2 (3%)
chills	2 (3%)/ 2 (3%)	1 (-2%)/ 1 (2%)
accidental injury	1 (2%)	0
neck pain	1 (2%)	0
headache	0	2 (3%)
pain	0	2 (3%)/ 1 (2%)
abscess	0	1 (2%)
inflammation	0	1 (2%)
chest pain	0	1 (2%)
CARDIOVASCULAR	3 (5%)	1 (2%)
angina pectoris	1 (2%)	0
arteriosclerosis	1 (2%)	0
hypertension	1 (2%)	0
arrhythmia	0	1 (2%)
DIGESTIVE	2 (3%)	2 (3%)
dyspepsia	1 (2%)	0
pancreatic disorder	1 (2%)	0
liver function abnormal	0	1 (2%)
tooth disorder	0	1 (2%)
ENDOCRINE	0	1 (2%)
goiter	0	1 (2%)
HEMATOLOGIC	1 (2%)	0
iron deficiency anemia	1 (2%)	0
INFECTION	0	1 (2%)
infection	0	1 (2%)
METABOLIC	3 (5%)/ 2 (3%)	2 (3%)/ 2 (3%)
edema, peripheral	2 (3%)/ 1 (2%)	0
edema	1 (2%)/ 1 (2%)	1 (2%)/ 1 (2%)
albuminuria	0	1 (2%)/ 1 (2%)
MUSCULOSKELETAL	3 (5%)/ 1 (2%)	2 (3%)
arthritis	1 (2%)	0
fibro tendon disorder	1 (2%)	0
joint disorder	1 (2%)/ 1 (2%)	0
arthralgia	0	1 (2%)
arthrosis	0	1 (2%)
NERVOUS	0	3 (5%)
depression	0	1 (2%)
dizziness	0	1 (2%)
neuralgia	0	1 (2%)
RESPIRATORY	1 (2%)	4 (7%)
rhinitis	1 (2%)	3 (5%)
cough increase	0	2 (3%)
pneumonia	0	1 (2%)
sinusitis	0	1 (2%)
SKIN	33 (57%)/28 (48%)	36 (59%)/24 (39%)
psoriasis worsened	12 (21%)/10 (17%)	7 (12%)/ 7 (12%)
burning	9 (16%)/ 9 (16%)	4 (7%)/ 4 (7%)
erythema	9 (16%)/ 8 (14%)	4 (7%)/ 3 (5%)
pruritus	8 (14%)/ 7 (12%)	13 (21%)/13 (21%)
desquamation	2 (3%)/ 2 (3%)	4 (7%)/ 3 (5%)
skin pain	2 (3%)/ 2 (3%)	2 (3%)/ 2 (3%)
skin dry	2 (3%)/ 1 (2%)	2 (3%)/ 2 (3%)
skin irritation	2 (3%)/ 2 (3%)	0
irritant contact dermatitis	1 (2%)/ 1 (2%)	3 (5%)/ 1 (2%)
skin fissure	1 (2%)/ 1 (2%)	1 (2%)/ 1 (2%)
lichen dermatitis	1 (2%)	0
urticaria	1 (2%)	0
atopic dermatitis	0	1 (2%)/ 1 (2%)
folliculitis	0	2 (-3%)
rash	0	1 (2%)
skin disorder	0	1 (-2%)
SPECIAL SENSES	0	2 (3%)
ear infection	0	1 (2%)
refractive disorder	0	1 (2%)
UROGENITAL	0	1 (2%)
menopause	0	1 (2%)

Total/Treatment-Related Adverse Events in Study R168-146-8606
Group 2: Dosing OD --> QOD

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>
ENROLLED	24 (100%)	25 (100%)
PATIENTS WITH AE	24 (100%)/23 (96%)	21 (84%)/20 (80%)
BODY	5 (21%)/2 (8%)	2 (8%)
fever	1 (4%)	1 (-4%)
- headache	1 (4%)	1 (4%)
flu	1 (4%)	0
pain	1 (4%)/1 (4%)	0
abdominal pain	1 (4%)	0
back pain	1 (4%)	0
itchy skin	1 (4%)/1 (4%)	0
abscess	0	1 (4%)
CARDIOVASCULAR	1 (4%)	0
hypertension	1 (4%)	0
DIGESTIVE	2 (8%)	1 (4%)
liver function abnormal	1 (4%)	0
duodenal ulcer	1 (4%)	0
diarrhea	0	1 (4%)
METABOLIC	0	3 (12%)/1 (4%)
creatinine increase	0	1 (4%)
edema, peripheral	0	1 (4%)/1 (4%)
gout	0	1 (4%)
MUSCULOSKELETAL	2 (8%)	0
arthralgia	2 (8%)	0
RESPIRATORY	4 (17%)	2 (8%)
rhinitis	4 (17%)	1 (4%)
cough increase	0	1 (4%)
SKIN	23 (96%)/22 (92%)	21 (84%)/20 (80%)
burning	10 (42%)/10 (42%)	5 (20%)/5 (20%)
psoriasis worsened	7 (29%)/4 (17%)	14 (56%)/11 (44%)
pruritus	7 (29%)/7 (29%)	6 (24%)/6 (24%)
skin pain	6 (25%)/5 (21%)	7 (28%)/7 (28%)
erythema	6 (25%)/6 (25%)	4 (16%)/4 (16%)
skin irritation	4 (17%)/4 (17%)	3 (12%)/3 (12%)
desquamation	2 (8%)/2 (8%)	2 (8%)/2 (8%)
skin erosion	2 (8%)/2 (8%)	0
dermatitis	1 (4%)/1 (4%)	0
irritant contact dermatitis	1 (4%)	0
skin focal edema	1 (4%)/1 (4%)	0
skin fissure	1 (4%)/1 (4%)	0
skin dry	1 (4%)/1 (4%)	0
urticaria	1 (4%)	0
SPECIAL SENSES	1 (4%)/1 (4%)	0
dry eyes	1 (4%)/1 (4%)	0
Trunk	1 (4%)/1 (4%)	0
itchy skin	1 (4%)/1 (4%)	0

Total/Treatment-Related Adverse Events in Study R168-146-8606
Group 3: Dosing OD --> QOD --> Q3D

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>
ENROLLED	11 (100%)	9 (100%)
PATIENTS WITH AE	9 (82%) / 8 (73%)	8 (89%) / 7 (78%)
BODY	0	2 (22%) / 1 (11%)
chills	0	1 (11%) / 1 (11%)
flu	0	1 (11%)
DIGESTIVE	1 (9%)	0
vomit	1 (9%)	0
METABOLIC	0	1 (11%) / 1 (11%)
edema	0	1 (11%) / 1 (11%)
MUSCULOSKELETAL	0	1 (11%)
osteoporosis	0	1 (11%)
NERVOUS	1 (9%)	0
neuralgia	1 (9%)	0
RESPIRATORY	2 (18%)	0
pneumonia	1 (9%)	0
rhinitis	1 (9%)	0
SKIN	9 (82%) / 8 (73%)	8 (89%) / 7 (78%)
erythema	5 (46%) / 5 (46%)	3 (33%) / 3 (33%)
skin irritation	4 (36%) / 4 (36%)	1 (11%) / 1 (11%)
pruritus	4 (36%) / 3 (27%)	1 (11%) / 0
burning	3 (27%) / 3 (27%)	4 (44%) / 4 (44%)
skin pain	2 (18%) / 2 (18%)	1 (11%) / 0
desquamation	1 (9%) / 1 (9%)	1 (11%) / 1 (11%)
eczema	1 (9%) / 1 (9%)	1 (11%) / 1 (11%)
burning face	1 (9%) / 1 (9%)	0
exfoliative dermatitis	1 (9%) / 1 (9%)	0
herpes zoster	1 (9%)	0
psoriasis worsened	0	5 (56%) / 4 (44%)
UROGENITAL	1 (9%)	0
Monilia vaginitis	1 (9%)	0

Table 1 (Page 1 of 9)

Treatment-Related a) Adverse Events
 Incidence by Body System and Reaction Term b)
 (Study A190168-001)
 Treatment Period

		TAZ/VEH	TAZ/SYNALAR	TAZ/ELOCON	TAX/LIDEX	Total
Total Patients Enrolled		75 (100.0%)	78 (100.0%)	73 (100.0%)	73 (100.0%)	299 (100.0%)
Patients with Adverse Events		39 (52.0%)	39 (50.0%)	29 (39.7%)	31 (42.5%)	138 (46.2%)
CV	All Patients	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	TELANGIECTASIAS	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
NER	All Patients	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
	TINGLING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
SKIN	All Patients	39 (52.0%)	38 (48.7%)	29 (39.7%)	31 (42.5%)	137 (45.8%)
	PRURITUS	17 (22.7%)	22 (28.2%)	9 (12.3%)	13 (17.8%)	61 (20.4%)
	BURNING SKIN	17 (22.7%)	15 (19.2%)	10 (13.7%)	9 (12.3%)	51 (17.1%)
	ERYTHEMA	8 (10.7%)	5 (6.4%)	6 (8.2%)	7 (9.6%)	26 (8.7%)
	PSORIASIS WORSENER	4 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.3%)
	IRRITATION SKIN	3 (4.0%)	4 (5.1%)	3 (4.1%)	6 (8.2%)	16 (5.4%)
	DERMATITIS CONTACT	3 (4.0%)	3 (3.8%)	4 (5.5%)	1 (1.4%)	11 (3.7%)
	IRRITANT					
	DESQUAMATION	2 (2.7%)	2 (2.6%)	0 (0.0%)	2 (2.7%)	6 (2.0%)
	SKIN TIGHTNESS	2 (2.7%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	3 (1.0%)
	PAIN SKIN	1 (1.3%)	3 (3.8%)	1 (1.4%)	4 (5.5%)	9 (3.0%)
	RASH	1 (1.3%)	2 (2.6%)	1 (1.4%)	1 (1.4%)	5 (1.7%)
	REACTION SKIN	1 (1.3%)	1 (1.3%)	1 (1.4%)	2 (2.7%)	5 (1.7%)
	DERMATITIS	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
	STINGING SKIN	1 (1.3%)	0 (0.0%)	3 (4.1%)	3 (4.1%)	7 (2.3%)
	FOLLICULITIS	1 (1.3%)	0 (0.0%)	2 (2.7%)	0 (0.0%)	3 (1.0%)
	EDEMA SKIN FOCAL	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	2 (0.7%)
	DISCOLOR SKIN	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	URTICARIA	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	FISSURE SKIN	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	EXCORIATION	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	2 (0.7%)
	RASH VESIC BULL	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.3%)

[a] Regardless of relationship to treatment.

[b] Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

Table 1 (Page 3 of 9)

Treatment-Related [a] Adverse Events
Incidence by Body System and Reaction Term [b]
(Study A190168-001)
Post Treatment Period

	TAZ/VEH	TAZ/SYNALAR	TAZ/ELOCON	TAX/LIDEX	Total
Total Patients Enrolled	52 (100.0%)	54 (100.0%)	65 (100.0%)	60 (100.0%)	231 (100.0%)
Patients with Adverse Events	7 (13.5%)	12 (22.2%)	5 (7.7%)	8 (13.3%)	32 (13.9%)
SKIN All Patients	7 (13.5%)	12 (22.2%)	5 (7.7%)	8 (13.3%)	32 (13.9%)
PRURITUS	3 (5.8%)	8 (14.8%)	2 (3.1%)	4 (6.7%)	17 (7.4%)
BURNING SKIN	1 (1.9%)	2 (3.7%)	1 (1.5%)	1 (1.7%)	5 (2.2%)
IRRITATION SKIN	1 (1.9%)	2 (3.7%)	0 (0.0%)	1 (1.7%)	4 (1.7%)
ERYTHEMA	1 (1.9%)	1 (1.9%)	0 (0.0%)	1 (1.7%)	3 (1.3%)
DISCOLOR SKIN	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PSORIASIS WORSENER	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
DERMATITIS	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
RASH	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (1.7%)	2 (0.9%)
REACTION SKIN	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.4%)
ULCER SKIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (0.4%)

[a] Regardless of relationship to treatment.

[b] Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

[HONG.190168001] A68001ADX6.SAS/24MAR97

Table 1 (Page 5 of 9)

All Adverse Events [a]
 Incidence by Body System and Reaction Term [b]
 (Study A190168-001)
 * Treatment Period

		TAZ/VEH	TAZ/SYNALAR	TAZ/ELOCON	TAX/LIDEX	Total
DIG	HEPATITIS	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.3%)
	ULCER MOUTH	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
HAL	All Patients	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
	ECCHYMOSIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
MAN	All Patients	2 (2.7%)	2 (2.6%)	1 (1.4%)	0 (0.0%)	5 (1.7%)
	EDEMA PERIPHERAL	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	WEIGHT INC	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	HYPOVOLEMIA	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	THIRST	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	GOUT	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.3%)
MS	All Patients	1 (1.3%)	0 (0.0%)	1 (1.4%)	3 (4.1%)	5 (1.7%)
	MYALGIA	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	2 (0.7%)
	BONE FRAC TRAUM	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.3%)
	ARTHRALGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
	PTOSIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
NER	All Patients	2 (2.7%)	2 (2.6%)	1 (1.4%)	3 (4.1%)	8 (2.7%)
	INSOMNIA	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	THINKING ABNORM	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	PARESTHESIA	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (1.4%)	2 (0.7%)
	VERTIGO	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	DEPRESSION	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	2 (0.7%)
	TINGLING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
RES	All Patients	11 (14.7%)	5 (6.4%)	9 (12.3%)	4 (5.5%)	29 (9.7%)
	INFECTION	4 (5.3%)	1 (1.3%)	5 (6.8%)	0 (0.0%)	10 (3.3%)
	PHARYNGITIS	2 (2.7%)	1 (1.3%)	1 (1.4%)	1 (1.4%)	5 (1.7%)
	SINUSITIS	2 (2.7%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	3 (1.0%)
	INFECTION SINUS	1 (1.3%)	1 (1.3%)	1 (1.4%)	0 (0.0%)	3 (1.0%)

[a] Regardless of relationship to treatment.

[b] Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

Table 1 (Page 7 of 9)

All Adverse Events[a]
 Incidence by Body System and Reaction Term[b]
 (Study A190168-001)
 * Treatment Period

		TAZ/VEH	TAZ/SYNALAR	TAZ/ELOCON	TAX/LIDEX	Total
SKIN	DERMATITIS FUNG	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.3%)
	HYPERPLASIA	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.3%)
	PSORIASIS	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.3%)
	RASH VESIC BULL	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.3%)
	EROSION SKIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
	ROSACEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
	ULCER SKIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
SS	All Patients	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.7%)	2 (0.7%)
	DIPLOPIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
	INFECTION EAR	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
UG	All Patients	2 (2.7%)	0 (0.0%)	1 (1.4%)	2 (2.7%)	5 (1.7%)
	CARCINOMA	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	INFECTION URIN TRACT	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
	MONILIA VAGINA	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.3%)
	HEM VAGINAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)
	VAGINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.3%)

[a] Regardless of relationship to treatment.

[b] Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

[HONG.190168001] A68001ADX6.SAS/24MAR97

Table 1 (Page 9 of 9)

All Adverse Events[a]
 Incidence by Body System and Reaction Term[b]
 (Study A190168-001)
 * Post Treatment Period

		TAZ/VEH	TAZ/SYNALAR	TAZ/ELOCON	TAX/LIDEX	Total
RES	All Patients	0 (0.0%)	1 (1.9%)	2 (3.1%)	3 (5.0%)	6 (2.6%)
	DYSPNEA	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	PHARYNGITIS	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (1.7%)	2 (0.9%)
	INFECTION	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.4%)
	COUGH INC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (0.4%)
	RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (0.4%)
SKIN	All Patients	9 (17.3%)	14 (25.9%)	9 (13.8%)	8 (13.3%)	40 (17.3%)
	PRURITUS	3 (5.8%)	8 (14.8%)	2 (3.1%)	4 (6.7%)	17 (7.4%)
	ERYTHEMA	2 (3.8%)	1 (1.9%)	0 (0.0%)	1 (1.7%)	4 (1.7%)
	PSORIASIS WORSENE	1 (1.9%)	3 (5.6%)	0 (0.0%)	0 (0.0%)	4 (1.7%)
	BURNING SKIN	1 (1.9%)	2 (3.7%)	2 (3.1%)	1 (1.7%)	6 (2.6%)
	IRRITATION SKIN	1 (1.9%)	2 (3.7%)	0 (0.0%)	1 (1.7%)	4 (1.7%)
	DERMATITIS	1 (1.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
	EDEMA SKIN FOCAL	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	2 (0.9%)
	DISCHARGE SKIN	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	DISCOLOR SKIN	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	EXCORIATION	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	FISSURE SKIN	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	HERPES ZOSTER	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	RASH	0 (0.0%)	0 (0.0%)	2 (3.1%)	1 (1.7%)	3 (1.3%)
	DERMATITIS FUNG	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.4%)
	PSORIASIS	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.4%)
	REACTION SKIN	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.4%)
	ULCER SKIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (0.4%)
SS	All Patients	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	2 (0.9%)
	INFECTION EAR	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	DIPLOPIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (0.4%)

[a] Regardless of relationship to treatment.

[b] Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

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Table 3 (Page 1 of 13)

Treatment-Related a) Adverse Events
Incidence by Body System and Reaction Term(b)
(Study A190168-002)
Phase I

		AGN 190168 0.1%	Vehicle	Total
Total Patients Enrolled		84 (100.0%)	82 (100.0%)	166 (100.0%)
Patients with Adverse Events		62 (73.8%)	17 (20.7%)	79 (47.6%)
BODY	All Patients	1 (1.2%)	0 (0.0%)	1 (0.6%)
	PHOTOSENSITIVITY	1 (1.2%)	0 (0.0%)	1 (0.6%)
MAN	All Patients	1 (1.2%)	0 (0.0%)	1 (0.6%)
	HYPERTRIGLYCERIDEM	1 (1.2%)	0 (0.0%)	1 (0.6%)
SKIN	All Patients	61 (72.6%)	17 (20.7%)	78 (47.0%)
	IRRITATION SKIN	21 (25.0%)	5 (6.1%)	26 (15.7%)
	ERYTHEMA	21 (25.0%)	0 (0.0%)	21 (12.7%)
	PRURITUS	13 (15.5%)	2 (2.4%)	15 (9.0%)
	BURNING SKIN	9 (10.7%)	0 (0.0%)	9 (5.4%)
	PAIN SKIN	8 (9.5%)	4 (4.9%)	12 (7.2%)
	PSORIASIS WORSENER	7 (8.3%)	5 (6.1%)	12 (7.2%)
	SKIN DRY	7 (8.3%)	3 (3.7%)	10 (6.0%)
	DESQUAMATION	6 (7.1%)	1 (1.2%)	7 (4.2%)
	ECZEMA	6 (7.1%)	0 (0.0%)	6 (3.6%)
	DERMATITIS	5 (6.0%)	0 (0.0%)	5 (3.0%)
	DERMATITIS CONTACT	5 (6.0%)	0 (0.0%)	5 (3.0%)
	IRRITANT			
	FISSURE SKIN	3 (3.6%)	4 (4.9%)	7 (4.2%)
	HEM SKIN	3 (3.6%)	2 (2.4%)	5 (3.0%)
	EDEMA SKIN FOCAL	3 (3.6%)	0 (0.0%)	3 (1.8%)
	EXCORIATION	2 (2.4%)	0 (0.0%)	2 (1.2%)

[a] Regardless of relationship to treatment.

[b] Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

[HONG.190168002] A68002ADX6.SAS/15JAN97

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Appendix III

Table 3 (Page 3 of 13)
 Treatment-Related (a) Adverse Events
 Incidence by Body System and Reaction Term (b)
 (Study A190168-002)
 Phase II

		AGN 190168 0.1%	Vehicle	Total
Total Patients Enrolled		61 (100.0%)	64 (100.0%)	125 (100.0%)
Patients with Adverse Events		43 (70.5%)	46 (71.9%)	89 (71.2%)
MAN	All Patients	1 (1.6%)	0 (0.0%)	1 (0.8%)
	HYPERTRIGLYCERIDEM	1 (1.6%)	0 (0.0%)	1 (0.8%)
SKIN	All Patients	42 (68.9%)	46 (71.9%)	88 (70.4%)
	IRRITATION SKIN	14 (23.0%)	22 (34.4%)	36 (28.8%)
	ERYTHEMA	12 (19.7%)	14 (21.9%)	26 (20.8%)
	PRURITUS	11 (18.0%)	14 (21.9%)	25 (20.0%)
	PSORIASIS WORSENER	9 (14.8%)	8 (12.5%)	17 (13.6%)
	DESQUAMATION	8 (13.1%)	12 (18.8%)	20 (16.0%)
	BURNING SKIN	6 (9.8%)	2 (3.1%)	8 (6.4%)
	SKIN DRY	5 (8.2%)	4 (6.3%)	9 (7.2%)
	DERMATITIS CONTACT IRRITANT	3 (4.9%)	1 (1.6%)	4 (3.2%)
	HEM SKIN	3 (4.9%)	0 (0.0%)	3 (2.4%)
	RASH	2 (3.3%)	5 (7.8%)	7 (5.6%)
	PAIN SKIN	2 (3.3%)	3 (4.7%)	5 (4.0%)
	FISSURE SKIN	2 (3.3%)	1 (1.6%)	3 (2.4%)
	EXCORIATION	2 (3.3%)	0 (0.0%)	2 (1.6%)
	ECZEMA	1 (1.6%)	4 (6.3%)	5 (4.0%)
	DERMATITIS	1 (1.6%)	2 (3.1%)	3 (2.4%)
	RASH MACULOPAPULAR	1 (1.6%)	1 (1.6%)	2 (1.6%)
	STINGING SKIN	1 (1.6%)	0 (0.0%)	1 (0.8%)
	DISCHARGE SKIN	0 (0.0%)	1 (1.6%)	1 (0.8%)

[a] Regardless of relationship to treatment.

[b] Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

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All Adverse Events [a]
Incidence by Body System and Reaction Term [b]
(Study A190168-002)
Phase I

		AGN 190168 0.1%	Vehicle	Total
Total Patients Enrolled		84 (100.0%)	82 (100.0%)	166 (100.0%)
Patients with Adverse Events		71 (84.5%)	49 (59.8%)	120 (72.3%)
BODY	All Patients	21 (25.0%)	19 (23.2%)	40 (24.1%)
	HEADACHE	12 (14.3%)	4 (4.9%)	16 (9.6%)
	FLU SYND	5 (6.0%)	3 (3.7%)	8 (4.8%)
	INJURY ACCID	3 (3.6%)	2 (2.4%)	5 (3.0%)
	PAIN BACK	2 (2.4%)	2 (2.4%)	4 (2.4%)
	PAIN	1 (1.2%)	2 (2.4%)	3 (1.8%)
	INFECTION	1 (1.2%)	0 (0.0%)	1 (0.6%)
	NECK RIGID	1 (1.2%)	0 (0.0%)	1 (0.6%)
	PAIN CHEST	1 (1.2%)	0 (0.0%)	1 (0.6%)
	PAIN FOOT	1 (1.2%)	0 (0.0%)	1 (0.6%)
	PHOTOSENSITIVITY	1 (1.2%)	0 (0.0%)	1 (0.6%)
	PAIN ARM	0 (0.0%)	2 (2.4%)	2 (1.2%)
	ASTHENIA	0 (0.0%)	1 (1.2%)	1 (0.6%)
	CELLULITIS	0 (0.0%)	1 (1.2%)	1 (0.6%)
	DRUG INTERACTION	0 (0.0%)	1 (1.2%)	1 (0.6%)
	EDEMA GENERAL	0 (0.0%)	1 (1.2%)	1 (0.6%)
	HANGOVER	0 (0.0%)	1 (1.2%)	1 (0.6%)
	PAIN NECK	0 (0.0%)	1 (1.2%)	1 (0.6%)
CV	All Patients	3 (3.6%)	2 (2.4%)	5 (3.0%)
	HEART ARREST	1 (1.2%)	0 (0.0%)	1 (0.6%)
	HYPERTENS	1 (1.2%)	0 (0.0%)	1 (0.6%)
	MIGRAINE	1 (1.2%)	0 (0.0%)	1 (0.6%)

[a] Regardless of relationship to treatment.

[b] Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

[HONG.190168002] A68002ADX6.SAS/15JAN97

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All Adverse Events (a)
 Incidence by Body System and Reaction Term (b)
 (Study A190168-002)
 Phase I

		AGN 190168 0.1%	Vehicle	Total
NER	HYPERTONIA	0 (0.0%)	1 (1.2%)	1 (0.6%)
	INSOMNIA	0 (0.0%)	1 (1.2%)	1 (0.6%)
RES	All Patients	23 (27.4%)	20 (24.4%)	43 (25.9%)
	INFECTION	16 (19.0%)	10 (12.2%)	26 (15.7%)
	INFECTION SINUS	3 (3.6%)	2 (2.4%)	5 (3.0%)
	PHARYNGITIS	3 (3.6%)	1 (1.2%)	4 (2.4%)
	RHINITIS	1 (1.2%)	6 (7.3%)	7 (4.2%)
	COUGH INC	1 (1.2%)	3 (3.7%)	4 (2.4%)
	SINUSITIS	1 (1.2%)	2 (2.4%)	3 (1.8%)
	EPISTAXIS	1 (1.2%)	0 (0.0%)	1 (0.6%)
	DYSPNEA	0 (0.0%)	1 (1.2%)	1 (0.6%)
SKIN	All Patients	65 (77.4%)	27 (32.9%)	92 (55.4%)
	IRRITATION SKIN	22 (26.2%)	5 (6.1%)	27 (16.3%)
	ERYTHEMA	21 (25.0%)	2 (2.4%)	23 (13.9%)
	PRURITUS	13 (15.5%)	5 (6.1%)	18 (10.8%)
	PSORIASIS WORSENER	9 (10.7%)	11 (13.4%)	20 (12.0%)
	BURNING SKIN	9 (10.7%)	1 (1.2%)	10 (6.0%)
	PAIN SKIN	8 (9.5%)	6 (7.3%)	14 (8.4%)
	SKIN DRY	7 (8.3%)	4 (4.9%)	11 (6.6%)
	DESQUAMATION	6 (7.1%)	2 (2.4%)	8 (4.8%)
	ECZEMA	6 (7.1%)	0 (0.0%)	6 (3.6%)
	DERMATITIS	5 (6.0%)	0 (0.0%)	5 (3.0%)
	DERMATITIS CONTACT	5 (6.0%)	0 (0.0%)	5 (3.0%)
	IRRITANT			
	FISSURE SKIN	3 (3.6%)	5 (6.1%)	8 (4.8%)

(a) Regardless of relationship to treatment.

(b) Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

[HONG.190168002] A68002ADX6.SAS/15JAN97

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All Adverse Events^[a]
Incidence by Body System and Reaction Term^[b]
(Study A190168-002)
Phase I

		AGN 190168 0.1%	Vehicle	Total
UG	HEMATURIA	0 (0.0%)	1 (1.2%)	1 (0.6%)
	PROSTAT DIS	0 (0.0%)	1 (1.2%)	1 (0.6%)

[a] Regardless of relationship to treatment.

[b] Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

[HONG.190168002] A68002ADX6.SAS/15JAN97

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All Adverse Events (a)
Incidence by Body System and Reaction Term (b)
(Study A190168-002)
Phase II

		AGN 190168 0.1%	Vehicle	Total
DIG	ABSCESS PERIODONT	0 (0.0%)	1 (1.6%)	1 (0.8%)
	DESPEPSIA	0 (0.0%)	1 (1.6%)	1 (0.8%)
ENDO	All Patients	0 (0.0%)	1 (1.6%)	1 (0.8%)
	ENDOMETR DIS	0 (0.0%)	1 (1.6%)	1 (0.8%)
HAL	All Patients	1 (1.6%)	1 (1.6%)	2 (1.6%)
	LYMPHADENO	1 (1.6%)	0 (0.0%)	1 (0.8%)
	ECCHYMOSIS	0 (0.0%)	1 (1.6%)	1 (0.8%)
MAN	All Patients	2 (3.3%)	2 (3.1%)	4 (3.2%)
	HYPERTRIGLYCERIDEM	1 (1.6%)	1 (1.6%)	2 (1.6%)
	HYPERCHESTEREM	1 (1.6%)	0 (0.0%)	1 (0.8%)
	HYPERGLYCEM	0 (0.0%)	1 (1.6%)	1 (0.8%)
	HYPERLIPEM	0 (0.0%)	1 (1.6%)	1 (0.8%)
MS	All Patients	4 (6.6%)	4 (6.3%)	8 (6.4%)
	BONE FRACT TRAUM	3 (4.9%)	1 (1.6%)	4 (3.2%)
	MYALGIA	2 (3.3%)	2 (3.1%)	4 (3.2%)
	BURSTIS	0 (0.0%)	1 (1.6%)	1 (0.8%)
NER	All Patients	2 (3.3%)	4 (6.3%)	6 (4.8%)
	DEPRESSION	1 (1.6%)	1 (1.6%)	2 (1.6%)
	HYPERTONIA	1 (1.6%)	1 (1.6%)	2 (1.6%)
	EMOTION LABIL	0 (0.0%)	1 (1.6%)	1 (0.8%)
	EXTRAPYR SYND	0 (0.0%)	1 (1.6%)	1 (0.8%)

[a] Regardless of relationship to treatment.

[b] Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

[HONG.190168002] A68002ADX6.SAS/15JAN97

Table 3 (Page 13 of 13)

All Adverse Events^(a)
 Incidence by Body System and Reaction Term^(b)
 (Study A190168-002)
 Phase II

		AGN 190168 0.1%	Vehicle	Total
SKIN	ACNE	1 (1.6%)	1 (1.6%)	2 (1.6%)
	HYPERKERATOSIS	1 (1.6%)	1 (1.6%)	2 (1.6%)
	RASH MACULOPAPULAR	1 (1.6%)	1 (1.6%)	2 (1.6%)
	ROSACEA	1 (1.6%)	1 (1.6%)	2 (1.6%)
	STINGING SKIN	1 (1.6%)	1 (1.6%)	2 (1.6%)
	CARCINOMA SKIN	1 (1.6%)	0 (0.0%)	1 (0.8%)
	DERMATITIS LICHEN	1 (1.6%)	0 (0.0%)	1 (0.8%)
	RASH VESIC BULL	0 (0.0%)	2 (3.1%)	2 (1.6%)
	DISCHARGE SKIN	0 (0.0%)	1 (1.6%)	1 (0.8%)
	FURUNCULOSIS	0 (0.0%)	1 (1.6%)	1 (0.8%)
	INFLAMMATION SKIN	0 (0.0%)	1 (1.6%)	1 (0.8%)
SS	All Patients	2 (3.3%)	2 (3.1%)	4 (3.2%)
	DEAF TRANS	1 (1.6%)	0 (0.0%)	1 (0.8%)
	STRABISMUS	1 (1.6%)	0 (0.0%)	1 (0.8%)
	INFECTION EAR	0 (0.0%)	1 (1.6%)	1 (0.8%)
	PHOTOPHOBIA	0 (0.0%)	1 (1.6%)	1 (0.8%)
	VITREOUS FLOATERS	0 (0.0%)	1 (1.6%)	1 (0.8%)
UG	All Patients	1 (1.6%)	3 (4.7%)	4 (3.2%)
	INFECTION URIN TRACT	1 (1.6%)	1 (1.6%)	2 (1.6%)
	HEMATURIA	0 (0.0%)	1 (1.6%)	1 (0.8%)
	URIN ABNORM	0 (0.0%)	1 (1.6%)	1 (0.8%)

[a] Regardless of relationship to treatment.

[b] Based on Allergan's modified COSTART dictionary.

Note: Percentage (%) may not add up due to rounding error or patients having more than one adverse event.

HONG.190168002) A68002ADX6.SAS/15JAN97

ADDENDUM TO MEDICAL OFFICER'S REVIEW OF NDA 20-600 AMENDMENT OF 1/17/97

Date completed: 5/7/97; revised 5/12/97

MAY 12 1997

Purpose of Addendum: 1. To accommodate information provided in submissions dated 3/17/97, 3/28/97 and 4/11/97
and 2. Labeling review.

Background and Material Reviewed:

1. The Applicant responded to an Approvable Letter dated 12/30/96 with a major amendment on 1/17/97. Deficiencies in the clinical part of this response were conveyed to the Applicant and these included:

- A. In the Safety Update associated with this response, case record forms for patients who discontinued due to adverse events were not submitted.
- B. Details of pregnancies and their outcomes in two of the three patients reported in this Safety Update were inadequate.
- and C. Adverse events data in the Safety Update were not properly tabulated according to body system.

The Applicant supplied such information in the three submissions (3/17/97, 3/28/97 and 4/11/97) and this material was reviewed.

2. A labeling meeting was held on 4/14/97 for discussion on the label for TAZORAC™. This label has been re-reviewed subsequently, with consideration for the suggestions made at this meeting and at the Scientific Rounds of 4/30/97.

1. Information Supplied by Applicant in New Submissions

A. Case Record Forms for Subjects Who Terminated Study due to Adverse Events

(i) Studies Included in the Safety Update

For subjects who discontinued due to adverse events in the three studies reported (safety data only) in the Safety Update (Studies R168-146-8606, 190168-001-00 and 190168-002-00), their CRFs have been reviewed and relevant analyses incorporated into my review of the major amendment of 1/17/97. These adverse events were primarily due to local irritation and do not affect previous conclusions made regarding the safety of TAZORAC™.

(ii) Studies not included in the Safety Update

In the submission of 3/17/97, the Applicant also included CRFs of subjects who discontinued due to adverse events in two ongoing, *still blinded* European studies which were not included in the Safety Update of 1/17/97 (Studies 190168-501 and 190168-502). There is no information on the treatment protocols or enrollment/disposition data for these studies. These CRFs cannot be adequately reviewed. The adverse events allegedly leading to discontinuation were similar to those in other reported studies (primarily symptoms of local irritation). However, any conclusion drawn must be provisional until full reports of these studies can become available for review.

B. Details of Pregnancies and Their Outcomes in Two of the Three Patients Reported in the Safety Update of 1/17/97

The submission of 3/28/97 provided more information on two subjects: [redacted] of Study 190168-901-00 and [redacted] of Study 190168-001-00. Patient [redacted] of Study 190168-002-00 already had details given in the major amendment of 1/17/97.

This new information is incorporated into the Table in Section 10.2.8 (Human Reproduction Data) in the Integrated Summary of Safety of the review for the 1/17/97 major amendment. This Table is updated as follows:

<u>Study/Pt no</u>	<u>Age</u>	<u>BL-BSA*</u>	<u>Pregnancy detected¹</u>	<u>Duration of exposure from last negative pregnancy test</u>	<u>Outcome of baby</u>	<u>? Days Exposed⁵</u>
<u>Psoriasis Trials</u>						
120-[redacted]	26	8%	63 d	33 d x tazarotene 0.1% qd	FT*/healthy	15
120-[redacted]	29	3%	121 d (32 d post-Tx)	0	FT/healthy	4
190168-001 [redacted]	37	6%	83 d	7 d x tazarotene 0.1% qd + 27 d x Synalar 0.01% qd	FT/healthy	14
190168-002 [redacted]	31	6%	86 d	33 d x tazarotene 0.1% q2d	FT/healthy	37
190168-901 [redacted]	35	N/A*	25 d	? d x tazarotene 0.1% qd (No documentation of negative pregnancy test)	FT/healthy	60
<u>Acne Trials</u>						
221-C14	20	N/A	37 d	31 d x tazarotene 0.1% qd	FT/healthy	19

*BL-BSA=Baseline body surface area involvement by psoriasis.

N/A=not applicable (in bilateral comparison psoriasis trial or in acne trial).

FT=full-term; the CRF for patient [redacted] did not state full-term but the Applicant's cover letter on 3/28/97 stated "healthy, full-term baby"

¹Pregnancy detected=time from start of treatment to detection by pregnancy test.

⁵Days Exposed= days exposed *in utero* based on calculation backwards from delivery, assuming "full term" as 280 days from LMP.

**Race=Japanese; all other patients were white.

The new data have not altered any conclusions reached previously. My comments in the review for the 1/17/97 submission are restated here:

Comments

1. Patient [redacted] was found pregnant in the posttreatment period, 32 days after her last dose. It is possible that she did not have exposure in pregnancy.
2. Only patient [redacted] had LMP information, so that her exposure from the time of conception could be determined (37 d).
3. The other 4 patients might have been exposed for a few days to more than 5 weeks during their pregnancy, depending on the timing and sensitivity of the pregnancy test. As the window of organogenesis in relation to tazarotene exposure is unknown in these patients, it is not appropriate to draw conclusions on the potential for reproductive toxicity in humans from these data.
4. There is limited information on the degree of exposure in relation to the size of the lesions treated.
5. Plasma levels were available for the following patients:
[redacted] However, [redacted] was found pregnant in the posttreatment period (see above) and [redacted] had blood drawn 13 days after her last dose. The blood level data are therefore not helpful in evaluating exposure.

6. For patient data on plasma drug levels were requested by the Agency. The Applicant states that there are no data, as there was difficulty in obtaining blood.

C. Adverse Events Data Not Properly Tabulated in the Submission of 1/17/97
Appropriate Tables have been submitted on 4/11/97 (see Appendices II and III of review).

Comment The new adverse events data have not significantly affected previously drawn conclusions. As the three studies in this Update used treatment regimens with lower frequencies of application or in combination with a topical corticosteroid to reduce irritation, their data may not be representative of those under clinical use conditions (daily monotherapy) as given in the label. Thus, the usefulness of these data is limited.

2. Labeling Review

The label has again been reviewed and further modifications made to the Applicant's proposed label, which had previously undergone changes as given in my review of the 1/17/97 submission. A copy of the proposed revised label is included as Attachment 1.

3 pages (4-6)
Deleted

Conclusions:

There are no new conclusions.

Regulatory Recommendations:

Other than those recommendations listed in the review, this Addendum would add a recommendation to the Applicant to revise the Patient Package Insert in accordance to the proposed sections of 21 CFR 208.20 and 208.22 (see Attachment 2) and based on the modified version in Attachment 1. The Applicant must revise the label for Physician Package Insert as shown in Attachment 1.

H. S. Ko 5-12-97
Hon-Sum Ko, M.D.

Just Will. 5/12/97

cc: Original NDA 20-600
HFD-540
HFD-340
HFD-540/CSO/Cross
HFD-540/CHEM/Gilman
HFD-540/PHARM/Nostrandt
HFD-715/BIOMETRICS/Thomson
HFD-880/BIOPHARM/Lee
HFD-540/MO/Ko