APPENDIX

NDA 50-777

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TABLE A1 PATIENT DEMOGRAPHIC DATA

SUBJECT	SEX	AGE (years)	WEIGHT (kg)*	HEIGHT (cm)*	ESTIMATED TOTAL BSA (m^2)
TREATMENT GROUP 1					
1001	F	19	58	168	1.656
1003	F	24	56	159	1.568
1024	F	18	56	164	1.604
1026	F	19	57	165	1.623
1027	M	21	68	175	1.826
1028	F	22	65	167	1.731
1030	F	35	75	170	1.864
1031	F	19	40	154	1.328
1032	F	18	63	170	1.730
1033	F	18	80	175	1.956
1035	F	22	65	170	1.754
MEAN	1 M / 10 F	21	62	167	1.694
TREATMENT GROUP 2					
1004	F	19	67	165	1.738
1005	F	23	56	169	1.639
1007	F	31	80	168	1.899
1010	M	26	78	188	2.038
1012	F	18	50	166	1.542
1013	M	28	79	182	2.002
1014	M	23	70	187	1.939
1016	M	29	75	177	1.919
1017	F	23	72	169	1.824
1018	M	22	76	182	1.969
1021	F	19	58	170	1.671
1023	F	20	46	155	1.416
MEAN	5 M / 7 F	23	67	173	1.800
TREATMENT GROUP 3					
1006	F	19	73	173	1.866
1009	F	37	53	152	1.483
1011	M	26	76	180	1.953
1015	F	19	52	163	1.547
1020	M	18	62	175	1.755
1022	F	32	50	167	1.548
1034	F	21	59	169	1.676
1036	F	38	62	163	1.667
1037	F	18	76	164	1.826
MEAN	2 M / 7 F	25	63	167	1.702

*weight at screening visit

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TABLE A2 TREATED BODY SURFACE AREA (BSA) AS AN ABSOLUTE VALUE AND AS A PERCENTAGE OF TOTAL BSA

Patient	Treated BSA (cm^2)	% of total BSA
Treatment Group 1		
1001	2940	18
1003	2800	18
1024	2990	15
1026	2500	28
1027	2750	17
1028	1900	12
1030	2465	15
1031	2540	16
1032	1800	12
1033	2000	13
1035	1820	11
Mean	2410	16
Treatment Group 2		
1004	3340	23
1005	3200	19
1007	3560	29
1010	4360	28
1012	3390	22
1013	6000	37
1014	4500	27
1016	4300	26
1017	4800	17
1018	3300	21
1021	5000	32
1023	3500	22
Mean	4159	25
Treatment Group 3		
1006	8880	56
1009	9500	57
1011	7800	46
1015	7000	55
1020	9300	56
1022	8790	52
1034	6110	36
1036	9900	60
1037	9700	58
Mean	8553	53

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TABLE A3 ADMINISTERED DOSES FOR PHARMACOKINETIC PROFILING

	PROFILE 1		PROFILE 2		PROFILE 3	
SUBJECT	g ointment/ application	mg/kg tacrolimus	g ointment/ application	mg/kg tacrolimus	g ointment/ application	mg/kg tacrolimus
TREATMENT GROUP 1						
1001	3.60	0.062	3.19	0.055	3.20	0.055
1003	2.39	0.043	2.39	0.043	2.01	0.036
1024	3.58	0.064	3.04	0.054	2.13	0.038
1026	4.06	0.071	2.70	0.047	1.14	0.020
1027	4.99	0.073	3.72	0.055	3.67	0.054
1028	2.13	0.033	3.23	0.050	0.93	0.014
1030	6.49	0.087	5.08	0.068	1.67	0.022
1031	2.50	0.063	1.54	0.039	1.30	0.033
1032	1.27	0.020	3.08	0.049	2.74	0.043
1033	2.24	0.028	2.00*	0.025	1.70	0.021
1035	3.06	0.047	2.05	0.032	2.30	0.035
MEAN	3.30	0.054	2.91	0.047	2.07	0.034
TREATMENT GROUP 2						
1004	4.89	0.073	4.39	0.066	5.25	0.078
1005	5.62	0.100	4.45	0.079	2.18	0.039
1007	3.04	0.038	3.70	0.046	2.73	0.034
1010	4.48	0.057	5.06	0.065	1.26	0.016
1012	3.04	0.061	2.69	0.054	2.91	0.058
1013	4.11	0.052	3.02	0.038	1.82	0.023
1014	1.46	0.021	1.62	0.023	1.21	0.017
1016	2.89	0.039	3.11	0.041	3.06	0.041
1017	2.65	0.037	1.97	0.027	2.90	0.040
1018	1.67	0.022	0.70	0.009	1.05	0.014
1021	0.54	0.009	1.87	0.032	0.69	0.012
1023	2.80	0.061	2.34	0.051	2.84	0.062
MEAN	3.13	0.047	2.96	0.044	2.28	0.036
TREATMENT GROUP 3						
1006	5.30	0.073	4.57	0.063	3.44	0.047
1009	9.53	0.180	9.99	0.188	9.20	0.174
1011	3.74	0.049	4.30	0.057	2.47	0.033
1015	6.49	0.125	4.84	0.093	2.29	0.044
1020	5.66	0.091	5.11	0.082	4.46	0.072
1022	7.71	0.154	4.43	0.089	2.56	0.051
1034	5.25	0.089	4.64	0.079	2.71	0.046
1036	7.07	0.114	7.60	0.123	7.90	0.127
1037	6.34	0.083	7.92	0.104	4.80	0.063
MEAN	6.34	0.106	5.93	0.097	4.43	0.073

* value taken from that recorded in the CRF

TABLE 1 DESCRIPTIVE STATISTICS OF BLOOD CONCENTRATIONS OF TACROLIMUS (ng/mL)

TREATMENT GROUP 1

PROFILE 1 – DAY 1

	Mean	Median	n	sd	Minimum	Maximum
Time (h)						
0	<0.025	<0.025	11	-		
2	0.118	0.065	10	0.125		
4	0.129	0.029	10	0.164		
6	0.116	0.049	11	0.138		
8	0.102	0.050	11	0.121		
10	0.078	0.038	11	0.085		
12	0.078	0.038	11	0.079		

PROFILE 2 – DAY 4

	Mean	Median	n	sd	Minimum	Maximum
Time (h)						
0	0.185	0.071	11	0.248		
2	0.171	0.090	11	0.187		
4	0.183	0.134	11	0.196		
8	0.170	0.076	11	0.185		
12	0.170	0.085	11	0.192		

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PROFILE 3 – DAY 14

Time (h)	Mean	Median	n	s.d.	Minimum	Maximum
0	0.641	0.086	10	1.705		
2	0.115	0.038	11	0.121		
4	0.098	0.044	11	0.096		
8	0.113	0.043	11	0.111		
12	0.106	0.050	11	0.105		
24	0.558	0.038	11	1.576		
48	0.089	0.029	11	0.095		
72	0.064	0.025	10	0.063		
96	0.055	0.042	10	0.048		
120	0.038	<0.025	9	0.031		
144	0.035	<0.025	11	0.027		
168	0.034	0.027	10	0.024		

TABLE 1 (contd.) DESCRIPTIVE STATISTICS OF BLOOD CONCENTRATIONS OF TACROLIMUS(ng/mL)

TREATMENT GROUP 2

PROFILE 1 – DAY 1

	Mean	Median	n	sd	Minimum	Maximum
Time (h)						
0	<0.025	<0.025	12	0.008		
2	0.076	<0.025	12	0.140		
4	0.169	0.037	12	0.385		
6	0.220	0.060	12	0.373		
8	0.179	0.052	12	0.295		
10	0.125	0.048	12	0.187		
12	0.111	0.046	12	0.158		

PROFILE 2 – DAY 4

	Mean	Median	n	sd	Minimum	Maximum
Time (h)						
0	1.030	0.081	12	2.787		
2	0.262	0.099	12	0.363		
4	0.273	0.116	12	0.380		
8	0.277	0.117	12	0.401		
12	0.251	0.110	12	0.352		

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PROFILE 3 – DAY 14

Time (h)	Mean	Median	n	s.d.	Minimum	Maximum
0	0.085	0.054	11	0.098		
2	0.142	0.091	12	0.128		
4	0.123	0.076	12	0.130		
8	0.118	0.066	12	0.129		
12	0.097	0.069	12	0.094		
24	0.167	0.078	12	0.209		
48	1.360	0.075	12	4.289		
72	0.101	0.073	12	0.093		
96	0.075	0.066	12	0.065		
120	0.061	0.053	12	0.052		
144	0.057	0.055	11	0.049		
168	0.044	<0.025	12	0.046		

TABLE 1 (contd.) DESCRIPTIVE STATISTICS OF BLOOD CONCENTRATIONS OF TACROLIMUS (ng/mL)

TREATMENT GROUP 3

PROFILE 1 – DAY 1

	Mean	Median	n	sd	Minimum	Maximum
Time (h)						
0	<0.025	<0.025	9	-		
2	0.385	0.170	9	0.585		
4	0.555	0.270	9	0.881		
6	0.469	0.385	9	0.507		
8	0.464	0.327	9	0.566		
10	0.339	0.186	8	0.481		
12	0.302	0.150	9	0.456		

PROFILE 2 – DAY 4

	Mean	Median	n	sd	Minimum	Maximum
Time (h)						
0	0.854	0.605	9	0.747		
2	0.868	0.646	9	0.753		
4	0.848	0.647	9	0.816		
8	0.644	0.657	8	0.435		
12	0.794	0.700	9	0.733		

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PROFILE 3 – DAY 14

Time (h)	Mean	Median	n	s.d.	Minimum	Maximum
0	0.554	0.510	8	0.401		
2	0.446	0.423	9	0.277		
4	0.463	0.455	9	0.285		
8	0.398	0.347	9	0.250		
12	0.474	0.482	9	0.289		
24	0.400	0.377	9	0.252		
48	0.339	0.395	9	0.221		
72	0.287	0.266	9	0.225		
96	0.238	0.270	9	0.175		
120	0.166	0.153	9	0.120		
144	0.171	0.167	9	0.123		
168	0.160	0.129	9	0.137		

TABLE A5: INDIVIDUAL PHARMACOKINETIC PARAMETERS OF TACROLIMUS
TREATMENT GROUP 1

PROFILE 1

Parameter		1001	1003	1024	1026	1027	1028	1030	1031	1032	1033	1035
C_{max}	ng/mL	0	0.207	0.027	0.442	0.404	0.214	0.05	0	0.038	0.159	0
t_{max}	h	0	4	2	4	6	2	8	0	12	4	0
AUC_{0-12}	ng.h/mL	0	1.72	0.05	3.51	3.46	1.67	0.45	0	0.04	1.16	0
$t_{1/2}$	h	-	12.20	-	9.34	6.05	9.33	8.44	-	-	6.21	-
n	-	-	5	-	4	4	4	3	-	-	5	-

PROFILE 2

Parameter		1001	1003	1024	1026	1027	1028	1030	1031	1032	1033	1035
C_{max}	ng/mL	0.134	0.175	0.041	0.255	0.476	0.817	0.197	0.082	0.038	0.06	0
t_{max}	h	4	12	2	4	0	0	2	12	12	0	0
AUC_{0-12}	ng.h/mL	1.05	1.93	0.41	2.73	5.16	7.55	2.23	0.85	0.34	0.61	0

PROFILE 3

Parameter		1001	1003	1024	1026	1027	1028	1030	1031	1032	1033	1035
C_{max}	ng/mL	0.031	5.486	0	0.044	0.267	0.368	0.121	0.233	0.039	0.06	0
t_{max}	h	4	0	0	4	2	2	2	4	0	0	0
AUC_{0-12}	ng.h/mL	0.27	7.82	0	0.51	2.84	3.14	1.39	2.40	0.35	0.38	0
$t_{1/2,z}$	h	-	60.71	-	60.09	64.75	58.28	92.29	85.89	-	-	-
n	-	-	6	-	3	6	7	4	8	-	-	-

\- Not determined

TREATMENT GROUP 2

PROFILE 1

Parameter		1004	1005	1007	1010	1012	1013	1014	1016	1017	1018	1021	1023
C_{max}	ng/mL	0.31	0	0	1.362	0.095	0.854	0	0.046	0.074	0.048	0.145	0.08
t_{max}	h	4	0	0	4	2	8	0	12	6	7.5	6	2
AUC_{0-12}	ng.h/mL	2.10	0	0	9.33	0.86	5.00	0	0.05	0.61	0.31	0.74	0.39
$t_{1/2}$	h	9.58	-	-	4.31	8.83	6.50	-	-	-	-	-	17.99
n	-	5	-	-	4	4	4	-	-	-	-	-	3

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PROFILE 2

Parameter		1004	1005	1007	1010	1012	1013	1014	1016	1017	1018	1021	1023
C_{max}	ng/mL	0.322	0.033	9.812	1.203	0.132	1.014	0	0.077	0.128	0.041	0.052	0.274
t_{max}	h	8	12	0	8	4	8	0	7.5	6	5.5	12	4
AUC_{0-12}	ng.h/mL	3.37	0.12	11.71	12.87	1.52	11.05	0	0.77	1.16	0.42	0.53	2.92

PROFILE 3

Parameter		1004	1005	1007	1010	1012	1013	1014	1016	1017	1018	1021	1023
C_{max}	ng/mL	0.723	0.08	0	0.369	0.083	0.283	0.048	0.114	0.126	0	0.054	0.413
t_{max}	h	24	2	0	4	4	8	2	24	2	0	0	8
AUC_{0-12}	ng.h/mL	2.17	0.84	0	3.49	0.81	3.06	0.32	-	1.15	0	0.39	3.97
$t_{1/2,z}$	h	55.15	50.78	-	84.73	135.54	-	-	81.09	90.30	-	-	54.28
n	-	6	4	-	7	5	-	-	5	5	-	-	7

- Not determined

TREATMENT GROUP 3

PROFILE 1

Parameter		1006	1009	1011	1015	1020	1022	1034	1036	1037
C_{max}	ng/mL	2.826	0.624	0.058	0.692	0.368	0.721	0.096	0.39	0.17
t_{max}	h	4	6	12	8	6	4	4	4	2
AUC_{0-12}	ng.h/mL	20.83	4.18	0.29	3.68	2.41	6.49	0.54	3.2	1.13
$t_{1/2}$	h	12.17	-	-	-	2.49	13.95	10.95	7.13	4.98
n	-	3	-	-	-	3	3	4	3	4

PROFILE 2

Parameter		1006	1009	1011	1015	1020	1022	1034	1036	1037
C_{max}	ng/mL	2.705	0.606	1.491	1.085	1.064	0.490	0.118	0.974	0.115
t_{max}	h	4	1	2	6	0	8	8	2	4
AUC_{0-12}	ng.h/mL	30.97	6.07	17.08	9.36	10.01	5.64	1.24	10.28	1.14

PROFILE 3

Parameter		1006	1009	1011	1015	1020	1022	1034	1036	1037
C_{max}	ng/mL	0.341	0.900	0.611	0.751	0.823	0.375	0.062	0.631	1.396
t_{max}	h	4	4	6	72	4	0	2	2	0
AUC_{0-12}	ng.h/mL	3.75	10.09	6.32	6.33	7.20	4.20	0.70	6.91	2.69
$t_{1/2,z}$	h	55.80	81.57	64.23	94.82	70.98	111.93	101.79	64.27	54.34
n	-	5	5	7	8	6	8	6	7	4

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TABLE 3 DESCRIPTIVE STATISTICS OF PRE-DOSE (TROUGH) CONCENTRATIONS OF TACROLIMUS

TREATMENT GROUP 1

	Day1 12h	Day1 24h	Day4 0h	Day4 12h	Day14 0h	Day14 12h	Day14 24h
Mean	0.078	0.078	0.208	0.170	0.641	0.106	0.558
Median	0.038	0.050	0.071	0.085	0.086	0.050	0.038
n	11	11	9	11	10	11	11
sd	0.079	0.072	0.270	0.192	1.705	0.105	1.576
Minimum	—	—	—	—	—	—	—
Maximum	—	—	—	—	—	—	—

TREATMENT GROUP 2

	Day1 12h	Day1 24h	Day4 0h	Day4 12h	Day14 0h	Day14 12h	Day14 24h
Mean	0.129	0.292	1.030	0.256	0.085	0.098	0.167
Median	0.051	0.044	0.081	0.110	0.054	0.069	0.078
n	12	12	12	12	11	12	12
sd	0.184	0.435	2.787	0.350	0.098	0.094	0.209
Minimum	—	—	—	—	—	—	—
Maximum	—	—	—	—	—	—	—

TREATMENT GROUP 3

	Day1 12h	Day1 24h	Day4 0h	Day4 12h	Day14 0h	Day14 12h	Day14 24h
Mean	0.355	0.545	0.900	0.800	0.554	0.474	0.400
Median	0.218	0.250	0.748	0.711	0.510	0.482	0.377
n	9	9	8	9	8	9	9
sd	0.440	0.636	0.785	0.729	0.401	0.289	0.252
Minimum	—	—	—	—	—	—	—
Maximum	—	—	—	—	—	—	—

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Pediatric Data

TABLE A1 PATIENT DEMOGRAPHIC DATA

SUBJECT	SEX	AGE (years)*	WEIGHT (kg)*	HEIGHT (cm)*	ESTIMATED TOTAL BSA (m^2)
TREATMENT GROUP 1					
1001	F	8	26	136	0.981
1004	F	11	40	141	1.255
1006	F	10	45	143	1.344
5002	F	7	19	114	0.773
5003	M	8	27	131	0.986
6002	M	8	25	128	0.983
6004	F	11	39	145	1.251
6005	M	8	28	124	0.984
6006	F	12	26	133	0.972
6008	M	8	18	113	0.748
6011	M	10	38	141	1.221
MEAN	**5 M / 6 F**	**9**	**30**	**132**	**1.041**
TREATMENT GROUP 2					
1002	M	12	50	156	1.472
1005	F	9	40	134	1.230
5001	M	6	23	117	0.865
6001	M	9	24	123	0.903
6003	M	8	24	122	0.900
6007	M	10	39	144	1.248
6012	F	6	18	108	0.735
MEAN	**5 M / 2 F**	**9**	**31**	**129**	**1.050**
TREATMENT GROUP 3					
6009	M	13	56	168	1.612
6010	M	11	51	148	1.457
MEAN	**2 M / 0 F**	**12**	**34**	**158**	**1.535**

*weight and height at screening visit

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TABLE A2 TREATMENT AREA AND ADMINISTERED DOSES FOR PHARMACOKINETIC PROFILING

SUBJECT	Treatment Area in cm^2 (% of total BSA)	Dose (g ointment) PROFILE 1	Treatment Area in cm^2 (% of total BSA)	Dose (g ointment) PROFILE 2
TREATMENT GROUP 1				
1001	786 (43%)	1.39	786 (43%)	1.69
1004	505 (17%)	4.97	505 (17%)	0.53
1006	1112 (33%)	2.70	1112 (21%)	2.41
5002	1200 (38%)	5.72	1000 (9%)	2.42
5003	1300 (21%)	2.27	900 (12%)	2.65
6002	550 (40%)	3.77	150 (10%)	1.56
6004	600 (26%)	1.44	300 (18%)	0.93
6005	750 (30%)	1.95	350 (16%)	0.67
6006	950 (39%)	1.74	400 (23%)	0.87
6008	1400 (36%)	4.55	650 (18%)	0.20
6011	1300 (41%)	4.23	400 (13%)	4.60
MEAN	**950 (33%)**	**3.16**	**596 (19%)**	**1.68**
TREATMENT GROUP 2				
1002	2179 (64%)	2.08	2179 (64%)	2.60
1005	1580 (57%)	1.37	1580 (55%)	1.14
5001	3000 (83%)	4.68	400 (2%)	4.64
6001	1600 (53%)	3.40	500 (16%)	1.23
6003	1750 (60%)	3.86	1000 (37%)	1.16
6007	1700 (52%)	2.84	500 (15%)	0.38
6012	2750 (74%)	2.53	1200 (38%)	1.96
MEAN	**2080 (63%)**	**2.97**	**1051 (32%)**	**1.87**
TREATMENT GROUP 3				
6009	3550 (49%)	0.37	1000 (25%)	0.94
6010	4900 (72%)	4.65	1650 (37%)	4.64
MEAN	**4225 (61%)**	**2.51**	**1325 (31%)**	**2.79**

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TABLE A3 INDIVIDUAL BLOOD CONCENTRATIONS OF TACROLIMUS (ng/mL)

PROFILE 1

	TREATMENT GROUP 1										
Time (h)	1001	1004	1006	5002	5003	6002	6004	6005	6006	6008	6011
0											
2											
4											
8											
24											

	TREATMENT GROUP 2						
Time (h)	1002	1005	5001*	6001	6003	6007	6012
0							
2							
4							
8							
24							

TREATMENT GROUP 3		
Time (h)	6009	6010
0		
2		
4		
8		
24		

PROFILE 2

	TREATMENT GROUP 1										
Time (h)	1001	1004	1006	5002	5003	6002	6004	6005	6006	6008	6011
0											
2											
4											
8											
24											
96											

	TREATMENT GROUP 2						
Time (h)	1002	1005	5001	6001	6003	6007	6012
0							
2							
4							
8							
24							
96							

TREATMENT GROUP 3		
Time (h)	6009	6010
0		
2		
4		
8		
24		
96		

- No sample
( ) Values in paratheses are extrapolated values, used in PK analysis

* Sample times were 0, 1.5, 3.5, 7.5 and 24 hours

TABLE A4: INDIVIDUAL PHARMACOKINETIC PARAMETERS OF TACROLIMUS

PROFILE 1

TREATMENT GROUP 1												
Parameter		1001	1004	1006	5002	5003	6002	6004	6005	6006	6008	6011
C_{max}	ng/mL	0.401	0.000	0.000	0.636	0.058	0.734	0.111	0.043	0.196	0.332	0.109
t_{max}	h	2	0	0	4	8	8	4	2	24	4	24
AUC_{0-24}	ng.h/mL	6.80	0.00	0.00	5.14	1.09	11.10	1.58	0.69	2.76	4.75	0.87

TREATMENT GROUP 2								
Parameter		1002	1005	5001	6001	6003	6007	6012
C_{max}	ng/mL	0.517	0.026	0.570	1.513	0.874	0.215	0.640
t_{max}	h	24	4	2	8	24	24	4
AUC_{0-24}	ng.h/mL	4.14	0.08	6.71	26.54	9.71	2.95	12.48

TREATMENT GROUP 3			
Parameter		6009	6010
C_{max}	ng/mL	0.000	1.390
t_{max}	h	0	24
AUC_{0-24}	ng.h/mL	0.00	21.14

PROFILE 2

TREATMENT GROUP 1												
Parameter		1001	1004	1006	5002	5003	6002	6004	6005	6006	6008	6011
C_{max}	ng/mL	0.767	0.176	0.025	0.093	0.190	0.063	0.038	0.000	0.269	0.115	0.066
t_{max}	h	8	24	24	2	0	4	4	0	2	0	2
AUC_{0-24}	ng.h/mL	11.90	3.73	0.20	1.91	4.28	1.41	0.49	0.00	5.89	2.21	1.13

TREATMENT GROUP 2								
Parameter		1002	1005	5001	6001	6003	6007	6012
C_{max}	ng/mL	0.593	0.064	0.117	0.185	0.224	0.054	0.219
t_{max}	h	4	8	24	4	0	2	4
AUC_{0-24}	ng.h/mL	11.40	1.37	2.09	4.11	4.29	0.69	4.38

TREATMENT GROUP 3			
Parameter		6009	6010
C_{max}	ng/mL	0.059	0.597
t_{max}	h	0	2
AUC_{0-24}	ng.h/mL	0.93	8.42

- Not determined

APPEARS THIS WAY
ON ORIGINAL

TABLE A5 PRE-DOSE (TROUGH) CONCENTRATIONS OF TACROLIMUS

TREATMENT GROUP 1

	Day1 24h	Day4 0h	Day14 0h	Day15 0h
1001				
1004				
1006				
5002				
5003				
6002				
6004				
6005				
6006				
6008				
6011				

APPEARS THIS WAY ON ORIGINAL

TREATMENT GROUP 2

	Day1 24h	Day4 0h	Day14 0h	Day15 0h
1002				
1005				
5001				
6001				
6003				
6007				
6012				

TREATMENT GROUP 3

	Day1 24h	Day4 0h	Day14 0h	Day15 0h
6009				
6010				

- No sample

TABLE A6 CALCULATED TRUNCATED AREA UNDER THE CONCENTRATION-TIME CURVE TO 12 HOURS ASSUMING LINEAR RELATIONSHIP FROM 8 TO 12 HOURS

TREATMENT GROUP 1		
	PROFILE 1	PROFILE 2
1001	3.85	7.85
1004	0.00	1.78
1006	0.00	0.00
5002	3.64	1.03
5003	0.54	2.18
6002	5.35	0.69
6004	0.88	0.32
6005	0.34	0.00
6006	0.89	3.01
6008	2.78	1.06
6011	0.07	0.60
TREATMENT GROUP 2		
	PROFILE 1	PROFILE 2
1002	0.28	6.26
1005	0.08	0.72
5001	4.37	0.90
6001	10.51	2.10
6003	2.21	2.37
6007	0.85	0.52
6012	5.98	2.33
TREATMENT GROUP 3		
	PROFILE 1	PROFILE 2
6009	0.00	0.46
6010	6.65	4.53

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 50-777

ADMINISTRATIVE DOCUMENTS

Electronic Mail Message

Date: 11/10/00 9:18:00 AM
From: Jerry Phillips (PHILLIPSJ)
To: Mildred Wright (WRIGHTM)
Cc: Sammie Beam (BEAMS)
Cc: Martin Himmel (HIMMELM)
Subject: Protopic (tacrolimus) Ointment; NDA 50-777

Millie:

OPDRA is in receipt of your 10/31/00 consult for a re-review of the proposed proprietary name of Protopic, which OPDRA found previously acceptable.

OPDRA has no objections to the approval of the proprietary name of Protopic for NDA 50-777.

If you have any questions please feel free to call Sammie Beam.

Jerry Phillips

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: February 13, 2000	**DUE DATE:** June 1, 2000	**OPDRA CONSULT #:** 00-0073

TO: Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Millie Wright, Project Manager
HFD-540

APPEARS THIS WAY
ON ORIGINAL

PRODUCT NAME: Protopic Ointment (tacrolimus ointment, 0.03% and 0.1%) **NDA #:** 50-777	**MANUFACTURER:** Fujisawa Healthcare, Inc. Deerfield, IL 60015-2548

SAFETY EVALUATOR: Carol Pamer, R.Ph.

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products (HFD-540), OPDRA conducted a review of the proposed proprietary name "Protopic" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA has no objections to the use of the name "Protopic". See the checked box below.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☑ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

N.S. No objections at this time.

/S/ 6/1/2000
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 6/1/00
Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 20, 2000

NDA NUMBER: 50-777

NAME OF DRUG: Protopic (tacrolimus ointment, 0.03% and 0.1%)

NDA HOLDER: Fujisawa Healthcare, Inc.
Deerfield, IL 60015-2548

I. INTRODUCTION

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540) for assessment of the proprietary name Protopic.

Protopic™ is an ointment containing tacrolimus, a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Protopic is supplied in two strengths: 0.03% and 0.1%. This product is indicated for the short-term and long-term treatment of the signs and symptoms of atopic dermatitis in adults and pediatric patients 2 years of age or older. The usual dosage is twice daily topical application of a thin layer to the affected areas of skin.

Tacrolimus is also available in oral and intravenous formulations, (Prograf™ Fujisawa), that is indicated for the prophylaxis of organ rejection in patients receiving allogenic liver or kidney transplants.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Protopic to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of

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[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).
[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.
[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.
[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three (3) prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

A group discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Protopic. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Three (3) product names were identified that were noted to have some look-alike or sound-alike properties, relative to Protopic. These products are *Protropin* (somatrem), *Protopam* (pralidoxime), and *Protostat* (metronidazole). The dosage forms and usual dosage of these products are as follows:

Product Name	Dosage form(s), Generic name	Usual adult dose*
Protopic	Ointment 0.03%, 0.1%; tacrolimus	Apply topically twice a day
Protropin	Injection, lyophilized powder, 5mg & 10mg per vial; somatrem	Subcutaneously 0.3mg per kg per week, divided into daily doses.
Protopam Chloride	Injection, lyophilized powder, 1 g per vial; pralidoxime (antidote)	Intravenously, 1-2 g, with dose repeated as needed to treat organophosphate toxicity
Protostat	Tablets, 250mg & 500mg; metronidazole	Orally, 250-750mg three times a day for 5-10 days.
		*Frequently used, not all-inclusive.

With consideration given to the differences in dosage forms, usual dosage regimen, and routes of administration, confusion of any of these products with Protopic seems unlikely.

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A study was conducted within FDA employing a total of 92 health care professionals (nurses, pharmacists, physicians) to determine the degree of confusion of Protopic with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote inpatient orders and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Protopic (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Outpatient: Protopic 0.1%, #1, sig: bid. No refills	*Outpatient*: Protopic 0.1%. Apply twice a day. Dispense one, no refills.
Inpatient: Protopic 0.1% bid	

2. Results

Results of this exercise are summarized below:

Study	No. of participants	# of responses (%)	"Protopic" response	Other response
Written: Outpatient	31	18 (58%)	17 (94%)	1 (6%)
Inpatient	31	20 (65%)	2 (10%)	18 (90%)
Verbal: Outpatient	30	17 (57%)	11 (65%)	6 (35%)
Total	92	55 (60%)	30 (55%)	25 (45%)

Among participants in the two written prescription studies, 50% of the respondents provided the correct spelling of the drug name. The other responses were generally phonetic variations of the name "Protopic".

Among the verbal prescription study participants, the majority of the respondents (65%) interpreted the name correctly. The other name interpretations were generally phonetic variations of "Protopic".

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Protopic", three product names were identified that had look-alike, sound-alike properties with respect to Protopic. These products were Protropin, Protopam, and Protostat. However, with consideration given to the differences in dosage forms, usual dosage regimen, and routes of administration, confusion of any of these products with Protopic seems unlikely.

We conducted prescription studies in an attempt to simulate the prescription ordering process. In this exercise, there were no erroneous interpretations of this proprietary name with other U.S. marketed drug products.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS

From a safety perspective, OPDRA has no objections to the use of the proprietary name "Protopic". OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

/S/

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

APPEARS THIS WAY
ON ORIGINAL

Concur:

/S/ 6/1/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 50-777
HFD-540; Division Files/Millie Wright, Project Manager
HFD-540; Jonathan Wilkin, Division Director
HFD-040; Mark Askine, Senior Regulatory Review Officer, DDMAC
HFD-430; Marilyn Pitts, Safety Evaluator, OPDRA
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Peter Honig, Director, OPDRA (electronic copy)
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (electronic copy)

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APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Fujisawa Healthcare, Inc.
3 Parkway North Center
Deerfield, IL 60015-2548

2. TELEPHONE NUMBER *(Include Area Code)*

(847) 317-8872

3. PRODUCT NAME

PROTOPIC (tacrolimus ointment)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

3794

6. LICENSE NUMBER / NDA NUMBER

NDA 50-777

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

[ ] THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

[ ] WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

[ ] A CRUDE ALLERGENIC EXTRACT PRODUCT

[ ] AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

[ ] AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

[ ] BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Dana C. Baker	Senior Director, Regulatory Affairs	9/8/99

FORM FDA 3397 (5/98)

Created by Electronic Document Services/USDHHS: (301) 443-3454 EF

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

Donald E. Baker, J.D.
Senior Director
Regulatory Affairs

September 8, 1999

Food and Drug Administration
P. O. Box 360909
Pittsburgh, PA 15251-6909

RE: NDA 50-777
Application Fee for:
PROTOPIC® (tacrolimus ointment)
Ointment 0.03%
Ointment 0.1%
User Fee Identification Number: 3794

Dear Sir:

Fujisawa Healthcare, Inc. (FHI) intends to submit to the FDA's Division of Dermatologic and Dental Drug Products on or about September 8, 1999 an original New Drug Application (NDA 50-777) with clinical data, for PROTOPIC® (tacrolimus) ointment, 0.03% and 0.1% concentrations for the treatment of atopic dermatitis.

Enclosed please find check number ——— in the amount of Two Hundred Seventy Two Thousand Two Hundred Eighty Two Dollars ($272,282.00), as payment in full for the assessed FY 1999 application fee.

Should you have any questions regarding this payment, please do not hesitate to contact me at (847) 317-8872.

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

cc: Ms. Beverly Friedman

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APPEARS THIS WAY
ON ORIGINAL

TACROLIMUS-PATENT CERTIFICATION

US Patent 4,894,366 covers the method of treatment and prevention of resistance by transplantation, graft-versus-host disease by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like by administering these compounds.

US Patent 4,929,611 covers the method of using FK506 to treat autoimmune disease by external administration.

US Patent 5,110,811 covers the method of inhibiting IL-2 production by the external application of FK506.

US Patent 5,260,301 covers the pharmaceutical solution containing FK506.

US Patent 5,385,907 covers the ointment formulation of FK506.

US Patent 5,366,971 covers the method of using the FK506 compound in the topical treatment of inflammatory and hyperpoliferative skin diseases or cutaneous manifestations of immunologically-induced illnesses, including psoriasis. Fujisawa Pharmaceutical Co., Ltd. of Osaka, Japan has been granted a license for this patent by Sandoz Pharma Ltd. pursuant to a license agreement with Sandoz Pharma Ltd. dated January 1, 1995.

US Patent 5,665,727 covers the method of using the FK506 compound in the topical treatment of inflammatory and hyperpoliferative skin diseases or cutaneous manifestations of immunologically-induced illnesses, including atopic dermatitis. Fujisawa Pharmaceutical Co., Ltd. of Osaka, Japan has been granted a license for this patent by Sandoz Pharma Ltd. pursuant to a license agreement with Sandoz Pharma Ltd. dated January 1, 1995.

Fujisawa Healthcare, Inc., the applicant for this NDA #50-777, is a wholly-owned subsidiary of Fujisawa Pharmaceutical Co., Ltd. of Osaka, Japan.

Mark J. Wanda
Senior Corporate Attorney

9/3/99
Date

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ON ORIGINAL

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United States Patent [19]

Okuhara et al.

[11] **Patent Number: 4,894,366**

[45] **Date of Patent: Jan. 16, 1990**

[54] **TRICYCLO COMPOUNDS, A PROCESS FOR THEIR PRODUCTION AND A PHARMACEUTICAL COMPOSITION CONTAINING THE SAME**

[75] Inventors: Masakuni Okuhara; Hirokazu Tanaka; Toshio Goto, all of Ibaraki; Tokru Kino, Tsuchiura; Hiroshi Hatanaka, Ibaraki, all of Japan

[73] Assignee: Fujisawa Pharmaceutical Company, Ltd., Osaka, Japan

[21] Appl. No.: 799,855

[22] Filed: Nov. 20, 1985

[30] **Foreign Application Priority Data**

Dec. 3, 1984 [GB] United Kingdom 8430455
Feb. 5, 1985 [GB] United Kingdom 8502869
Apr. 1, 1985 [GB] United Kingdom 8508420

[51] Int. Cl.[4] A61K 31/395; A61K 31/695; C07D 498/16; C07F 7/04

[52] U.S. Cl. 514/63; 514/291; 514/411; 540/452; 540/456; 435/898; 435/886; 435/118

[58] Field of Search 540/452, 456; 514/63, 514/291, 411; 435/598, 886, 118

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,244,592 4/1966 Arai 424/115
4,212,881 7/1980 Sasaki et al. 540/456

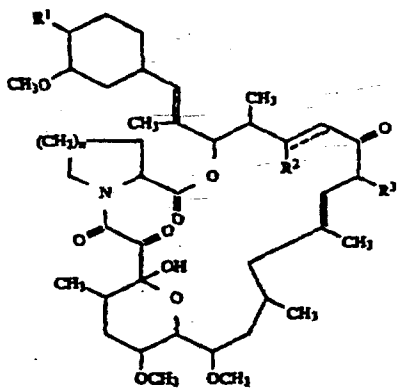
OTHER PUBLICATIONS

J. A. Findlay: Canadian Journal of Chemistry, vol. 58 (1980), pp. 579–590.
Arai et al., Journal of Antibiotics, vol. 15, (1962), pp. 231–232.
Korzybski, "Antibiotics-Origin, Nature and Properties", vol. II, 1978.
Chemical Abstracts, vol. 90, No. 3, 1979, p. 635, Abstract No. 22856u.
Chemical Abstracts, vol. 97, No. 21, 1982, p. 793, Col. 1, Abstract No. 182063f.

Primary Examiner—Robert T. Bond
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] **ABSTRACT**

This invention relates to tricyclo compounds useful for treatment and prevention of resistance by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like, which can be represented by the following formula:



(I)

to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

12 Claims, 10 Drawing Sheets

APPEARS THIS WAY
ON ORIGINAL

United States Patent [19]

Okuhara et al.

[11] **Patent Number: 4,929,611**

[45] **Date of Patent: May 29, 1990**

[54] **METHOD FOR IMMUNOSUPPRESSION**

[75] Inventors: Masakuni Okuhara; Hirokazu Tanaka; Toshio Goto, all of Ibaraki; Tohru Kino, Tsuchiura; Hiroshi Hatanaka, Ibaraki, all of Japan

[73] Assignee: Fujisawa Pharmaceutical Company, Ltd., Osaka, Japan

[21] Appl. No.: 868,749

[22] Filed: May 30, 1986

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 799,855, Nov. 24, 1985, Pat. No. 4,894,366.

[30] **Foreign Application Priority Data**

Dec. 3, 1984 [GB] United Kingdom 8430455
Feb. 5, 1985 [GB] United Kingdom 8502869
Apr. 1, 1985 [GB] United Kingdom 8508420

[51] Int. Cl.[5] A61K 31/395

[52] U.S. Cl. 514/183; 514/63; 514/291; 514/411; 540/452; 540/456

[58] Field of Search 540/452, 456; 514/63, 514/291, 411, 183

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,244,592 4/1966 Arai 514/183

OTHER PUBLICATIONS

J. A. Findlay: Canadian Journal of Chemistry, vol. 58 (1980), pp. 579–590.

Arai et al., Journal of Antibiotics, vol. 15, (1962), pp. 231–232.

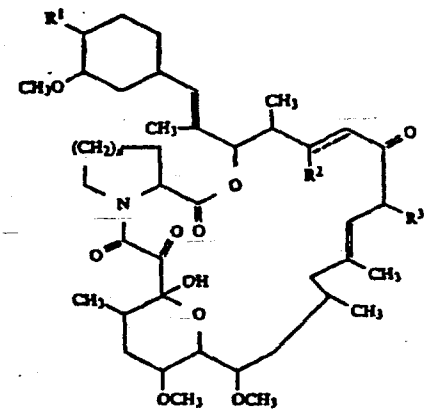
Korzybski, "Antibiotics–Origin Nature and Properties", vol. II, 1978.

Primary Examiner—Robert T. Bond

Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] **ABSTRACT**

This invention relates to tricyclo compounds useful for treatment and prevention of resistance by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like, which can be represented by the following formula:



(I)

to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

5 Claims, No Drawings

APPEARS THIS WAY
ON ORIGINAL

US005110811A

United States Patent [19]

Okuhara et al.

[11] Patent Number: 5,110,811

[45] Date of Patent: * May 5, 1992

[54] TRICYCLO COMPOUNDS, A PROCESS FOR THEIR PRODUCTION AND A PHARMACEUTICAL COMPOSITION CONTAINING THE SAME

[75] Inventors: Masakuni Okuhara; Hirokazu Tanaka; Toshio Goto, all of Sakuramura; Tohru Kino, Tsuchiura; Hiroshi Hatanaka, Sakuramura, all of Japan

[73] Assignee: Fujisawa Pharmaceutical Company, Ltd., Osaka, Japan

[*] Notice: The portion of the term of this patent subsequent to May 29, 2007 has been disclaimed.

[21] Appl. No.: 491,205

[22] Filed: Mar. 9, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 868,749, May 30, 1986, Pat. No. 4,929,611, which is a continuation-in-part of Ser. No. 799,855, Nov. 20, 1985, Pat. No. 4,894,366.

[30] Foreign Application Priority Data

Dec. 3, 1984 [GB] United Kingdom 8430455
Feb. 5, 1985 [GB] United Kingdom 8502869
Apr. 1, 1985 [GB] United Kingdom 8508420

[51] Int. Cl.[5] A61K 31/395
[52] U.S. Cl. 514/183; 514/63; 514/291; 514/411
[58] Field of Search 514/183, 63, 291, 411

[56] References Cited

U.S. PATENT DOCUMENTS

4,929,611 5/1990 Okuhara et al. 514/183

FOREIGN PATENT DOCUMENTS

0315978 5/1989 European Pat. Off. 514/291

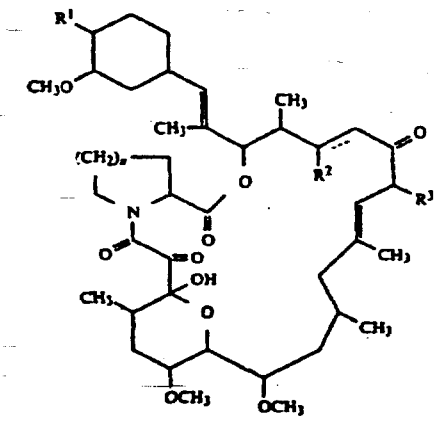
OTHER PUBLICATIONS

Baker et al., "British Journal of Dermatology" (1984), vol. 110, pp. 555-564.
Valdimareson et al., "Immunology Today", vol. 7, No. 9, 1986, pp. 256-259.
Biren et al., "Arch. Dermatol.", vol. 122, Sep. 1986, pp. 1028-1032.
J. A. Findlay: Canadian Journal of Chemistry, vol. 58 (1980), pp. 579-590.

Primary Examiner—Robert T. Bond
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

This invention relates to tricyclo compounds useful for treatment and prevention of resistance by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like, which can be represented by the following formula:



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to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

6 Claims, 10 Drawing Sheets

APPEARS THIS WAY ON ORIGINAL

US005260301A

United States Patent [19]

Nakanishi et al.

[11] Patent Number: 5,260,301

[45] Date of Patent: Nov. 9, 1993

[54] PHARMACEUTICAL SOLUTION CONTAINING FK-506

[75] Inventors: Shigeo Nakanishi, Neyagawa; Iwao Yamanaka, Osaka, both of Japan

[73] Assignee: Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan

[21] Appl. No.: 984,239

[22] Filed: Dec. 1, 1992

Related U.S. Application Data

[63] Continuation of Ser. No. 662,443, Feb. 28, 1991, abandoned.

[30] Foreign Application Priority Data

Mar. 1, 1990 [JP] Japan 2-51110

[51] Int. Cl.[5] A61K 31/44; A61K 47/00

[52] U.S. Cl. 514/291; 514/294; 514/786; 514/789; 514/943; 514/970; 514/975

[58] Field of Search 514/291, 294, 786, 789; 424/554, 555

[56] References Cited

U.S. PATENT DOCUMENTS

3,997,590	12/1976	Lester	260/470
4,082,780	4/1978	Miki et al.	514/182
4,894,366	1/1990	Okuhara et al.	514/63
5,023,262	6/1991	Caufield et al.	514/291
5,064,835	11/1991	Bochis et al.	514/21

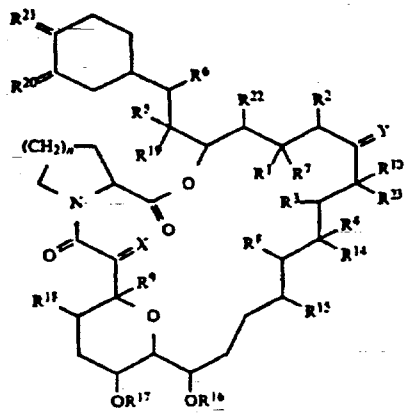
FOREIGN PATENT DOCUMENTS

0323042	7/1989	European Pat. Off. .
61-148181	4/1986	Japan .

Primary Examiner—Frederick E. Waddell
Assistant Examiner—T. J. Criares
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

A pharmaceutical solution which contains the compound of the general formula having the immusuppresive activity is disclosed.



8 Claims, No Drawings

APPEARS THIS WAY ON ORIGINAL

US005385907A

United States Patent [19]

Asakura et al.

[11] Patent Number: 5,385,907

[45] Date of Patent: Jan. 31, 1995

[54] OINTMENTS CONTAINING FK-506 OR DERIVATIVES THEREOF

[75] Inventors: Sotoo Asakura, Kyoto; Yoshio Murakami, Kobe; Nobuto Kanagawa, Takaoka; Toshiomi Nakate, Kobe, all of Japan

[73] Assignee: Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan

[21] Appl. No.: 62,330

[22] Filed: May 17, 1993

Related U.S. Application Data

[63] Continuation of Ser. No. 750,942, Aug. 28, 1991, abandoned.

[30] Foreign Application Priority Data

Sep. 4, 1990 [JP] Japan 2-235177

[51] Int. Cl.[6] A61K 31/445; A61K 31/40

[52] U.S. Cl. 514/291; 514/214; 514/411; 514/947; 514/969

[58] Field of Search 514/214, 291, 411, 947, 514/969

[56] References Cited

U.S. PATENT DOCUMENTS

5,061,700 10/1991 Dow et al. 514/169

FOREIGN PATENT DOCUMENTS

315978 5/1989 European Pat. Off. .
423714 4/1991 European Pat. Off. .

OTHER PUBLICATIONS

Chemical Abstracts 111:89968c (1989).
Chemical Abstracts 112:91786f (1990).

Primary Examiner—Marianne M. Cintins
Assistant Examiner—William R. A. Jarvis
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

An ointment comprising a tricyclic compound such as FK 506 substance which is 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone, or the like, a solubilizing and/or absorption-promoting agent and an ointment base, which is useful for treating various skin diseases.

24 Claims, No Drawings

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United States Patent *5,366,971*
Grassberger, et al. **November 22, 1994**

Use of 11,28-dioxa-4-azatricyclo[22.3.1.0.sup.4,9]octacos-18-ene derivatives and pharmaceutical compositions containing them

Abstract

New use of 11,28-dioxa-4-azatricyclo[22.3.1.0.sup.4,9]octacos-18-ene derivatives and pharmaceutical compositions containing them The compounds of formula I, ##STF 1## have been found to have excellent topical activity. They are thus indicated for use in the topical treatment of inflammatory and hyperpoliferative skin diseases and of cutaneous manifestations of immunologically-induced illnesses, such as psoriasis.

Inventors: **Grassberger; Maximilian** (Vienna, AT); **Meingassner; Josef G.** (Perchtoldsdorf, AT); **Stutz; Anton** (Vienna, AT); **Stutz; Peter** (Vienna, AT)
Assignee: **Sandoz Ltd.** (Basel, CH)
Appl. No.: **982925**
Filed: **November 30, 1992**

U.S. Class: 514/291; 514/411
Intern'l Class: A61K 031/44; A61K 031/40
Field of Search: 514/291,411

References Cited [Referenced By]

U.S. Patent Documents

4139563	Feb., 1979	Metcalf et al.	260/583.

Foreign Patent Documents

0090378	Oct., 1983	EP.
0127426	Dec., 1984	EP.
0147476	Jul., 1985	EP.
0240773	Apr., 1986	EP.
0184162	Jun., 1986	EP.
WO8607359	Dec., 1986	WO.

Other References

Chem. Abstract, vol. 93, 1981, 197620t.
Chem. Abstract, vol. 94, 1981, 150,334s.
Chem. Abstract, vol. 78, 1973, 92678p.
Chem. Abstract, vol. 86, 1977, 37594y.
Chem. Abstract, vol. 78, 1973, 69958w.
Chem. Abstract, vol. 70, 1969, 113403x.
Chem. Abstract, vol. 84, 1976, 130015d.
Chem. Abstract, vol. 71, 1969, 59514g.

APPEARS THIS WAY
ON ORIGINAL

United States Patent [19]

Grassberger et al.

[11] Patent Number: 5,665,727

[45] Date of Patent: Sep. 9, 1997

[54] USE OF 11,28-DIOXA-4-AZATRICYCLO [22.3.1.0^{4,7}]OCTACOS-18-ENE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

[75] Inventors: Maximilian Grassberger, Vienna; Josef Gottfried Meingassner, Perchtoldsdorf; Anton Stütz; Peter Stütz, both of Vienna, all of Austria

[73] Assignee: Sandoz Ltd., Basel, Switzerland

[21] Appl. No.: 291,010

[22] Filed: Aug. 15, 1994

Related U.S. Application Data

[62] Division of Ser. No. 982,925, Nov. 30, 1992, Pat. No. 5,366,971, which is a continuation of Ser. No. 604,430, Nov. 2, 1990, abandoned, which is a continuation of Ser. No. 268,114, Nov. 7, 1988, abandoned.

[30] Foreign Application Priority Data

Nov. 9, 1987 [AT] Austria 2952/87
Dec. 17, 1987 [DE] Germany 37 42 805.5

[51] Int. Cl.^{6} A61K 31/44; A61K 31/40

[52] U.S. Cl. 514/291; 514/411

[58] Field of Search 514/291, 411

[56] References Cited

U.S. PATENT DOCUMENTS

4,139,563 2/1979 Metcalf et al. ..... 260/583 H

FOREIGN PATENT DOCUMENTS

0090378 10/1983 European Pat. Off. .
0127425 12/1984 European Pat. Off. .
0147476 7/1985 European Pat. Off. .
0240773 4/1986 European Pat. Off. .
0184162 6/1986 European Pat. Off. .
184162 6/1986 European Pat. Off. 514/291
WO8607359 12/1986 WIPO .

OTHER PUBLICATIONS

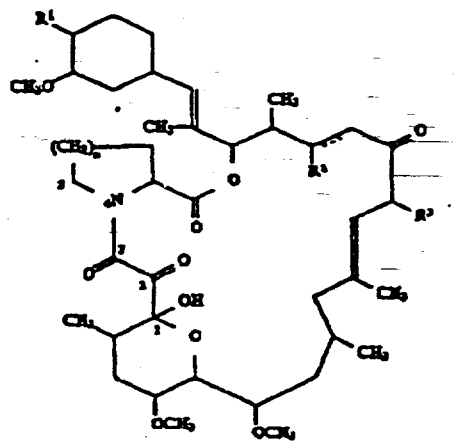
Chem. Abstract, vol. 93, 1981, 197620t.
Chem. Abstract, vol. 94, 1981, 150,334s.
Chem. Abstract, vol. 78, 1973, 92678p.
Chem. Abstract, vol. 86, 1977, 37594y.
Chem. Abstract, vol. 78, 1973, 69958w.
Chem. Abstract, vol. 70, 1969, 113403x.
Chem. Abstract, vol. 84, 1976, 130015d.
Chem. Abstract, vol. 71, 1969, 59514q.
Script No. 1717 (May 13, 1987).
Arch. Derm. 123, 165–166 (1987).
J. Invest. Derm. 88 52–54 (1987).
Transplan. 44, 83–87 (1987).
The Lancet, Apr. 4, 1987—p. 806.
Surgical. Forum. vol. 37, 1986, pp. 603–604.
J. Am. Acad. Dermatol 14:785–791 (1986).
Clin. Exp. Immunol. 66, 582–589 (1986).
Clinical Research, vol. 34, No. 4, 1986—p. 1007A.
The Lancet, Oct. 4, 1986—pp. 803–804.
Lancet 1986/II, pp. 971–972.
The Lancet, Jan. 19, 1985—p. 160.
Clin. Exp. Immunol. 59, 23–28 (1985).
New Engl. J. Med. 301, 555 (1979).
Clin. Exp. Immunol. 45, 173–177 (1981).
Transplan. Proc. vol. XV, No. 4, Suppl. 1 (1983) pp. 3084–3085 and 3091.
Arch. Derm. 122, 1028–1032 (1986).
Clin. Exp. Immunol. (1985) 59, 23–28.
J. Org. Chem. 1985, 50, 2582–2583.
Chemical Abstracts, vol. 104, 1986.
J. Invest. Derm. 82, 419 (1984).
Clin. Res. 1986, 34, 1007A.
The Lancet, vol. 339, May 2, 1992, p. 1120.
Transplan. Proc. vol. XIX, No. 5, 1987: pp. 79–83, Suppl. 8.
Transplan. Proc. (1987), vol. XIX, No. 5, Supply. 6, pp. 40–44.
The Journal of Antibiotics, vol. XL, No. 9—pp. 1249–1255, Sep. 1987.
The Journal of Antibiotics, vol. XL, No. 9 (1987), Index, pp. 1256–126.
J. Am. Chem. Soc. 1987, 109, 5031–5033.
Chemical Abstracts—vol. 107, No. 3, 1987, 17437y.
Transplan. Proc. vol. XIX, No. 5, Supply 6, (1987) pp. 84–86.
Dermatology in General Medicine, 3rd Edition, 1987.
Arch. Dermatol Res (1983) 275: 181–189.
J. Allergy Clin. Immol. vol. 71, No. 1, Part 1, pp. 47–56.
Contact Dermatitis vol. 19, pp. 129–132 (1988).

Div.

Primary Examiner—Jerome D. Goldberg
Attorney, Agent, or Firm—Robert S. Honor; Melvyn M. Kassenoff; Thomas O. McGovern

[57] ABSTRACT

The compounds of formula I,



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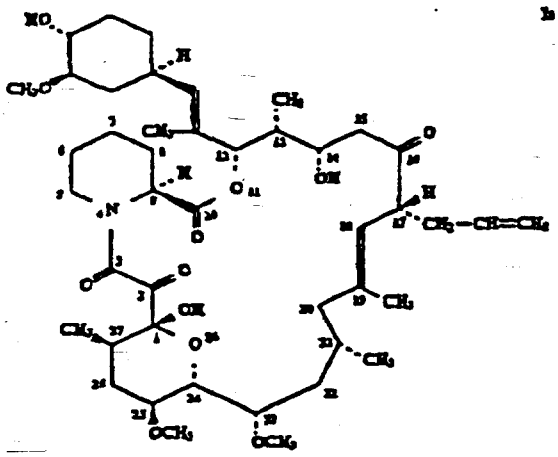
have been found to have excellent topical activity. They are thus indicated for use in the topical treatment of inflammatory and hyperpoliferative skin diseases and of cutaneous manifestations of immunologically-induced illnesses, such as psoriasis.

18 Claims, No Drawings

1249–1255 and T. Taga et al., *Acta Cryst.* C43 (1987) 751–753, and appears to be as follows:



By implication, since in EP 184 162 the preparation of compounds B, C, D and E is effected starting from FK 506 and using reaction steps which do not modify the configuration, compounds B, C, D and E also have a configuration corresponding to that shown above for compound A.

An aspect of the invention is thus the use of the compounds of formula I in free form or in pharmaceutically acceptable salt form in the topical treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated illnesses, such as: psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, *Lichen planus*, Pemphigus, *bullous Pemphigoid*, *Epidermolysis bullosa*, *urticaria*, *angioedemas*, *vasculitides*, *erythemas*, *cutaneous eosinophilias*, *Lupus erythematosus* and *Alopecia areata*.

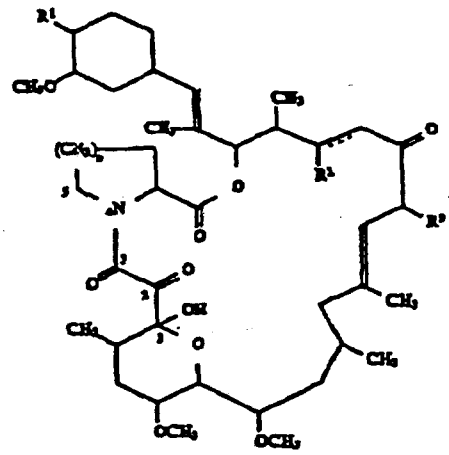
Preferred are the compounds of formula I wherein R^1, R^2 and n are as defined above for formula I, R^3 is propyl or allyl and the symbol of a line and dotted line is a single bond in particular, the compound wherein R^1 and R^2 are hydroxy, R^3 is allyl, n is 2, and the symbol of a line and dotted line is a single bond; especially preferred is compound A.

For the above use the dosage to be administered is of course dependent on the compound to be administered, the mode of administration and the type of treatment. Satisfactory results are obtained in larger mammals with local administration of a 1–3% concentration of active substance several times daily, e.g. 2 to 5 times daily. Examples of indicated galenical forms are lotions, gels and creams.

A further aspect of the invention is a pharmaceutical composition for the above topical uses, containing a compound of formula I in free form or in pharmaceutically acceptable salt form, together with a pharmaceutically acceptable carrier or diluent.

We claim:

1. A method of topically treating inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically-mediated illnesses, in a mammal in need of said treatment, which comprises administering topically to said mammal in an amount effective for the treatment of inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically mediated illnesses a compound of formula I



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wherein

R^1 is optionally protected hydroxy,

R^2 is hydrogen or optionally protected hydroxy,

R^3 is methyl, ethyl, propyl or allyl,

n is 1 or 2 and

the symbol of a line and dotted line is a single bond or a double bond,

in free form or in pharmaceutically acceptable salt form.

2. A method according to claim 1, wherein

R^3 is propyl or allyl,

in free form or in pharmaceutically acceptable salt form.

3. A method according to claim 1,

wherein R^1 and R^2 are hydroxy,

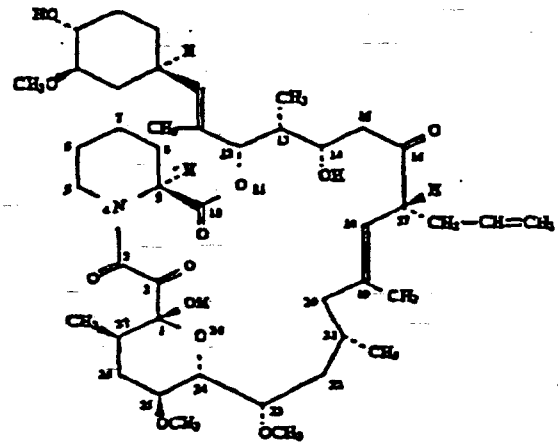
R^3 is allyl,

n is 2, and

the symbol of a line and dotted line is a single bond,

in free form.

4. A method according to claim 1 in which the compound is

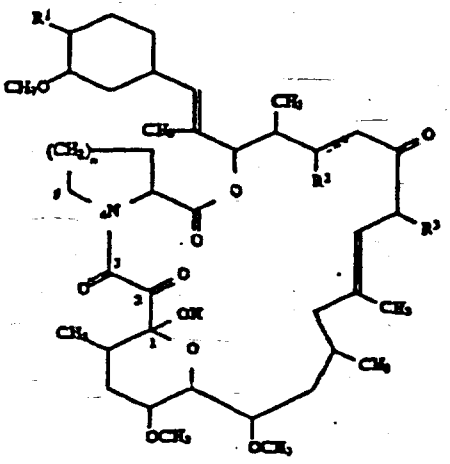


in free form.

5. A method according to claim 1 in which the compound is administered 2 to 5 times daily in the form of a lotion, gel or cream comprising 1 to 3% of the compound.

6. A method of topically treating atopical dermatitis, contact dermatitis, eczematous dermatitises, seborrhoeic dermatitis, *Lichen planus*, *Pemphigus*, *bullous* Pemphigoid,

Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, or *Alopecia areata* in a mammal in need of said treatment, which comprises administering topically to said mammal in an amount effective for the treatment of atopical dermatitis, contact dermatitis, eczematous dermatitises, seborrhoeic dermatitis, *Lichen planus, Pemphigus, bullous* Pemphigoid, *Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias,* or *Alopecia areata* a compound of formula I



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wherein

R^1 is optionally protected hydroxy,

R^2 is hydrogen or optionally protected hydroxy,

R^3 is methyl ethyl, propyl or allyl,

n is 1 or 2 and

the symbol of a line and dotted line is a single bond or a double bond,

in free form or in pharmaceutically acceptable salt form.

7. A method according to claim 6, wherein

R^3 is propyl or allyl,

in free form or in pharmaceutically acceptable salt form.

8. A method according to claim 6,

wherein

R^1 and R^2 are hydroxy,

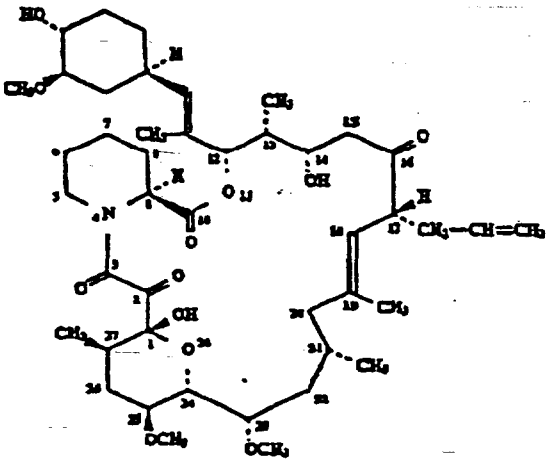
R^3 is allyl,

n is 2, and

the symbol of a line and dotted line is a single bond,

in free form.

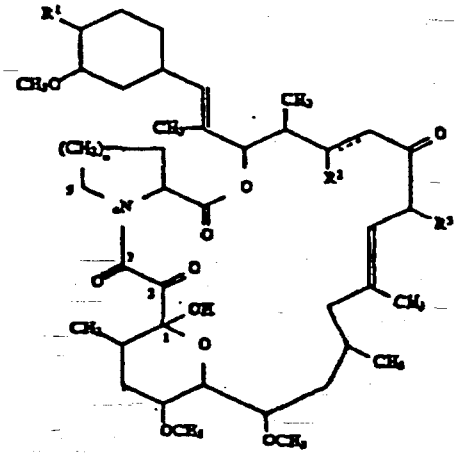
9. A method according to claim 6 in which the compound is



in free form.

10. A method according to claim 6 in which the compound is administered 2 to 3 times daily in the form of a lotion, gel, or cream comprising 1 to 3% of the compound.

11. A method of topically treating atopical dermatitis, contact dermatitis, eczematous dermatitises, or seborrhoeic dermatitis in a mammal in need of said treatment, which comprises administering topically to said mammal in an amount effective for the treatment of atopical dermatitis, contact dermatitis, eczematous dermatitises, or seborrhoeic dermatitis a compound of formula I



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wherein

R^1 is optionally protected hydroxy,

R^2 is hydrogen or optionally protected hydroxy,

R^3 is methyl, ethyl, propyl or allyl,

n is 1 or 2 and

the symbol of a line and dotted line is a single bond or a double bond,

in free form or in pharmaceutically acceptable salt form.

12. A method according to claim 11, wherein

R^3 is propyl or allyl

in free form or in pharmaceutically acceptable salt form.

13. A method according to claim 11,

wherein

R^1 and R^2 are hydroxy,

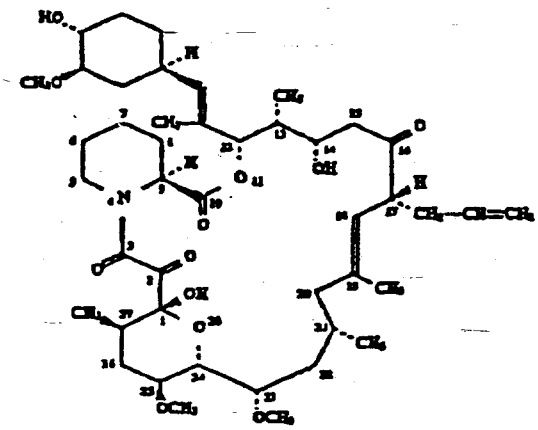
R^3 is allyl,

n is 2, and

the symbol of a line and dotted line is a single bond,

in free form.

14. A method according to claim 11 in which the compound Ir



in free form.

15. A method according to claim 11 in which the compound is administered 2 to 5 times daily in the form of a lotion, gel, or cream comprising 1 to 3% of the compound.

16. A method according to claim 11 of topically treating atopical dermatitis.

17. A method according to claim 11 of topically treating contact dermatitis or eczematous dermatitises.

18. A method according to claim 11 of topically treating seborrhoeic dermatitis.

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Debarment Certification

Fujisawa Healthcare, Inc., certifies that in support of this New Drug Application, the company did not and will not use in any capacity the services of any person or firm debarred under sections 306 (a) or (b).

By: Jerry D. Johnson Date: 27 August '99

Jerry D. Johnson, Ph.D.
Vice President
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 50-777 SUPPL # _____

Trade Name Protopic Ointment, 0.03 & 0.1% Generic Name tacrolimus

Applicant Name Fujisawa Healthcare, Inc. HFD-540

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/X/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /X/

      If yes, what type(SE1, SE2, etc.)? N/A

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /X/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #50-708 **Prograf (tacrolimus) Capsules,1mg & 5mg**

NDA #50-709 **Prograf (tacrolimus) IV, 5mg/1mL**

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/ **N/A**

APPEARS THIS WAY
ON ORIGINAL

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

APPEARS THIS WAY
ON ORIGINAL

2. A clinical investigation is "essential to the approval" if the

Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/ N/A

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #97-0-035

Investigation #2, Study #97-0-036

Investigation #3, Study #97-0-037

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon: **N/A**

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 97-0-035 YES /___/ NO /X/

Investigation #2 97-0-036 YES /___/ NO /X/

Investigation #3 97-0-037 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study #97-0-035

Investigation #2, Study #97-0-036

Investigation #3, Study #97-0-037

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #_____ YES /X/ NO /___/ Explain: _____

Investigation #2

IND #_____ YES /X/ NO /___/ Explain: _____

IND #_____ YES /X/ NO

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? **N/A**

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all

rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

_____ _____
Signature of Preparer Date
Title: _____

_____ _____
Signature of Office of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 50-777
HFD-540/Division File
HFD-540/Wright
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

/s/

Mildred Wright
12/11/00 02:47:03 PM
CSO

N/A--Dr. Okun approved Checklist for Dr. Wilkin 12/8/00

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA 50-777 _____ Supplement # _____ Circle one: SE[1] SE2 SE3 SE4 SE5 SE6

HFD-540 __ Trade and generic names/dosage form: **Protopic (tacrolimus)Ointment 0.03 & 0.1%**

Action: AP AE NA **AP Action**

Applicant Fujisawa Healthcare, Inc. _____ Therapeutic Class **Dermatologic**

Indication(s) previously approved N/A _____

Pediatric information in labeling of approved indication(s) is **X** adequate __ inadequate __

Proposed indication in this application: **Both 0.03% and 0.1% for adults and *only 0.03%* for children aged 2 to 15 years for the short term and intermittent long term therapy in the treatment of patients with moderate to severe atopic dermatitis in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies.**

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? **X** Yes (Continue with questions) ___ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___ Neonates (Birth-1month) ___ Infants (1month-2yrs) **X** Children (2-12yrs)

X Adolescents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use. **See #5**

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.

__ (1) Studies are ongoing,

__ (2) Protocols were submitted and approved.

__ (3) Protocols were submitted and are under review.

__ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply**, attach an explanation, as necessary **Sponsor is required to conduduct a Phase 4 PK study to obtain further data to evaluate Protopic use in children down to 2 years .**.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? X Yes No (Based on results of above study (in #5), a determination will be made about additional further studies.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from **Team Leader** (e.g., medical review, medical officer, team leader).

Millie Wright, Project Manager _____ 12/7/00

Signature of Preparer and Title Date

cc: Archival NDA 50-777
HFD-540 _/Div File
NDA/PLA Action Package
HFD-104/Peds/T.Crescenzi (revised 3/6/00)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, TERRIE CRESCENZI, HFD-104 (CRESCENZIT)

APPEARS THIS WAY
ON ORIGINAL

/c/

Mildred Wright
12/11/00 04:23:54 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Richard J. Tajak	Senior Vice President, Finance
FIRM/ORGANIZATION	
Fujisawa Healthcare, Inc., Deerfield, IL 60015	
SIGNATURE	DATE
Richard J. Tajak	8/13/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Created by Electronic Document Services/USDHHS: (301) 443-3454 EF

8.7.3.2 List of INDs/NDAs

Product	FDA Number
Protopic Ointment	[redacted]
FK506 – [redacted]	[redacted]
Prograf Capsules/Ampules	NDA 50-708/50-709

8.7.4 Financial Disclosure

All studies were completed prior to February 1999. No investigator was given equity in Fujisawa Healthcare, Inc. No investigator was compensated based upon outcome. No one site/investigator enrolled a substantial number of patients.

8.7.5 List of Obligations Transferred

A list of the obligations that were transferred to outside agencies is presented in Table 8. In addition, in the U.S. clinical trials, tacrolimus blood concentrations were measured by Fujisawa Research Institute of America (FRIA).

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Amy S. Paller, M.D.
Head, Division of Dermatology
Children's Memorial Hospital
2300 Children's Plaza, # 107
Chicago, Illinois 60614

JUN 29 2000

Dear Dr. Paller:

Between January 18 and 24, 2000, Ms. Jeanne M. Morris, representing the Food and Drug Administration (FDA), met with you to review your conduct of the clinical studies (Protocols 97-0-036 and 97-0-037) of the investigational drug Protopic (tacrolimus 0.03% and 0.01%) performed for Fujisawa USA, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report and your January 31, 2000, written response to the items listed on the Form FDA 483, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Morris presented and discussed with you her inspectional observations. The discussion included your failure to perform the study according to the relevant protocols in that: a) subject #154758 was not withdrawn from the study despite the use of prohibited oral corticosteroids during the trial; b) not all required blood laboratory samples were collected for subjects #154602, #154606, #154611 in protocol 97-0-36; c) laboratory abnormalities were not reported as adverse drug events for subject #154611; and d) concomitant medications were not always reported in the case report form for subjects #154611, #154709 and #154758. We acknowledge your responses and your promise to make corrections/changes in your procedures to ensure that the findings discussed above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown investigator Morris during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

Sincerely,

/S/

for Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Doc. Ron

Food and Drug Administration
Rockville MD 20857

MAY 18 2000

David M. Pariser M.D.
Virginia Clinical Research, Inc.
601 Medical Tower
Norfolk, Virginia 23507

Dear Dr. Pariser:

Between February 22 and March 2, 2000, Ms. Marya Ricks and Mr. Stephen C. Eason, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of the clinical studies (Protocols 97-0-037 and 97-0-035) of the investigational drug Protopic (tacrolimus 0.03% and 0.01%), performed for Fujisawa USA, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report and your March 7, 2000, written response to the items listed on the Form FDA 483, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Eason presented and discussed with you their inspectional observations. The discussion included:

1) your failure to perform the study according to the relevant protocol in that: a) not all baseline and visit Week 12 vital sign measurements were properly recorded on the case report form for thirteen out of the sixteen subjects records audited; and b) you did not discontinue subject # 215702 from the study despite using a prohibited medication in the treatment area during the study; and

2) your failure to maintain adequate records in that source documents for subjects # 215510 were not available for review at the time of the inspection.

We acknowledge your responses and your promise to make corrections/changes in your procedures to ensure that the findings discussed above are not repeated in any ongoing or future studies.

APPEARS THIS WAY
ON ORIGINAL

We appreciate the cooperation shown our staff during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL