Appendix I

Adverse Events in CT1101-01

System	AE	Number (%) of Patients Active (N=73)	Vehicle (N=77)
Cardiovas-cular	Sinus bradycardia	1 (1%)	0
Musculo-skeletal	Hypokinesia	0	1 (1%)
Respiratory	URI	0	1 (1%)
Skin and appendages*	"Application site reaction"	11 (15%)	4 (5%)
	Bursitis	0	1 (1%)
	Adenocarcinoma	0	1 (1%)
	Dry skin	16 (22%)	2 (3%)
	Edema	7 (10%)	3 (4%)
	Herpes zoster	0	1 (1%)
	Hyperesthesia	1 (1%)	2 (3%)
	Infection	0	1 (1%)
	Paresthesia	7 (10%)	1 (1%)
	Pruritus	16 (22%)	6 (8%)
	Rash	21 (29%)	7 (9%)
	Seborrhea	1 (1%)	0
	Skin melanoma	1 (1%)	1 (1%)
	Surgical procedure	0	1 (1%)
Special senses	Conjunctivits	0	1 (1%)

*The only significant contrast between treatment groups, with 30 patients (81 AEs) in active group and 18 patients (31 AEs) in vehicle group (p=0.03).

Appendix II

Adverse Events in CT1101-02

	Diclofenac (N=65)	Vehicle (N=65)
Patients with at least One AE	34 (52%)*	32 (49%)
Body as a Whole		
Headache	0	3 (5%)
Dizziness	0	1 (2%)
Leg infection	0	1 (2%)
Herpes zoster	0	1 (2%)
Cardiovascular System		
Angina	0	1 (2%)
Digestive System		
Dyspepsia	0	1 (2%)
Hearburen	0	1 (2%)
Skin and Appendages		
Pruritus	12 (18%)	13 (20%)
Rash	20 (31%)	19 (29%)
Exfoliation	7 (11%)	2 (3%)
Burning/stinging	7 (11%)	4 (6%)
Irritation	6 (9%)	1 (2%)
Papules	2 (3%)	0
Hemorrhage	1 (2%)	0
Pain	0	7 (11%)
Paresthesia	0	2 (3%)
Dry skin	1 (2%)	2 (3%)
Skin ulcer	2 (3%)	0
Edema	3 (5%)	0
Abrasion	1 (2%)	0
Dermatitis	1 (2%)	0
Rough skin	0	1 (2%)

*Data given as number of patients with the adverse event and percent (in parenthesis).

Appendix III

Adverse Events in CT1101-03

System/AE	Number (%) of Patients Active (N=58)	Vehicle (N=59)
Any Adverse Event	**52 (90%)**	**48 (81%)**
Skin & appendages	**46 (79%)**	**38 (64%)**
Pruritus	32 (55%)	29 (49%)
Application site reaction	20 (34%)	12 (20%)
Dry skin	21 (36%)	10 (17%)
Rash	19 (33%)	9 (15%)
Erythema	15 (26%)	4 (7%)
Carcinoma of skin	2 (3%)	1 (2%)
Vesiculobullous rash	3 (5%)	0
Skin exfoliation	3 (5%)	0
Ulcer skin	3 (5%)	0
Hypertrophy of skin	1 (2%)	1 (2%)
Maculopapular rash	1 (2%)	0
Seborrhea	1 (2%)	0
Skin irritation	0	1 (2%)
Urticaria	1 (2%)	0
Xerosis	0	1 (2%)
Nervous System	**18 (31%)**	**20 (34%)**
Paresthesia	8 (14%)	9 (15%)
Hyperesthesia	4 (7%)	5 (8%)
Tingling	3 (5%)	3 (5%)
Dizziness	0	4 (7%)
Hypertonia	3 (5%)	1 (2%)
Tenderness	2 (3%)	1 (2%)
Nervousness	0	1 (2%)
Somnolence	1 (2%)	0
Vertigo	1 (2%)	0
Body as a whole	**12 (21%)**	**12 (20%)**
Headache	3 (5%)	5 (8%)
Accidental injury	1 (2%)	3 (5%)
Flu syndrome	2 (3%)	2 (3%)
Back pain	2 (3%)	1 (2%)
Allergic reaction	0	3 (5%)
Infection	1 (2%)	1 (2%)
Pain	2 (3%)	0
Photosensitivity reaction	2 (3%)	0
Asthenia	1 (2%)	0
Common cold	0	1 (2%)
Face edema	1 (2%)	0
Fever	0	1 (2%)
Abdominal pain	1 (2%)	0
Sinus headache	1 (2%)	0
Metabolic and nutritional	**10 (17%)**	**2 (3%)**
CPK increase	4 (7%)	1 (2%)
Edema	4 (7%)	0
SGOT increase	3 (5%)	0
SGPT increase	2 (3%)	0
BUN increase	0	1 (2%)
Creatinine increase	0	1 (2%)
GGTP increase	1 (2%)	0
Hypercholesterolemia	1 (2%)	0
Hyperglycemia	1 (2%)	0
LDH increase	1 (2%)	0
Digestive system	**5 (9%)**	**6 (10%)**
Diarrhea	2 (3%)	3 (5%)
Dyspnea	3 (5%)	2 (3%)
Constipation	0	2 (3%)
Rectal disorder	1 (2%)	1 (2%)
Nausea	0	1 (2%)
Vomiting	0	1 (2%)
Respiratory system	**4 (7%)**	**5 (8%)**
Pharyngitis	2 (3%)	3 (5%)
Bronchitis	1 (2%)	1 (2%)
Rhinitis	1 (2%)	1 (2%)

Adverse Events in CT1101-03 (Continued)

System/AE	Number (%) of Patients Active (N=58)	Vehicle (N=59)
Cough increase	0	1 (2%)
Dyspnea	1 (2%)	0
Pneumonia	0	1 (2%)
Sore throat	1 (2%)	0
Urogenital system	**2 (3%)**	**5 (8%)**
Hematuria	2 (3%)	1 (2%)
Dysmenorrhea	0	1 (2%)
Epididymitis	0	1 (2%)
Infection urinary tract	0	1 (2%)
Pyuria	0	1 (2%)
Urination frequency	0	1 (2%)
Musculoskeletal system	**2 (3%)**	**3 (5%)**
Arthralgia	0	2 (3%)
Myalgia	2 (3%)	0
Arthritis	0	1 (2%)
Special senses	**4 (7%)**	**1 (2%)**
Conjunctivitis	3 (5%)	1 (2%)
Lacrimal disorder	1 (2%)	0
Eye pain	1 (2%)	0
Cardiovascular system	**3 (5%)**	**1 (2%)**
Feeling of warmth	0	1 (2%)
Hemorrhage	1 (2%)	0
Hypertension	1 (2%)	0
Migraine	1 (2%)	0
Unknown	**1 (2%)**	**2 (3%)**
Procedure	0	2 (3%)
Eye pain	1 (2%)	0
Hemic and lymphatic system	**1 (2%)**	**1 (2%)**
Eosinophilia	1 (2%)	0
Leukocytoisis	0	1 (2%)

*Data given as number of patients with the adverse event and percent (in parenthesis).

Adverse Events in CT1101-04

Body System	COSTART	d-30 (N=49)	v-30 (N=49)	d-60 (N=48)	v-60 (N=49)
Skin	Pruritus	20 (41%)	27 (55%)	15 (31%)	31 (63%)
	Rash	14 (29%)	12 (25%)	19 (40%)	16 (33%)
	Dry Skin	10 (20%)	6 (12%)	16 (33%)	10 (20%)
	ASR	14 (29%)	8 (16%)	8 (17%)	11 (22%)
	Derm Contact	0	0	4 (8%)	1 (2%)
	Acne	0	0	0	3 (6%)
	Carcinoma	0	2 (4%)	0	2 (4%)
	Eczema	1 (2%)	0	2 (4%)	0
	Herpes simplex	0	1 (2%)	-	1 (42%)
	Hypertrophy	2 (4%)	0	0	0
	Skin Ulcer	0	0	2 (4%)	0
	Hypokinesia	0	0	1 (2%)	0
	Skin Nodule	0	0	0	1 (2%)
Nervous System	Alopecia	0	0	1 (2%)	0
	Paresthesia	8 (16%)	7 (14%)	4 (8%)	1 (2%)
	Hyperesthesia	2 (4%)	1 (2%)	3 (6%)	4 (8%)
	Anxiety	0	0	0	1 (2%)
Body as a Whole	Insomnia	0	1 (2%)	0	0
	Flu Syndrome	0	1 (2%)	5 (10%)	3 (6%)
	Infection	0	1 (2%)	2 (4%)	3 (6%)
	Headache	0	2 (4%)	0	3 (6%)
	Edema	0	0	1 (2%)	1 (2%)
	Pain Back	0	0	2 (4%)	0
	Pain Chest	0	0	1 (2%)	0
	Pain Neck	1 (2%)	0	0	0
	Pain Abdoment	0	0	1 (2%)	0
	Pain	0	0	1 (2%)	1 (2%)
	Photosensitivit	0	0	0	1 (2%)
	Accidentl injury	1 (2%)	0	0	0
	Asthesia	0	1 (2%)	0	0
Respiratory	Allergic reaction	0	0	1 (2%)	0
	Chills	0	0	1 (2%)	0
	Pharyngitis	1 (41%)	1 (2%)	1 (2%)	4 (8%)
	Bronchitis	0	2 (4%)	0	0
	Pneumonia	0	1 (2%)	1 (2%)	0
	Rhinitis	0	0	1 (2%)	1 (2%)
	Asthma	0	0	1 (2%)	0
Cardiovascular	Cough Inc	1 (41%)	0	0	0
	Dyspnea	0	0	1 (2%)	0
	Angina pectoris	0	1 (2%)	0	0
	Hypertension	1 (2%)	0	1 (2%)	0
Digestive	Migraine	0	0	0	1 (2%)
	Phlebitis	0	0	0	1 (2%)
	Colitis	1 (2%)	0	0	0
	Diarrhea	0	1 (2%)	1 (2%)	0
	Dyspnea	0	0	1 (2%)	0
	Nausea	1 (2%)	0	0	0
Hemat/Lymphatic	Rectal Disorder	1 (2%)	0	0	0
	Stomatitis Ulcer	1 (2%)	0	0	0
Metabol/Nutrition	HIV Test Postive	0	1 (2%)	0	0
	Lymphadenopathy	0	1 (2%)	0	0
	Creatinine inc.	0	0	1 (2%)	1 (2%)
	Hypercholesterol	0	0	0	1 (2%)
Musculoskeletal	Hyperglycemia	0	0	0	1 (2%)
	Weight decrease	1 (2%)	0	0	0
	Arthralgia	0	0	1 (2%)	0
Special Senses	Arthrosis	0	0	1 (2%)	0
Urogenital	Myalgia	0	0	1 (2%)	0
	Conjunctivitis	0	0	1 (2%)	0
	Hematuria	0	1 (2%)	0	0

*Data given as number of patients with the adverse event and percent (in parenthesis). ASR=application site reaction.

Adverse Events in CT1101-07

System	AE	Number (%) of Patients		p-value
		Active (N=56)	Vehicle (N=55)	(if ≤0.05)
Body	Accidental injury	1 (2%)	1 (2%)	
as a whole	Allergic reaction	1 (2%)	0	
	Asthenia	1 (2%)	0	
	Chest pain	1 (2%)	0	
	Fever	1 (2%)	0	
	Flu syndrome	0	1 (2%)	
	Headache	4 (7%)	2 (4%)	
	Infection	4 (7%)	4 (7%)	
	Malaise	0	1 (2%)	
	Neck pain	2 (4%)	0	
	Pain	1 (2%)	2 (4%)	
Cardiovas-	Cardiomyopathy	1 (2%)	0	
cular	Congestive heart failure	0	1 (2%)	
	Coronary artery disorder	1 (2%)	0	
Digestive	Dyspepsia	0	2 (4%)	
	Oral ulcer	1 (2%)	0	
	Nausea	1 (2%)	0	
	Stomach ulcer	0	1 (2%)	
	Vomiting	1 (2%)	0	
Musculo-	Myalgia	1 (2%)	1 (2%)	
skeletal				
Nervous	Anxiety	0	1 (2%)	
	Dizziness	0	1 (2%)	
Respiratory	Dyspnea	1 (2%)	0	
	Pharyngitis	0	1 (2%)	
	Rhinitis	1 (2%)	1 (2%)	
	Sinusitis	2 (4%)	0	
Skin and	Acne	0	1 (2%)	
appendages	Application site reaction	59 (89%)	41 (75%)	0.0430
	Acne	1 (2%)	0	
	Alopecia	1 (2%)	1 (2%)	
	Contact dermatitis	30 (54%)	3 (5%)	<0.0001
	Dry skin	14 (25%)	12 (22%)	
	Exfoliation	12 (21%)	7 (13%)	
	Hyperesthesia	2 (4%)	1 (2%)	
	Pain	12 (21%)	19 (35%)	
	Paresthesia	11 (20%)	11 (20%)	
	Photosensitivity	2 (4%)	0	
	Pruritus	28 (50%)	23 (42%)	
	Rash	24 (43%)	8 (15%)	0.0010
	Skin carcinoma	1 (2%)	0	
	Vesiculobullous rash	1 (2%)	1 (2%)	
	Rash	1 (2%)	0	
	Skin carcinoma	0	1 (2%)	
Special	Conjunctivits	1 (2%)	0	
senses	Ear pain	0	1 (2%)	
Urogenital	Nephritis	1 (2%)	0	
	Prostate carcinoma	1 (2%)	0	
	Urinary tract infection	1 (2%)	0	

*Data given as number of patients with the adverse event and percent (in parenthesis).

Adverse Events in Actinic Keratosis Studies

A. Phase 3 Controlled Studies Combined (CT1101-03, -04 & -07)

Body System	Diclofenac (N=211)			Vehicle (N=212)		
	mild	mod	sev	mild	mod	sev
Procedure	1			2	1	
BODY AS A WHOLE						
Asthenia	2			1		
Accidental injury	2	2	1	1	1	
Abdominal pain	1	1				
Allergic reaction		1		3		
Back pain	3	1		2		
Chest pain	1		1			
Chills				1		
Eye pain					1	
Face edema		1				
Fever	1				1	
Flu syndrome	4	2		5	2	1
Headache	6	1	1	9	3	
HIV positive				1		
Infection	5	2		5	5	
Malaise				1		
Neck pain	2	1				
Pain	3			1	1	
Photosensitivity reaction	1					
HEMIC & LYMPHATIC SYSTEM						
Eosinophilia	1					
Leukocytosis				1		
Lymphadenopathy				1		
DIGESTIVE SYSTEM						
Colitis		1				
Constipation				2		
Diarrhea	2	1		4		
Dyspepsia	4			4		
Mouth ulcer	1					
Nausea		1 (&1 unclassified)		1		
Rectal disorder		2		1		
Stomach ulcer				1		
Ulcerative stomatitis		1				
Vomiting		1		1		
NERVOUS SYSTEM						
Anxiety				1	1	
Dizziness				5		
Hypokenesia		1				
Hypertonia		1				
Insomnia					1	
Nervousness				1		
Somnolence	1					
Vertigo		1				
RESPIRATORY SYSTEM						
Asthma		1				
Bronchitis		1			3	
Cough increased	1				1	
Dyspnea	1	2				
Pharyngitis		3	1		7	2
Pneumonia			1		1	1
Rhinitis	3			2	1	
Sinusitis		2				
CARDIOVASCULAR SYSTEM						
Angina pectoris					1	
Cardiomyopathy			1			
Coronary artery disorder			1			
Congestive heart failure						1
Hypertension	2	1				
Migraine	1				1	
Phlebitis					1	

A. Phase 3 Controlled Studies Combined (CT1101-03, -04 & -07) (Continued)

Body System	Diclofenac (N=211)			Vehicle (N=212)		
	mild	mod	sev	mild	mod	sev
MUSCULOSKELETAL SYSTEM						
Arthralgia		1		1	1	
Arthritis					1	
Arthrosis		1				
Myalgia	4				1	
UROGENITAL SYSTEM						
Dysmenorrhea				1		
Epididymitis				1		
Hematuria	1	1		1 (& 1 unclassified)		
Nephritis			1			
Prostatic carcinoma	1					
Pyuria				1		
Urinary frequency				1		
Urinary tract infection			1		1	
METABOLIC & NUTRITIONAL DISORDERS						
BUN increase				1		
CPK increase	3	1		1		
Creatinine increase	1			1	1	
Edema					1	
GGT increase	1					
Hypercholesterolemia	1			1		
Hyperglycemia	1				1	
LDH increase	1					
SGOT increase	3					
SGPT increase	2					
Weight loss	1					
SPECIAL SENSES						
Conjunctivitis	5				1	
Ear pain				1		
Eye pain	1	1				
SKIN & APPENDAGES						
Acne				1	1	
Contact dermatitis		1				
Herpes simplex					2	
Skin hypertrophy	1			1		
Skin nodule				1		
Skin cancer	2			4	1	1 (& 1 unknown)
Pain	1	1		2		
Paresthesia		1				
Pruritus	7			3	3	
Rash	4	1		4	3	
Maculopapular rash				1		
Seborrhea	1					
Dry Skin	2	1		2	1	
Skin ulcer	2					
Urticaria	1					
Application site reaction (ASR)*						
Acne	1			2		
Alopecia	2			1		
Contact dermatitis	17	24	6	3	3	
Exfoliation (scaling)	30	2	1	16	1	
Edema	1	3	1			
Hyperesthesia	2	1		1		
Hypertonia					1	
Skin hypertrophy	2					
Lacrimal disorder	1					
Pain	40	11	1	35	14	3
Paresthesia		29	15 1		28	4
Photosensitivity	3			1		
Pruritus	73	16	4	89	15	1
Rash	60	20	3	32	6	1
Maculopapular rash		2				
Purpuric rash			1			
Vesiculobullous rash	3	1		1		
Dry skin	43	5	1	29	1	
Vasodilation				1		
Skin cancer	1					

*ASR include only AEs clearly indicated on the treatment site on CRFs. Severity given as mild, moderate (mod) and severe (sev).

B. Phase 2 Controlled Studies Combined (CT1101-01 & -02)

Body System	Diclofenac (N=138)			Vehicle (N=142)		
	mild	mod	sev	mild	mod	sev
BODY AS A WHOLE						
Infection						1
Dental procedure						1
MUSCULOSKELETAL SYSTEM						
Bursitis						1
Hypokinesia				1		
Joint disorder						1
RESPIRATORY SYSTEM						
URTI					1	
CARDIOVASCULAR SYSTEM						
Sinus bradycardia			1			
Angina				(2 unclassified)		
SPEICAL SENSES						
Conjunctivitis				1		
SKIN & APPENDAGES						
Generalized rash			1			
Melanoma		1				1
Skin carcinoma	(1 unclassified)					1
Lymphoma	(1 unclassified)					
Edema				1		
Herpes zoster					1	
Application site reaction (ASR)*						
Contact dermatitis		2	3 (& 1 unclassified)	1		
Dry skin	8	6	2 (& 2 unclassified)	2 (& 1 unclassified)		
Edema	1	4	1 (& 4 unclassified)			
Exfoliation		1	2 (& 2 unclassified)			
Maculopapular rash		1	1			
Pain	1	4		1	2	
Paresthesia		1	6 (& 2 unclassified)		1 (& 1 unclassified)	
Pruritus	8	7	1 (& 7 unclassified)	4	1	1
Rash	7	12	3 (& 15 unclassified)	7	1	1 (& 3 unclassified)

*ASR include only those AEs clearly indicated on the treatment site on CRFs. Relationship to treatment was either "not related" or "unknown" for non-ASR adverse events, and "related" for ASRs, except for 15 cases of "rash" in the diclofenac group under ASR but not considered as "related". Severity given as mild, moderate (mod) and severe (sev).

C. Phase 2 Uncontrolled Studies Combined (TDHA-AK-CDN-93-01 & ST5101-AUS-01): Diclofenac Only (N=50)

Body System	Adverse Events
BODY AS A WHOLE	Flu syndrome 3 (mild)#, headache 2 (1 mild, 1 mod), infection 4 (3 mild, 1 not classified), back pain 1 (mod)
DIGESTIVE SYSTEM	Tooth disorder 1 (mod)
ENDOCRINE SYSTEM	Diabetes mellitus 1 (severity not classified)
MUSCULSKELETAL SYSTEM	Joint disorder 1 (mod), myalgia 1 (mod)
NERVOUS SYSTEM	Dizziness 1 (mild)
RESPIRATORY SYSTEM	Pharyngitis 1 (mod)
SKIN AND APPENDAGES	Skin carcinoma 1 (mod), contact dermatitis 1 (mod), dry skin 2 (1 mild, 1 mod), paresthesia 1 (mod), pruritus 1 (mod), rash 2 (2 mild), seborrhea 1 (mild)
	Application site reaction (ASR)*: Contact dermatitis 8 (1 mod, 7 not classified), edema 2 (2 mod), exfoliation 1 (mild), pain 3 (1 mild, 2 mod), paresthesia 3 (2 mild, 1 mod), pruritus 6 (4 mild, 2 mod), rash 9 (5 mild, 4 mod), dry skin 3 (3 mod), skin ulcer 2 (1 mild, 1 mod)

#severity given in parentheses as mild, moderate (mod) and severe (sev).
*ASR include only those AEs clearly indicated on the treatment site on CRFs. Relationship to treatment was all "not related" for AEs not under Skin and Appendages and "related" for those under Skin and Appendages, except for the following: one case each of skin carcinoma, seborrhea, edema, skin ulcer, contact dermatitis, dry skin, rash, the last 3 (contact dermatitis, dry skin and rash) being under ASR.

Medical Officer's Review of NDA 21-005 Amendment

NDA 21-005

Submission Dates: 10/11 & 12/00 (by FAX and Electronic)
Assigned Date: 10/12/00
Review Completed: 10/12/00

Drug name: SOLARAZE™ Gel

Generic name: Diclofenac sodium gel 3%

Applicant: SkyePharma Inc.
10450 Science Center Dr
San Diego, CA 92121

Pharmacologic Category: Non-steroidal antiinflammatory drug

Indication(s): Actinic keratosis

Resume: This submission is a response to the Agency's request of information on the adverse reactions section of the draft label submitted previously by email on 10/3/00.

Background:
On 10/3/00, the Sponsor submitted by email a revised draft label incorporating the comments from the Agency conveyed on 9/15/00. There are minor errors in the Clinical Studies section and the Adverse Reactions section contains a Table with data not consistent with data provided in the study reports of the phase 3 trials. The Applicant has been asked to address these issues. The FAX on 10/11/00 and the email of 10/12/00 address these issues.

FAX of 10/11/00:
This FAX contains : -

- part of the integrated summary of safety from the original NDA, which explains the recoding of some adverse events under "Application Site Reaction", e.g., "Application Site Reaction - Pruritus"
- Table of Adverse Events of Study CT1101-03 as recoded
- Table of Adverse Events of Study CT1101-07 as recoded
- Table of Combined Data for Adverse Events of Studies CT1101-03 and -07 as recoded
- Table of Adverse Events of Study CT1101-04 as recoded
- Revised Draft Label

Email of 10/12/00:
This email contains the data listings of adverse events recoded as stated above.

Review of FAX of 10/11/00 and Email of 10/12/00:
1. The recoded adverse event data provided in the FAX of 10/11/00 are consistent with the information in the original NDA (volume 46, Table 15.1 - 15.29). In the original NDA, the recoded data are as follows:

ASR	CT1101-04 60 day Treatment		CT1101-03 90 day Treatment		CT1101-07 90 day Treatment		CT1101-03 & -07 90 day Treatment	
	Active N=48	Vehicle N=49	Active N=58	Vehicle N=59	Active N=56	Vehicle N=55	Active N=114	Vehicle N=114
Acne	0	2 (4%)	0	0	1 (2%)	0	1 (1%)	0
Alopecia	1 (2%)	0	0	0	1 (2%)	1 (2%)	1 (1%)	1 (1%)
Cellulitis	0	0	0	0	0	0	0	0
Conjunctivitis	0	0	0	0	0	0	0	0
Contact dermatitis	9 (19%)	2 (4%)	7 (12%)	1 (2%)	30 (54%)	3 (5%)	37 (32%)	4 (4%)
Cyst	0	0	0	0	0	0	0	0
Dry skin	13 (27%)	6 (12%)	15 (26%)	7 (12%)	14 (25%)	12 (22%)	29 (25%)	19 (17%)
Edema	2 (4%)	0	3 (5%)	0	0	0	3 (3%)	0
Exfoliation	3 (6%)	2 (4%)	15 (26%)	8 (14%)	12 (21%)	7 (13%)	27 (24%)	15 (13%)
Hyperesthesia	0	0	1 (2%)	0	2 (4%)	1 (2%)	3 (3%)	1 (1%)
Hypertonia	0	0	0	1 (2%)	0	0	0	1 (1%)
Hypesthesia	0	0	0	0	0	0	0	0
Lacrimal disorder	0	0	1 (2%)	0	0	0	1 (1%)	0
MP rash	0	0	1 (2%)	0	0	0	1 (1%)	0
Nail disorder	0	0	0	0	0	0	0	0
Pain	7 (15%)	11 (22%)	18 (31%)	15 (25%)	12 (21%)	19 (35%)	30 (26%)	34 (30%)
Paresthesia	4 (8%)	2 (4%)	12 (21%)	12 (20%)	11 (20%)	11 (20%)	23 (20%)	23 (20%)
Petechial rash	0	0	0	0	0	0	0	0
Photosensitivity d	0	1 (2%)	1 (2%)	0	2 (4%)	0	3 (3%)	0
Pruritus	15 (31%)	28 (57%)	31 (53%)	28 (47%)	28 (50%)	23 (42%)	59 (52%)	51 (45%)
Purpuric rash	0	0	1 (2%)	0	0	0	1 (1%)	0
Pustular rash	0	0	0	0	0	0	0	0
Rash	17 (35%)	10 (20%)	28 (48%)	11 (19%)	24 (43%)	8 (15%)	52 (46%)	19 (17%)
Skin carcinoma	0	0	0	0	1 (2%)	0	1 (1%)	0
Skin hypertrophy	0	0	0	0	0	0	0	0
Skin ulcer	0	0	0	0	0	0	0	0
Urticaria	0	0	0	0	0	0	0	0
Vasodilatation	0	0	0	1 (2%)	0	0	0	1 (1%)
Vesiculobullous ra	0	0	3 (5%)	0	1 (2%)	1 (2%)	4 (4%)	1 (1%)

The data listings submitted by email on 10/12/00 contain a list of the adverse events by patient as recoded. They form the basis for the Tables in the FAX of 10/11/00. These listings are a reformulation of what has been previously submitted, and do not constitute new information.

Comment The data in the Application Site Reaction part of the Table in the Adverse Reaction section of the label is acceptable. Although there are some minor differences in the non-Application Site Reaction part of that Table when compared with raw data from the Clinical Study Reports, these were reviewed by the Biometrics Reviewer, Dr. Valeria Freidlin, who found that the Applicant's figures in the Table are valid. Thus, it may be concluded that the Table itself is valid.

2. Revised Draft Label. The Applicant has revised the Clinical Studies section of the label to correct for the errors in the version submitted on 10/3/00. However, there were some editorial changes which had not been conveyed in the FAX of 9/15/00 from the Agency (see Medical Officer Review Addendum signed off by Division Director 9/28/00). Appropriate changes will be brought to the attention of the Applicant.

Recommendation:

This NDA may be approved when the Applicant satisfactorily revises the label as recommended by the Agency.

/S/ 10-12-00
Hon-Sum Ko, M.D.

cc: NDA 21-005
HFD-540
HFD-540/CSO/White
HFD-540/CHEM/Decamp
HFD-540/PHARM/Reid
HFD-880/BIOPHARM/Tandon
HFD-880/MICRO/Vincent
HFD-540/MO/Walker/Ko
HFD-725/BIOMETRICS/Freidlin

✓ Not in DFS 10/12/00

The attached Physicians Insert (based on spaces email of 10/12/00) & Patient package insert (based on spaces submission of 10/3/00) are recommended for approval with NDA 21-005.

/S/ - 10/12/00.

As above per MO & TL.

/S/ - 10/13/00

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 8 PAGE (S)

Draft

Labeling

Medical Officer's Review of NDA 21-005 Amendment

SEP 7 2000

NDA 21-005	**Submission Dates:**	6/2/00
BL	**Received Dates:**	6/5/00
DDDDP#005978	**Assigned Dates:**	6/9/00
	Review Completed:	7/21/00

Drug name: Solarase™ Gel

Generic name: Diclofenac sodium 3% gel

Applicant: SkyePharma Inc.
10450 Science Center Dr
San Diego, CA 92121

Pharmacologic Category: Non-steroidal antiinflammatory drug

Indication(s): Actinic keratosis

Resume: This submission completes the response to a FAX from the Agency providing labeling comments (conveyed 5/9/00). This review also addresses additional comments since an internal labeling meeting dated 6/22/00.

Background: Since the NA action in October, 1999 for NDA 21-005, ownership of this NDA has been purchased by SkyePharma Inc., and the Agency has been notified on 12/24/99. The new Applicant submitted a complete response to the NA letter on 1/21/00. After the Medical Officer's review of this submission was signed off by the Division Director, labeling comments were conveyed to the Applicant on 5/9/00.

The Applicant responded on 5/18/00, giving revisions on the draft label, with data in one Table in the Clinical Studies section to follow. The current submission addresses the blanks in that Table. In the response of 5/18/00, the Applicant also requested the Agency to provide Hyal's patient package insert (PPI) so that comments on that PPI (FAXed on 5/9/00) could be addressed. Apparently the PPI by Hyal had been lost with the transfer of ownership, and that PPI has never been submitted in hard copy. However, in the original NDA submission, the PPI in the Canadian label was included as hard copy. The Canadian PPI was almost identical to Hyal's lost PPI, with only slight differences, and the Medical Officer's labeling review for the 5/18/00 submission used this Canadian PPI for revision.

An internal labeling meeting was held on 6/22/00, and a version of the revised draft label has been given to this Medical Officer by the Kevin White. The PPI has also been reviewed by DDMAC. Ms Karen Lechter provided comments and revisions before the internal labeling meeting (6/9/00) and after that meeting (6/23/00). Ms Lechter has sent the comments and revisions dated 6/23/00 to this Medical Officer on 7/17/00.

Post-Labeling Meeting Revisions to Draft Label

The current submission contains only additions in one Table of the Clinical Studies section. The figures have been reviewed by Dr. V. Freidlin, the Biometrics Reviewer and found to be acceptable.

The following version of the package insert contains updated changes from and since the labeling meeting of 6/22/00 by this Medical Officer. Additions are underlined, and deletions given strikethrough (x————x). Comments are in parentheses [ ] and underlined.

The key changes to the version immediately following the labeling meeting are as follows:

1. The labeling meeting recommended changing all wordings of "diclofenac" and "sodium diclofenac" to "diclofenac sodium". These changes should not be indiscriminate. Some of the context pertain only to diclofenac and not its sodium or potassium salt, e.g., assays for diclofenac levels, and reactions to diclofenac. Thus, only appropriate changes to "diclofenac sodium" are made.
2. The data submitted on 6/2/00 for the Clinical Studies section have been inserted.
3. The Pharm/Tox Reviewer has had additional changes after the labeling meeting. These have not been incorporated into the following label. The CSO should get the lastest changes from the Pharm/Tox Reviewer for incorporation. The language in her earlier versions is not compatible with a recommendation of Pregnancy Category B, since it states: "Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless the benefits to the mother justify the potential risk to the fetus." This statement suggests Pregnancy ——— . For Category B, the wording should be ————————

A clean text is given after the proposed revisions shown below.

I. Physician Package Insert

WITHHOLD 16 PAGE (S)

Draft

Labeling

Recommendations:

1. The tradename Solarase™ should be reconsidered, as it may inadvertently suggest that the drug product has some action on the skin effects by the sun.

2. This application is approvable if the Applicant revises the label as suggested in this review.

/S/ 7-21-00

Hon-Sum Ko, M.D.

cc: NDA 21-005
HFD-540
HFD-540/CSO/White
HFD-540/CHEM/Decamp
HFD-540/PHARM/Reid
HFD-880/BIOPHARM/Tandon
HFD-880/MICRO/Vincent
HFD-540/MO/Walker/Ko
HFD-725/BIOMETRICS/Freidlin

7/24/00 gw

✓ Not in DFS 7-21-00

Tradename is now Solaraze, and labeling day meeting on 9/6/00 is latest labeling update.

/S/ 9/7/00

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-005 Amendment

JUL 16 2000

NDA 21-005	**Submission Dates:**	4/24/00 & 5/18/00
BL	**Received Dates:**	4/25/00 & 5/19/00
DDDDP#005767 & 005888	**Assigned Dates:**	5/1/00 & 5/24/00
	Review Completed:	5/31/00

Drug name: Solarase™ Gel

Generic name: Diclofenac sodium 3% gel

Applicant: SkyePharma Inc.
10450 Science Center Dr
San Diego, CA 92121

Pharmacologic Category: Non-steroidal antiinflammatory drug

Indication(s): Actinic keratosis

Resume:
The submission of 4/24/00 contains the original label and addresses the issues of (a) financial disclosure and (b) pediatric studies.
The submission of 5/18/00 is a response to the Agency's labeling comments conveyed on 5/9/00.

Original Label:
The original label as resubmitted on 4/24/00 does not conform to the requirements of 21 CFR 201.57. The CSO conveyed the labeling comments from this Medical Officer to the Applicant by FAX on 5/9/00, and this is addressed in a new submission of 5/18/00 (see below).

Pediatric Studies:
There are no pediatric studies in this NDA. Since the indication sought is one that primarily occurs in association with photoaging, a waiver for pediatric studies should be allowed. However, a request for waiver from the Applicant was not made in the original submission. In the submission of 4/24/00, the current Applicant requests a full waiver. This is acceptable.

Financial Disclosure:
The Applicant contends that the Financial Disclosure Final Rule took effect on 2/2/99 and therefore does not apply to NDA 21-005, since it was submitted on October 20, 1998 and filed on December 21, 1998. This position has been upheld by Ms Linda Carter of CDER.

Responses to Labeling Comments (5/18/00 Submission):

The Applicant has revised the label incorporating the Agency's comments, with the exception of the following:

- "Subsections for laboratory tests and drug/laboratory test interactions were not added. There are no laboratory tests that "may be helpful in following the patient's response or in identifying possible adverse reactions" as specified in 21 CFR 201.57(f)(3). Also, there are no known interferences of Solarase™ with laboratory tests as specified in 21 CFR201.57(f)(4)(ii)."

Comment This is acceptable.

- For the Clinical Studies section, data for the Table on clearance of actinic keratosis lesions stratified by location are not yet available and will be provided to the Agency in the near future.

Comment This is acceptable.

- For the Adverse Reactions section, incidence of discontinuations due to adverse experiences has not been stratified according to treatment. Only an overall rate of 18% has been provided.

Comment As the following Table shows, there were many more patients on active treatment discontinuing than patients on vehicle. Thus, it would be misleading to give an overall incidence of 18%. The incidence for both treatment groups should be given.

Discontinuations due to Adverse Events in Clinical Trials on Actinic Keratosis

		Diclofenac	Vehicle
Controlled Studies			
CT1101-03		ASR 6, ASR* 7	ASR 2, ASR* 2
CT1101-04	30-d	ASR 2	ASR 1
	60-d	Contact dermatitis 3, ASR 1	ASR 1
CT1101-07		Contact dermatitis 18, pruritus 1, ca prostate 1, cardiomyopathy 1	ASR 1, ASR* 1, contact dermatitis 1,heart failure 1
AK-CT1101-01		ASR 9, ASR* 6, sick sinus syndrome 1	Adenocarcinoma 1, ASR 1, bursitis/edema 1
ST-5101-AUS-01		ASR* 14, rash (due to Renitec®)	ASR* 2
Uncontrolled Studies			
TDHA-AK-CDN-93-01		Contact dermatitis 1, eczema 6, ASR* 5	Not applicable
ST5101-GRK-01		None	Not applicable

*ASR (application site reaction) here includes rash, pruritus, dry skin, edema, paresthesia, hyperesthesia at treatment site: those given with asterisk in the Table may not necessarily be classified as such in the study report, and ASR without asterisk refers to actual designation as such in the study report.

- For comments on the "Information for the Consumer", the Applicant states that they are not aware of this leaflet, and requests the Agency to forward a copy so that the comments can be addressed.

Comments

1. It is unclear what has been transferred from the previous Applicant, Hyal, to SkyePharma. By a letter from Ms Patricia Anderson dated 12/22/99, FDA has been notified that the assets of Hyal had been purchased by SkyePharma Inc. The "Information for the Consumer" leaflet was submitted previously together with the package insert by Hyal in electronic format, but not as hard copy. Although it might have been lost in the transfer process, it was an asset of Hyal and would have been subject to the purchase. The Agency does not automatically require patient package inserts, but this is a case where the original owner of the NDA intended to have one. As such, this document should be provided to SkyePharma for the comments to be addressed.
2. This document should also be reviewed by DDMAC.

Review of Draft Label:

Additions are underlined, and deletions given strikethrough (x————x). Comments are in parentheses [ ] and underlined.

I. Physician Package Insert

The following provides for recommended changes to the draft label submitted on 5/18/00.

WITHHOLD 7 PAGE (S)

Draft

Labeling

Comment As with other patient package inserts, this document should be reviewed by DDMAC. Nevertheless, it does not appear to be promotional in nature, as the content is essentially on safe and effective use of the drug product.

Recommendations:

1. The tradename Solarase™ should be reconsidered.
2. The patient package insert should be reviewed by DDMAC.
3. SkyePharma should be referred to volume 45, pp 28-29 of the original NDA for the patient package insert.
4. The above labeling recommendations should be discussed at a labeling meeting.

/S/

Hon-Sum Ko, M.D.

cc: NDA 21-005
HFD-540
HFD-540/CSO/White
HFD-540/CHEM/Decamp
HFD-540/PHARM/Reid
HFD-880/BIOPHARM/Tandon
HFD-880/MICRO/Vincent
HFD-540/MO/Walker/Ko
HFD-725/BIOMETRICS/Freidlin

✓ Not in DFS

/S/ 6/9/00

/S/ 7/14/00

APPEARS THIS WAY
ON ORIGINAL

OCT 17 1999

Addendum to Medical Officer Review for NDA 21-005

Date of submission	10/20/98
CDER stamp date	10/22/98
Date submission received by reviewer	11/3/99
Date review begun	12/2/98
Date review completed	9/29/99

Generic name	Sodium diclofenac
Proposed trade name	Solarase™
Chemical name	2-{2,6 dichlorophenyl)amino} benzeneacetic acid monosodium salt
Molecular formula	$C_{14}H_{10}Cl_2NNaO_2$
Molecular weight	318.13
Applicant identification	Hyal Pharmaceutical Corp 2425 Skymark Ave Mississauga, Ont. Canada L4W 4Y6
Dosage form	Gel
Route of Administration	Topical

Purpose of Addendum: Review of

(a) Requested material submitted on 8/25/99 and

(b) Review of proposed label (from original submission of 10/20/98)

Background:

This pending NDA had three phase 3 studies to determine the safety and efficacy of Hyal's diclofenac gel in the treatment of actinic keratosis. Two issues with labeling implications were not clearly presented in the original submission:

1. The clinical protocols mention the use of an applicator to deliver the required amount of test drug (0.5 Gm per 5 cm x 5 cm treatment "block") or use of one finger tip unit (FTU) of gel on the area. However, the study reports do not clearly document the pattern of usage of these options.

2. The clinical study reports describe the need for sun avoidance during the studies and for informing patients on such measures. This information cannot be located in the protocols or consent forms.

In order to have more informative labeling, the Applicant was requested to address the above discrepancies by providing documentation (a) of the actual application method for the test drugs in the studies, and (b) on the advice to patients regarding sun avoidance. The Applicant responded with a submission on 8/25/99.

Response to Information Request:
Because the phase 3 studies were performed 3 to 4 years ago, and there was no recording of the above information at the time the trials were conducted, the Applicant telephoned the Investigators in an attempt to obtain the requested information. The following was obtained:

Study	Applicator Use	Sun Avoidance Advice
CT1101-03		
Dr. Wolf	Believes 100% use	Yes
Dr. Kang	Cannot recall	Cannot recall unless in protocol
Dr. Tschen	100% at first visit; declined after 1st visit to 60-75%	Yes
Dr. Taylor	100% use	Yes
CT1101-04		
Dr. Rivers	100% at first visit; declined after 1st visit to 0%	Yes
Dr. Poulin	100% at first visit; declined after 1st visit to 0%	Yes
Dr. Arlette	Not used (all patients used finger-tip unit)	Advised limiting sun exposure; protective clothing
Dr. Guenther	Not used (all patients used finger-tip unit)	Advised limiting sun exposure; protective clothing
Dr. Shear	Majority at first visit; declined after 1st visit to 0%	Advised limiting sun exposure; protective clothing
Dr. Carey	Majority at first visit; declined after 1st visit to <20%	Advised limiting sun exposure
CT1101-07		
Dr. Welch	Majority at first visit; declined after 1st visit to 0%	Advised limiting sun exposure; protective clothing

Comments and Conclusions on Applicator Use and Sun Avoidance Advice:

1. Applicator Use. The two adequate and well controlled trials (CT1101-03 and -04) gave opposite information on applicator use: most of the patients in CT1101-03 used it while most of those in CT1101-04 did not. Most patients in CT1101-07 also did not. As the dose (0.5 Gm/5 cm x 5 cm, or 20 mg/cm^2) is in excess, it is unlikely that accurate dosing is of paramount importance and that use of applicator or finger-tip unit would make much difference. The excess gel would easily be subject to loss over clothing, pillows and bed sheets. Moreover, in one of the phase 2 studies (CT1101-01), where the dose was supposed to be 0.25 Gm/25 cm^2, the instruction was to apply the gel with an amount of the ——— . This is the same description for 0.5 Gm ——— —) in the proposed labeling under DOSAGE AND ADMINISTRATION. It may be concluded that the quantity of drug applied and bioavailable to the lesions in these studies can only be estimated but not defined.

2. Sun Avoidance Advice. According to the Investigators' responses, besides one Investigator who could not recall, all provided such advice to the patients in the trials.

Labeling Review:
I. The Package Insert
The proposed label is not consistent with current regulations under 21 CFR 201.57. Specifically, -

1. The WARNINGS section contains material other than "serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur."

2. INFORMATION FOR PATIENTS should be a subsection of the PRECAUTIONS section.

3. ——— , drug interactions, ——————— , pediatric use and geriatric use subsections of the PRECAUTIONS section are lacking.

4. The Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the PRECAUTIONS section should precede the pregnancy subsection.

5. The pregnancy subsection of the PRECAUTIONS section should contain the headings "teratogenic effects" and ——————— and use language consistent with that in 21 CFR 201.57(f)(6).

6. ADVERSE REACTIONS section should also list reactions of "drugs in the same pharmacologically active and chemically related class, if applicable", i.e. other formulations of diclofenac and NSAIDs.

The Applicant is recommended to address the above deficiencies. In addition, the following comments require attention:

1. Under CLINICAL PHARMACOLOGY:

[ ]

The contribution of hyaluronan sodium should be stated. The ——————— ——— as a possible mechanism of action should be considered.

[ ]

Study CT1101-04 is the only trial with histopathologic data. There were no significant differences between diclofenac and vehicle groups with regard to the above parameters.

2. Under CLINICAL PHARMACOLOGY, Pharmacokinetics:

"When Solarase™ is applied topically, diclofenac is absorbed into the epidermis. ———

Although a small amount of diclofenac is absorbed systemically, the NDA has not provided documentation of epidermal levels of diclofenac to warrant stating "diclofenac is absorbed *into* the epidermis."

"In a study in patients with compromised epidermis (mainly —— and other dermatitic conditions) of the hands, arms or face, approximately 10% of the applied dose of diclofenac was absorbed systemically in both normal and compromised epidermis after seven days."

This statement is misleading, because in the PK study on patients with dermatitic skin (EP105), application of study medication was primarily to the extremities. Absorption from the skin in the head and neck region has not been adequately determined other

than through therapeutic drug monitoring. The term ——— should be qualified with the adjective "atopic", since that was what was studied.

"Blood drawn at the end of treatment from 60 patients treated ——— ' in three adequate and well controlled trials were assayed for diclofenac levels. Serum concentrations were on average at, or below 20 ng/mL. — data indicates that systemic absorption of diclofenac in patients is ——— that occurring ——— oral daily dosing of diclofenac."

- The dose and sites of application should be stated.
- The serum level achieved with oral diclofenac should be stated for comparison.

[ ]

The Applicant should explain the basis of this statement.

In addition, under CLINICAL PHARMACOLOGY, Pharmacokinetics, the fate of the ——— applied to skin should be addressed.

3. Under INDICATIONS AND USAGE:

——— gel is indicated for the topical treatment of actinic keratoses."

This statement should be qualified ———

——— As the drug product was used in conjunction with sun avoidance during the clinical trials, the Applicant should consider their treatment as part of a regime in the management of actinic keratosis.

4. The CLINICAL ——— section should be renamed to be the CLINICAL STUDIES section.

5. Under CLINICAL STUDIES:

"Clinical trials were conducted involving a total of 427 subjects — 213 —— treated with ——— and 214 — gel vehicle. Each subject had no — than five actinic keratosis lesions ——— ——— 5 cm by 5 cm ——— completion of treatment was the primary efficacy variable."

- The locations of the 5 cm x 5 cm areas and the dose should be provided.
- The enrollment restrictions and restrictions during study should be given.
- The primary variable was complete clearing and not ———
- The lack of long-term follow-up for detection of recurrence should be stated.

The description of data may be summarized in tabular format as follows, and the Applicant is requested to supply data for the blanks :

	Complete Clearance of Actinic Keratosis Lesions 30 days Post-Treatment		
	Diclofenac	Vehicle	p-value
Study 1 90 days treatment	27/58 (47%)	11/59 (19%)	<0.001
Study 2 90 days treatment	18/53 (34%)	10/55 (18%)	0.061
Study 3 60 days treatment	15/48 (31%)	5/49 (10%)	0.021
30 days treatment	7/49 (14%)	2/49 (4%)	0.221

	Complete Clearance of Actinic Keratosis Lesions 30 days Post-Treatment				
	Scalp	Forehead	Face	Arm/Forearm	Back of Hand
Study 1 90 days treatment —— Vehicle p-value					
Study 2 90 days treatment —— Vehicle p-value					
Study 3 60 days & 30 days treatment —— Vehicle p-value					

*N/S=not studied

6. Under WARNINGS:

There are statements not appropriate in the WARNINGS section of the label: -

- The following statement deemphasizes hazard and should not be included:

[ ]

- The third sentence in the following statements deemphasizes hazard and should not be included:

"As with other NSAIDs, —— may occur.

[ ]

- The following statement deemphasizes hazard and should not be included:

[ ]

- The first sentence in the following paragraph provides anecdotal data and is not useful information to be conveyed. The second sentence suggests "serious adverse reactions and potential safety hazards" upon —— when using diclofenac without evidence.

[ ]

7. Within the PRECAUTIONS section, pertinent information on ——, drug interactions, —— pediatric use and geriatric use should be provided according to formats in their relevant subsections as given in 21 CFR 201.57.

8. Under PRECAUTIONS, Information for Patients:

[ ]

This paragraph is vague and should be substituted with more specific language.

[ ]

The clinical studies specifically prohibited use of cosmetics, including hyaluronan-containing cosmetics, as well as sunscreens. The term —— may be

misinterpreted to mean solely drugs. The Applicant is encouraged to be more informative on the restrictions.

9. The Applicant is requested to provide a rationale for classifying their product as Pregnancy ——— in the "Teratogenic Effects" portion of the Pregnancy subsection under PRECAUTIONS, when no evidence of teratogenicity has been provided. Moreover, the oral diclofenac label uses Pregnancy Category B.

10. The subsection ——————— under PRECAUTIONS should be retitled and show consistency with recommendations in 21 CFR 201.57(g).

11. The ADVERSE REACTIONS section should be revised to show the incidence of adverse events and discontinuations under both active and vehicle treatments. Reporting of the incidence of adverse events should be based on ALL adverse events and not only those "causally related to therapy". Greater details should be presented for application site reactions, including incidences of the components.

It is recommended that the following statements be removed, as they do not contribute to the understanding of the occurrence of toxicity:

[ ]

12. Under DOSAGE AND ADMINISTRATION:

"Normally 0.5 g of gel ——————— is used on each 5 cm x 5 cm lesion site. The recommended duration of therapy is from ——— to 90 days."

As discussed above, the drug product was used in excess in the clinical trials, and it may be adequate to state that instead of using terms like ——————— In one of the phase 2 studies (CT1101-01), where the dose was supposed to be 0.25 Gm/25 cm^2, the instruction was also to apply the gel with an amount of the ——————— . This may be confusing. In addition, since the ——— treatment group in CT1101-04 did not show superiority by the drug product over vehicle, it is not appropriate to state the "recommended duration of therapy is from ——— to 90 days."

[ ]

Actinic keratosis is not an indication in children. The drug product is not supposed to be used by children. This statement may open the door to off-label use for — indications.

II. Information for the Consumer

The NDA does not include this circular in the section on labeling. This was provided to the Agency in electronic format when an electronic version of the label was requested. It is unclear whether the purpose of this leaflet is for promotion or to serve as a patient package insert. The Applicant should clarify their intent on this.

The document lacks specifics on the indication for which the product is intended. There is a concern that this may lead to off-label use for — indications.

The instruction on drug application is confusing, as it specifies an amount to be used and yet goes on to say that it is variable depending on size of lesion area:

The amount of gel needed upon the size of the lesion

Recommendation:

The Applicant should address the above comments on labeling. From a clinical standpoint, the application is approvable with proper labeling changes. It is not possible to provide the Applicant with definitive changes for their draft label. A revised draft of the label which takes into consideration the above recommendations should be submitted before the Agency can help the Applicant finalize their product label.

/S/ 10-7-99

Hon-Sum Ko, M.D.

cc: NDA 21-005
HFD-540
HFD-540/CSO/White
HFD-540/CHEM/Decamp
HFD-540/PHARM/Reid
HFD-880/BIOPHARM/Tandon /S/ 10/13/99
HFD-880/MICRO/Vincent
HFD-540/MO/Walker/Ko
HFD-725/BIOMETRICS/Freidlin /S/ 10/17/99

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-005 Amendment

NDA 21-005

Submission Date: 10/03/00 (Electronic)
Assigned Date: 10/04/00
Review Completed: 10/08/00

Drug name: SOLARAZE™ Gel

Generic name: Diclofenac sodium gel 3%

Applicant: SkyePharma Inc.
10450 Science Center Dr
San Diego, CA 92121

Pharmacologic Category: Non-steroidal antiinflammatory drug

Indication(s): Actinic keratosis

Resume: This submission is a response to the Approvable Letter of 7/19/00, and a copy of the recommended draft label FAXed from the Agency on 9/15/00. It contains a revised draft label from the Applicant.

Revised Draft Label from Applicant

1. The Applicant has accepted all the recommendations from the Agency on the draft label, with the exception of the INDICATIONS AND USAGE section.

The Agency recommended the following wording for the INDICATIONS AND USAGE section:

> Solaraze™ (diclofenac sodium) gel is indicated for the topical treatment of actinic keratoses (AK) ——— ——— . Sun avoidance is indicated during therapy.

The Applicant has removed reference to ——— in this section of the package insert and patient package insert:

> Solaraze™ (diclofenac sodium) gel is indicated for the topical treatment of actinic keratoses (AK). Sun avoidance is indicated during therapy.

Comment The combined data from the phase 3 studies show the following:

Proportion of Patients with Complete Clearing of AK* Lesions

	active	vehicle	Active/Vehicle Ratio	p-value
Scalp	8/22 = 36%	3/24 = 13%	2.9	0.0903
Forehead	43/109 = 39%	21/111 = 19%	2.4	0.0013
Face	26/55 = 47%	11/56 = 20%	2.4	0.0016
Arm/Forearm	9/21 = 43%	4/20 = 20%	2.1	0.2043
Back of Hand	9/50 = 18%	5/48= 10%	1.7	0.3662

*AK=actinic keratosis

- The active/vehicle ratios on clearing range from 1.7 to 2.9, i.e., active always giving more clearing than placebo, suggesting that it may be a matter of power to show statistical significance. The studies were not powered to show regional differences.
- The actual numbers of lesions are small and easily swayed by tiny changes.
- The hand lesions do show less responsiveness, but they may also be less responsive to other treatments, which have ———————— in labeling.

It may be undesirable to have too restrictive wording in the Indication and Usage section, as it may result in the denial of necessary treatment. The essential information can be provided in the clinical studies section, whose data would indicate that it is less responsive on the hands and arms. Therefore, it may be acceptable to remove the ———————— in the Indications and Usage section.

2. There are figures provided by the Applicant in the Clinical Studies section and in the Adverse Reactions section that are either inaccurate or unverifiable.

a) In the following Table in the Clinical Studies section, the errors and unverifiable information have been highlighted. The zero values in Study 3 should have denominators so that the total values can be verified. This has been brought to the attention of the Statistical Reviewer and the Applicant has been asked to revise the Table.

	Complete Clearance of Actinic Keratosis Lesions 30 days Post-Treatment (by location)				
	Scalp	Forehead	Face	Arm/Forearm	Back of Hand
Study 1 90 days treatment					
Solaraze™	1/4 (25%)	17/30 (57%)	9/17 (53%)	4/12 (33%)	6/16 (38%)
Vehicle	3/9 (33%)	8/24 (33%)	5/17 (29%)	4/12 (33%)	0/14 (0)
p-value	0.7646	0.0908	0.1682	1.000	0.0650
Study 2 90 days treatment					
Solaraze™	2/6 (33%)	9/19 (47%)	4/5 (80%)	5/8 (63%)	1/17 (6%)
Vehicle	0/4 (0)	6/22 (27%)	2/8 (25%)	0/5 (0)	6/16 (19%)
p-value	0.4235	0.1870	0.0727	0.0888	0.2818
Study 3 60 days treatment					
Solaraze™	3/7 (43%)	13/31 (42%)	10/19 (53%)		2/8 (25%)
Vehicle	—	5/36 (14%)	2/13 (15%)		1/9 (11%)
p-value	0.2271	0.0153	0.0433		0.4637
30 days treatment					
Solaraze™	2/5 (40%)	4/29 (14%)	3/14 (21%)		—
Vehicle	—	2/29 (7%)	2/18 (11%)		1/9 (11%)
p-value	0.2299	0.3748	0.4322		0.6521
All data combined					
Solaraze™	8/22 (36%)	109 (39%)	26/55 (47%)	9/21 (43%)	9/50 (18%)
Vehicle	3/24 (13%)	21/111 (19%)	11/56 (20%)	4/20 (20%)	5/48 (10%)
p-value	0.0903	0.0013	0.0016	0.2043	0.3662

b) The Adverse Reactions section contains information inconsistent with the raw data from the phase 3 studies as presented in the original submission. In addition, there are adverse events in the "Skin and Appendages" that are classified both under and not under the term "Application Site Reactions." It is not possible to know how these figures have been split by the Applicant. These data under "Skin and Appendages" require documentation for support in order to be listed in the Table.

- The following Table contains corrections by this Reviewer for the non-Skin and Appendages adverse events and some Skin and Appendages adverse events that can be verified (corrections in parentheses). The remainder has been left blank because these cells need further documentation. Documentation should also be provided for the footnote concerning "Skin and Appendages" adverse events of less that 1%. The Applicant should clearly indicate how adverse events were classified within or outside of the title "Application Site Reaction."
- The Applicant should also revise the figures for the organ systems after verification of the errors for the individual adverse events.
- The adverse event item "Other" should be moved to the end of the Table and the "Procedure" identified in a footnote.

Table 1. Adverse events reported (>1% in any treatment group) during Solaraze phase 3 clinical trials Incidences for 60-day and 90-day treatments

	60-day Treatment	90-day Treatment

Skin and Appendages Adverse Events Reported for Solaraze at less than 1% Incidence in the phase 3 studies: skin hypertrophy, paresthesia, seborrhea, urticaria, application site reactions (skin carcinoma, hypertonia, skin hypertrophy lacrimation disorder, maculopapular rash, purpuric rash, vasodilation).

Comments that Can be Conveyed to the Applicant:

1. In the following Table in the Clinical Studies section, the errors and unverifiable information have been highlighted. The zero values in Study 3 should have denominators so that the total values can be verified.

	Complete Clearance of Actinic Keratosis Lesions 30 days Post-Treatment (by location)				
	Scalp	Forehead	Face	Arm/Forearm	Back of Hand
Study 1 90 days treatment					
Solaraze™	1/4 (25%)	17/30 (57%)	9/17 (53%)	4/12 (33%)	6/16 (38%)
Vehicle	3/9 (33%)	8/24 (33%)	5/17 (29%)	4/12 (33%)	0/14 (0)
p-value	0.7646	0.0908	0.1682	1.000	0.0650
Study 2 90 days treatment					
Solaraze™	2/6 (33%)	9/19 (47%)	4/5 (80%)	5/8 (63%)	1/17 (6%)
Vehicle	0/4 (0)	6/22 (27%)	2/8 (25%)	0/5 (0)	6/16 (19%)
p-value	0.4235	0.1870	0.0727	0.0888	0.2818
Study 3 60 days treatment					
Solaraze™	3/7 (43%)	13/31 (42%)	10/19 (53%)		2/8 (25%)
Vehicle	—	5/36 (14%)	2/13 (15%)		1/9 (11%)
p-value	0.2271	0.0153	0.0433		0.4637
30 days treatment					
Solaraze™	2/5 (40%)	4/29 (14%)	3/14 (21%)		—
Vehicle	—	2/29 (7%)	2/18 (11%)		1/9 (11%)
p-value	0.2299	0.3748	0.4322		0.6521
All data combined					
Solaraze™	8/22 (36%)	109 (39%)	26/55 (47%)	9/21 (43%)	9/50 (18%)
Vehicle	3/24 (13%)	21/111 (19%)	11/56 (20%)	4/20 (20%)	5/48 (10%)
p-value	0.0903	0.0013	0.0016	0.2043	0.3662

2. The Adverse Reactions section contains information inconsistent with the raw data from the phase 3 studies as presented in the original submission. In addition, there are adverse events in the "Skin and Appendages" that are classified both under and not under the term "Application Site Reactions." It is not possible to know how these figures have been split by the Applicant. These data under "Skin and Appendages" require documentation for support in order to be listed in the Table.

- The following Table contains corrections by this Reviewer for the non-Skin and Appendages adverse events and some Skin and Appendages adverse events that can be verified (corrections in parentheses). The remainder has been left blank because these cells need further documentation. Documentation should also be provided for the footnote concerning "Skin and Appendages" adverse events of less that 1%. The Applicant should clearly indicate how adverse events were classified within or outside of the title "Application Site Reaction."
- The Applicant should also revise the figures for the organ systems after verification of the errors for the individual adverse events.
- The adverse event item "Other" should be moved to the end of the Table and the "Procedure" identified in a footnote.

Table 1. Adverse events reported (>1% in any treatment group) during Solaraze phase 3 clinical trials Incidences for 60-day and 90-day treatments

	60-day Treatment	90-day Treatment

	60-day Treatment	90-day Treatment

Skin and Appendages Adverse Events Reported for Solaraze at less than 1% incidence in the phase 3 studies: skin hypertrophy, paresthesia, seborrhea, urticaria, application site reactions (skin carcinoma, hypertonia, skin hypertrophy lacrimation disorder, maculopapular rash, purpuric rash, vasodilation).

Recommendation:

This NDA may be approved when the Applicant satisfactorily revises the label as recommended by the Agency.

/S/ 10/8/00

Hon-Sum Ko, M.D.

cc: NDA 21-005
HFD-540
HFD-540/CSO/White
HFD-540/CHEM/Decamp
HFD-540/PHARM/Reid
HFD-880/BIOPHARM/Tandon
HFD-880/MICRO/Vincent
HFD-540/MO/Walker/Ko
HFD-725/BIOMETRICS/Freidlin

✓ Not in DFS 10/8/00

/S/ 10/12/00
See MO Review dated 10/12/00 for additional comments on sponsor date submitted since this review. This review is superseded by review (MO) of 10/12/00. /S/

As done per MO & TL.

/S/ 10/15/00

Addendum to Medical Officer's Review of NDA 21-005 Amendment

NDA 21-005
BL
DDDDP#006416

Submission Date: 8/15/00
Received Date: 8/16/00

SEP 28 2000

Date of Addendum: 9/6/00

Drug name: Solaraze™ Gel

Generic name: Diclofenac sodium 3% gel

Applicant: SkyePharma Inc.
10450 Science Center Dr
San Diego, CA 92121

Purpose of Addendum: Comments on proposed label to be conveyed to Applicant

Proposed Draft Label and Comments:
The proposed label has been revised by Kevin White with incorporation of comments from different review disciplines. A hard copy has been distributed on 9/5/00 for further comments before conveying to the Applicant.

The following comments are made:

1. Under CLINICAL PHARMACOLOGY, Pharmacokinetics:
a) The first paragraph under "Absorption" should restore the exact conditions being treated in Study EP105:

> "When Solaraze™ is applied topically, diclofenac is absorbed into the epidermis. In a study in patients with compromised skin (mainly atopic — and other — dermatitic conditions) of the hands, arms or face, approximately 10% of the applied dose (2 grams of 3% gel over 100 cm^2) of diclofenac was absorbed systemically in both normal and compromised epidermis after seven days, with four times daily applications."

b) The use of "mL" vs "ml" should be consistent.

c) The third paragraph under "Absorption" should be modified for clarity as follows:

> "Blood drawn at the end of treatment — from 60 patients with Solaraze™ in three adequate and well-controlled clinical trials were assayed for diclofenac — levels. Each patient was administered 0.5g of Solaraze™ gel twice a day for up to 105 days. — There were up to three 5 cm X 5 cm treatment sites per patient on the face, forehead, hands, forearm, and scalp. Serum concentrations of diclofenac were on average at, or below 20 ng/ml. — These data — indicate that the systemic absorption of diclofenac — in patients treated topically with Solaraze™ is much lower —— than that occurring after oral daily dosing of diclofenac sodium."

d) The paragraph on "Metabolism" should be corrected and clarified as follows:

> "Biotransformation of diclofenac — following oral administration involves conjugation at the carboxyl group of the side chain or single or multiple hydroxylations resulting in several phenolic metabolites, most of which are converted to — glucuronide conjugates. Two of these phenolic metabolites are biologically active, however to a much smaller extent than diclofenac. Metabolism of diclofenac following

topical administration is thought to be similar to that after oral administration. The small amounts of diclofenac appearing in the plasma following topical administration makes the ——— of specific metabolites ———————————————————

d) The first sentence in the paragraph on "Elimination" should be corrected as follows:

"Diclofenac —— and its metabolites are excreted mainly in the urine after oral dosing."

2. The title for the section INDICATIONS AND USAGE should be corrected":

"INDICATIONS — AND USAGE"

3. The first paragraph under CLINICAL STUDIES should restore the sentence "In addition, all patients were instructed to avoid ——— sun exposure" but without the word —

"Clinical trials were conducted involving a total of 427 patients (213 treated with Solaraze™ and 214 with gel vehicle). Each patient had no fewer than five AK lesions in a major body area, which was defined as one of five 5 cm by 5 cm regions: scalp, forehead, face,, forearm, and hand. Up to three major body areas were studied in any patient. All patients were 18 years of age or older (male and female) with no clinically significant medical problems outside of the AK lesions and had undergone a 60-day washout period from disallowed medications (masoprocol, 5-fluorouracil, cyclosporine, retinoids, trichloroacetic acid/lactic acid/peel, 50% glycolic acid peel) and hyaluronan-containing cosmetics. Patients were excluded from participation for reasons of known or suspected hypersensitivity to any Solaraze™ ingredient, pregnancy, allergies to aspirin or other nonsteriodal antiinflammatory drugs (NSAIDs), or other dermatological conditions which might affect the absorption of the study medication. Application of dermatologic products such as sunscreens, cosmetics, and other drug products were not permitted. In addition, all patients were instructed to avoid — sun exposure. [Add details of drug administration.] Complete clearing of the AK lesions 30 days after completion of treatment was the primary efficacy variable. No long term patient follow-ups after the 30-day assessments were performed for the detection of recurrence."

4. Under PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility:
a) Changes should be made in the first two paragraphs re "Solaraze™ contains 3% diclofenac", as it is diclofenac sodium. The second sentence also needs to clarify whether diclofenac doses are based on diclofenac or diclofenac sodium.

"There did not appear to be any increase in drug-related neoplasms following daily topical applications of diclofenac gel for 2 years at concentrations up to 0.035% diclofenac and 2.5% hyaluronate in albino mice. (Note: Solaraze™ contains 3% diclofenac sodium.) When administered orally for 2 years, —— no evidence of carcinogenic potential ——— in rats given diclofenac at up to 2 mg/kg/day (3 times the estimated systemic human exposure*), or in mice given diclofenac sodium at up to 0.3 mg/kg/day in males and 1 mg/kg/day in females (25% and 83%, respectively, of the estimated systemic human exposure).

"A photococarcinogenicity study with up to 0.035% diclofenac in the Solaraze™ vehicle gel was conducted in hairless mice at topical doses up to 2.8 mg/kg/day. Median tumor onset was earlier in the 0.035% group (Solaraze™ contains 3% diclofenac sodium)."

b) It is assumed that the third paragraph refers to diclofenac sodium and not diclofenac:

"Diclofenac —— was not genotoxic in *in vitro* point mutation assays in mammalian mouse lymphoma cells and Ames microbial test systems, or when tested in mammalian *in vivo* assays including dominant lethal and male germinal epithelial chromosomal studies in mice, and nucleus anomaly and chromosomal aberration studies in Chinese hamsters. It was also negative in the transformation assay utilizing BALB/3T3 mouse embryo cells."

c) The paragraph with asterisk is a footnote.

** Based on body surface area and assuming 10% bioavailability following topical application of 2 g Solaraze™ gel per day (1 mg/kg diclofenac sodium).*

5. Under PRECAUTIONS, Pregnancy:
The language should be consistent with that in 21 CFR 201.57.

6. Under PRECAUTIONS, Nursing Mothers:
The language should be consistent with that in 21 CFR 201.57.

7. Under ADVERSE REACTIONS:
a) The items in the Table with Application Site Reactions do not need to be underlined:

Skin and Appendages
Skin carcinoma
Pruritus
Rash
Application Site Reaction
• Contact dermatitis
• Dry skin
• Exfoliation (scaling)
• Edema
• Pain
• Paresthesia
• Pruritus
• Rash
• Vesiculobullous rash

b) The title of the "Adverse Reactions Reported for *Oral* Diclofenac Dosage Form (not topical Solaraze Gel)" paragraphs should have the TM symbol inserted after "SOLAZRAZE".

8. Under DOSAGE AND ADMINISTRATION:
The third sentence should have the word gel inserted:

"Assure that enough Solaraze™ gel is applied to adequately cover each lesion."

9. Under HOW SUPPLIED, Storage:
Editorial change is recommended:

"Store at controlled temperatures: 15°- —°C (59°- — °F). Protect from heat ——

10. In the PPI, under "What is SOLARAZE?"
———————, should be replaced by SOLARAZE (SOLE-ar-aze).

11. It is not clear whether it is necessary to use the TM symbol for SOLARAZE in the PPI.

Recommendation:
It is recommended that the above comments be considered.

/S/ 9-6-00
Hon-Sum Ko, M.D.

cc: NDA 21-005
HFD-540
HFD-540/CSO/White
HFD-540/CHEM/Decamp
HFD-540/PHARM/Reid
HFD-880/BIOPHARM/Tandon
HFD-880/MICRO/Vincent
HFD-540/MO/Walker/Ko
HFD-725/BIOMETRICS/Freidlin

/S/ 9/6/00

✓ Not in DFS

As above, except under 1. a), where "atopic dermatitis" should be substituted for "atopic ——".

/S/ 9/28/00

APPEARS THIS WAY
ON ORIGINAL

SEP 7 2000

Medical Officer's Review of NDA 21-005 Amendment

NDA 21-005	**Submission Dates:**	8/15/00
BL	**Received Dates:**	8/16/00
DDDDP#006416	**Assigned Dates:**	8/25/00
	Review Completed:	8/25/00

Drug name: Solaraze™ Gel

Generic name: Diclofenac sodium 3% gel

Applicant: SkyePharma Inc.
10450 Science Center Dr
San Diego, CA 92121

Pharmacologic Category: Non-steroidal antiinflammatory drug

Indication(s): Actinic keratosis

Resume: This submission is a response to the Approvable Letter of 7/19/00. It contains (1) draft labeling of the immediate container and carton labels for the proposed product and (2) a statement regarding safety update.

Response in Current Submission:

There is no new information.

- The draft container/carton labels are now versions with the company's logo and put on a black (or color) background; previous version in the submission of 7/17/00 was text only.
- Regarding safety update, the Applicant states that there have been no new clinical studies and no new safety data are available.

Comments

1. The container/carton labels should be reviewed by the CMC Reviewer. The "USUAL ADULT DOSE" information should follow what is in the package insert, which is to be finalized.
2. The Applicant needs to modify the package insert according to the Agency's recommendations. This Reviewer's recommendations are in the reviews for the submissions dated 6/2/00 and 7/17/00.

Comments Which May be Conveyed to Applicant by CSO:

The Applicant needs to modify the package insert according to the Agency's recommendations.

Recommendations:

1. The container/carton labels should be reviewed by the Chemist. The "USUAL ADULT DOSE" in the carton labels should follow the information in the finalized package insert.
2. This NDA may be approved when the Applicant satisfactorily revises the label as recommended by the Agency.

/S/ 8-25-00

Hon-Sum Ko, M.D.

cc: NDA 21-005
HFD-540
HFD-540/CSO/White
HFD-540/CHEM/Decamp
HFD-540/PHARM/Reid
HFD-880/BIOPHARM/Tandon
HFD-880/MICRO/Vincent
HFD-540/MO/Walker/Ko
HFD-725/BIOMETRICS/Freidlin

/S/ 8/31/00

Not in DFS 8/25/00

/S/ 9/7/00

APPEARS THIS WAY
ON ORIGINAL

AUG 15 2000

Medical Officer's Review of NDA 21-005 Amendment

NDA 21-005	**Submission Dates:**	7/17/00
BL	**Received Dates:**	7/18/00
DDDDP#006199	**Assigned Dates:**	7/24/00
	Review Completed:	7/27/00

Drug name: Solaraze™ Gel

Generic name: Diclofenac sodium 3% gel

Applicant: SkyePharma Inc.
10450 Science Center Dr
San Diego, CA 92121

Pharmacologic Category: Non-steroidal antiinflammatory drug

Indication(s): Actinic keratosis

Resume: This submission updates the draft label with (1) change in the proposed tradename, (2) revision of the Geriatric Use subsection and (3) proposed carton labels.

Background: Since the NA action in October, 1999 for NDA 21-005, ownership of this NDA has been purchased by SkyePharma Inc., and the new Applicant submitted a complete response to the NA letter on 1/21/00. The Applicant has responded to the Agency's suggestions on the label with two previous submissions dated 5/18/00 and 6/2/00. The current submission updates the draft label with (1) change in the proposed tradename, (2) revision of the Geriatric Use subsection and (3) proposed carton labels.

It is noted that an Approvable Letter for this NDA has been issued to the Applicant on 7/19/00.

I. Change in Tradename Proposal

The proposed tradename has been changed from Solarase to Solaraze. This is acceptable.

II. Changes in the Geriatric Use Subsection

The new proposed Geriatric Use subsection is as follows:

> Of the 211 subjects treated with Solaraze™ in controlled clinical studies, 143 subjects were 65 and over. Of those 143 subjects, 55 subjects were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out."

Comment The proposed Geriatric Use subsection is in compliance with the language in 21 CFR 201.57(f)(10)(ii)(B), except for the addition of the first sentence [ ] This sentence appears to be redundant, as the last

part of the subsection has the required language "…. greater sensitivity of some older individuals cannot be ruled out."

III. Carton Labels

They are as follows:

Comment These carton labels should be reviewed by the Chemist. The "USUAL ADULT DOSE" should follow what is in the package insert, which is to be finalized.

Comments Which May be Conveyed to Applicant by CSO:

None until the Applicant has provided a complete response to the Approvable Letter of 7/19/00.

Recommendations:

1. The proposed tradename, Solaraze, is acceptable.

2. The proposed Geriatrics Use subsection appears to be acceptable, but the first sentence is redundant and may be removed.

3. The carton labels should be reviewed by the Chemist. The "USUAL ADULT DOSE" in the carton labels should follow the information in the finalized package insert.

/S/ 7-27-00

Hon-Sum Ko, M.D.

cc: NDA 21-005
HFD-540
HFD-540/CSO/White
HFD-540/CHEM/Decamp
HFD-540/PHARM/Reid
HFD-880/BIOPHARM/Tandon
HFD-880/MICRO/Vincent
HFD-540/MO/Walker/Ko
HFD-725/BIOMETRICS/Freidlin

/S/ 7/31/00

Not in DFS ✓ 7/27/00

/S/ 8/15/00

APPEARS THIS WAY
ON ORIGINAL