CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-769

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OCT 2 2 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

45-DAY MEETING **DATE: 10/23/96**

NDA: 20-769 **SUBMISSION DATE:** 8/30/96

PRODUCT: Hydrocortisone Butyrate Cream, 0.1% (Locoid Lipocream®)

SPONSOR: Yamanouchi Europe BV
Elisabethhof 19, P.O. Box 108
2350 AC Leiderdorp, The Netherlands

TYPE OF SUBMISSION: Original Submission **REVIEWER:** Sue-Chih Lee, Ph.D.

I. BACKGROUND:

Hydrocortisone-17-butyrate is a corticosteroid with anti-inflammatory, anti-pruritic and vasoconstrictive actions. Hydrocortisone Butyrate Cream, 0.1%, is currently marketed in the U.S. under the trade name Locoid® Cream (NDA 18-514) for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The proposed product, Locoid Lipocream®, has a different formulation than Locoid® Cream. This new formulation was developed around 1980 in Germany and has demonstrated better cosmetic appeal in Europe. The sponsor states that the new formulation is more acceptable for use in a wider range of skin conditions than the Locoid® Cream or Ointment.

There are no human PK studies for the Lipocream®. Related clinical studies include an adrenal suppression study (Study No. 92-LOC-02), a multi-point vasoconstriction study (Protocol No. 94-MCK-04) and some clinical studies conducted in the Netherlands, and a double-blind safety and efficacy trial (Study 92-LOC-04) conducted in the U.S.

II. FORMULATION and DOSAGE REGIMEN:

The formulation is given below. The cream should be applied to the affected area as a thin film two or three times daily depending on the severity of the condition. Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

COMPONENT	PER GRAM DOSE
Hydrocortisone Butyrate, U.S.P.	1.0 mg
Mineral Oil (Light Liquid Paraffin, Ph. Eur.)	[redacted] mg
White Petrolatum, U.S.P. (White Soft Paraffin)	[redacted] mg
Ceteth-20 (Cetomacrogol 1000, BP)	[redacted] mg
Cetostearyl Alcohol, NF	[redacted] mg
Citric Acid, Anhydrous, U.S.P.	[redacted] mg
Sodium Citrate, Anhydrous, U.S.P.	[redacted] mg
Propyl Paraben, NF	[redacted] mg
Butyl Paraben, NF	[redacted] mg
Purified Water, U.S.P.	[redacted] gm

III. COMMENTS:

1. Qualitatively, the components of Locoid Lipocream® and Locoid® Cream are identical. Quantitatively, the two creams are quite different in that the ratio of aqueous to nonaqueous phase is approximately 1:2 for Locoid Lipocream® and 2:1 for Locoid® Cream.

2. Although there are no human pharmacokinetic studies performed on the Locoid Lipocream®, both the vasoconstriction study and adrenal suppression study have been conducted to aid in the assessment of the product safety and efficacy. Therefore, the application is considered fileable. However, if the adrenal suppression study was not carried out under occlusive condition, the risk of using the product under occlusion cannot be assessed.

3. Although not as the primary reviewer for the vasoconstriction study (Protocol No. 94-MCK-04) and adrenal suppression study (Study No. 92-LOC-02), we need to evaluate the studies from biopharmaceutics standpoint. Therefore, we would appreciate having the volumes containing these two studies.

IV. RECOMMENDATION:

From the biopharmaceutics standpoint, the application is fileable. Please convey Comment #2 to the Medical Officer. Comment #3 should be communicated to the sponsor.

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD Initialed by Dennis Bashaw, Pharm.D. _____
FT Initialed by Dennis Bashaw, Pharm.D. _____

CC:
NDA 20-769
HFD-540 (2 copies)
HFD-880 (DPE3)
HFD-880 (TL - Bashaw)
✓ HFD-880 (Reviewer - Lee)
✓ Drug File (Clarence Bott, HFD-870, Pkln 13B31)
HFD-340 (Viswanathan)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-769 **SUBMISSION DATE:** 08/30/96
12/12/96

PRODUCT: Hydrocortisone Butyrate Cream, 0.1%
(Locoid Lipocream®)

SPONSOR: Yamanouchi Europe BV
Elisabethhof 19, P.O. Box 108
2350 AC Leiderdorp, The Netherlands

TYPE OF SUBMISSION: Original Submission **REVIEWER:** Sue-Chih Lee, Ph.D.

SYNOPSIS:

The proposed product, Locoid Lipocream® (hydrocortisone butyrate cream, 0.1%), is a topical corticosteroid to be indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The currently maketed product (Locoid® Cream 0.1%; NDA 18-514), containing the same active ingredient but in a different formulation, is used for the same indication.

There are no human PK studies for the Lipocream®. Related clinical studies include three adrenal suppression studies, a multi-point vasoconstriction study, several clinical studies conducted in the Netherlands, and a double-blind safety and efficacy trial (Study 92-LOC-04) conducted in the U.S. This review evaluates the vasoconstriction study and adrenal suppression studies from biopharmaceutics standpoint.

The vasoconstriction assay (Protocol No. 94-MCK-04) showed that, after the creams were in contact with the skin for 11 hours without occlusion, Locoid Lipocream® had a skin blanching effect greater than Locoid® Cream. There was no significant differences in the blanching score between Locoid Lipocream and Temovate cream (clobetasol propionate 0.05%/Glaxo).

Out of the three adrenal suppression studies submitted, only one study (Study no. 92-LOC-02) was evaluable. This study was conducted in healthy volunteers with occlusion to compare Locoid Lipocream® to Elocon® cream (0.1% mometasone furoate/Schering). The sponsor concluded that the decrease in plasma cortisol concentration during treatment with Locoid Lipocream® was transient in nature and was to a lesser extent when compared to Elocon cream. Upon challenge with Synacthen, the increase in the plasma cortisol concentration was comparable before and after treatment with either Locoid Lipocream® or Elocon® cream, indicating no suppression of HPA axis during treatment.

COMMENTS:

1. Healthy subjects were used in the adrenal suppression study to compare Locoid Lipocream® with Elocon® cream and the results indicated no adrenocortical insufficiency had developed under the prescribed treatment (16 grams once daily for 5 days with occlusion). However, study in healthy subjects cannot predict the outcome in patients with dematoses due

to possible greater percutaneous absorption in the latter population. (The sponsor intends to allow use of Locoid Lipocream® with occlusion. It is unclear why Elocon® cream was chosen for comparison since the labeling for this product has specific instruction against use with occlusion.)

Although Locoid Lipocream® may appear as a line extension of the Locoid® cream, the vasoconstriction assay results suggested a greater percutaneous absorption of this new formulation. From biopharmaceutics standpoint, it is necessary that the sponsor conduct a study in adult patients with large surface area of the diseased skin (>20% BSA). The proposed dosage regimen for this product should be considered in the study design. The Division medical officer should be consulted in regard to treatment duration for the adrenal suppression study. We suggest that Locoid Lipocream® be compared to a marketed product that also allows use with occlusion. If HPA axis suppression is not observed in adult patients, the study should be repeated in pediatric patients to assess the safety for use in children. If HPA axis suppression is observed in patients, a pharmacokinetic study should be conducted to determine the extent of systemic absorption.

The sponsor may conduct the above study as a Phase IV commitment if the Division of Dermatological and Dental Drug Products considers that the benefit of the product justifies this approach, particularly when an ointment formulation of this drug (Locoid ointment) has been on the market for the same use.

2. One subject had plasma cortisol concentrations of less than 10 μg/L during treatment with Locoid Lipocream® under occlusion.

3. The Locoid Lipocream used in the study was manufactured by If the sponsor intends to market the product manufactured at other sites, equivalence of the product to that manufactured by should be established.

4. The sponsor should be advised that in vitro release testing may be the basis for some post-approval changes per SUPAC-SS Guidance.

RECOMMENDATION:

From the biopharmaceutics standpoint, the application is not approvable. Please convey Comments #1 and 2 to the Medical Officer. Comments 3 and 4 should be communicated to the sponsor. Comment #1 is to be communicated to the sponsor after consultation with the Division of Dermatological and Dental Drug Products.

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD Initialed by Dennis Bashaw, Pharm.D. _____
FT Initialed by Dennis Bashaw, Pharm.D. _____

CC:
NDA 20-769
HFD-540 (2 copies)
HFD-880 (DPE3 File, Bashaw, Lee)
Drug File (Barbara Murphy, CDR)
HFD-340 (Viswanathan)

TABLE OF CONTENTS

BACKGROUND:

Hydrocortisone-17-butyrate is a corticosteroid with anti-inflammatory and anti-pruritic actions. Both the cream and ointment formulations have been approved in the U.S. under the trade name Locoid® Cream (NDA 18-514) and Locoid ointment. The proposed product, Locoid Lipocream®, has a different cream formulation which was developed around 1980 in Germany. The sponsor stated that the new formulation had better cosmetic appeal and would be more acceptable for use in a wider range of skin conditions than the Locoid® Cream or Ointment.

Listed below are some physico-chemical properties of hydrocortisone-17-butyrate:

Mol. wt.: 432.56

Solubility: practically insoluble in water, sparingly soluble in propylene glycol %), soluble in % ethanol %) and freely soluble in methanol %)

Stability: The sponsor requests a shelf-life of 36 months for the drug product when stored at 15-25°C.

FORMULATION and DOSAGE REGIMEN:

The formulation is given below. Qualitatively, the components of Locoid Lipocream® and Locoid® Cream are identical. Quantitatively, the two creams are quite different in that the ratio of aqueous to nonaqueous phase is approximately 1:2 for Locoid Lipocream® and 2:1 for Locoid® Cream.

The cream is to be applied to the affected area as a thin film two or three times daily depending on the severity of the condition. Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

COMPONENT	PER GRAM DOSE
Hydrocortisone Butyrate, U.S.P.	1.0 mg
Mineral Oil (Light Liquid Paraffin, Ph. Eur.)	[redacted]mg
White Petrolatum, U.S.P. (White Soft Paraffin)	[redacted]mg
Ceteth-20 (Cetomacrogol 1000, BP)	[redacted]mg
Cetostearyl Alcohol, NF	[redacted]mg
Citric Acid, Anhydrous, U.S.P.	[redacted]mg
Sodium Citrate, Anhydrous, U.S.P.	[redacted]mg
Propyl Paraben, NF	[redacted]mg
Butyl Paraben, NF	[redacted]mg
Purified Water, U.S.P.	[redacted]gm

VASOCONSTRICTION STUDY (PROTOCOL NO. 94-MCK-04):

Assessment of Relative Bioavailability of Topical Corticosteroid Preparations in Human Volunteers, Using Skin Blanching As a Parameter

INVESTIGATOR AND LOCATION:

OBJECTIVES:
Determination of relative bioavailability of Locoid Lipocream versus Locoid cream in a vasoconstriction test in human volunteers using high and low potency products as calibrators.

TEST PRODUCTS:
A. Hytone cream/Dermik (hydrocortisone 2.5%; low potency calibrator)
B. Locoid Lipocream;
C. Temovate cream/Glaxo (clobetasol propionate 0.05%; high potency calibrator)
D. Locoid Cream;
E. untreated

STUDY DESIGN:
This is a double-blind, single-dose study in 15 healthy volunteers (10 F & 5 M, age: 21-25 yrs). Each volunteer had 5 treatment sites (4 formulation sites + 1 untreated site) on each arm. The allocation scheme for both arms were the same. The right arm of each volunteer was designated for the 4-hour incubation and the left arm for an 11-hour incubation, both without occlusion. The application sites were covered with a non-occlusive guard
which was held in place with a ring of surgical tape
At the end of the incubation time, the medication was removed with mild soap and lukewarm water.

Applied volume: 10 μL/site
Application sites: 5 sites of 2.25 cm^2 on flexor sides of each forearm

ASSAY:

RESULTS:

After analysis of variance and Tukey's multiple comparison testing of the AUCs, it was determined that the visual scores were more discriminating among preparations. The visual scores was then used to assess potency differences between preparations.

There was no difference between Hytone cream and the untreated site in blanching effect after 4 or 11 hours of incubation.

After 4 hours of incubation, Temovate had a significantly higher blanching effect than all other preparations. Both Locoid preparations scored significantly higher than the "untreated" site and Hytone cream.

After 11 hours of incubation, Lipocream had significantly higher score than Locoid cream. There was no significant differences in the blanching score between Locoid Lipocream and Temovate cream.

COMMENTS:

1. The sponsor stated that the study used a 5x5 Latin square design for allocating drug products along the forearm. In fact, many patterns were used and the Latin square design was not strictly followed. However, the purpose of randomization and balance was achieved.

2. In the individual subject data, the measurements listed as the 0 time measurements were actually the baseline measurements before drug application and not the measurements taken right after drug removal. The AUC should be calculated for 1 to 24 hours after drug removal.

3. In this study, the scores at the untreated site as measured by the chromameter fluctuated with time to a greater extent than that determined visually. Because of this, the instrumental method appeared less discriminating among preparations which led the sponsor to select visual scores for the final data analysis. It is noted, however, that no validation of the instrumental method was provided.

4. The mean AUC's were calculated but the standard deviations were not indicated. Besides, the statistical analysis results were not provided.

5. The new formulation (Locoid Lipocream) showed greater percutaneous absorption of hydrocortisone-17-butyrate than Locoid cream.

Table 1. Preparation allocation per arm

volunteer	site	1	2	3	4	5

Table 2. MEAN AUC's
AUC(1-24): Area under incubation time vs. response curve from 1-24 h; Visual score: Mean score of two scorers on a scale of 0-4.
L*-value: Brightness parameter obtained from the chromameter.

PREPARATION	AUC visual score 4 hrs	11 hrs	AUC L*-value chromameter 4 hrs	11 hrs
HYTONE® cream	0.40	1.58	0.28	-0.34
LOCOID LIPOCREAM®	24.48	33.03	31.97	32.66
TEMOVATE® cream	34.52	39.35	41.40	40.37
LOCOID® cream	14.58	20.05	18.07	26.46
untreated	0.23	1.43	-3.44	4.64

(Program: D:\BATCH\MCK9404S.SAS) STUDY 94-MCK-04
Mean response per form

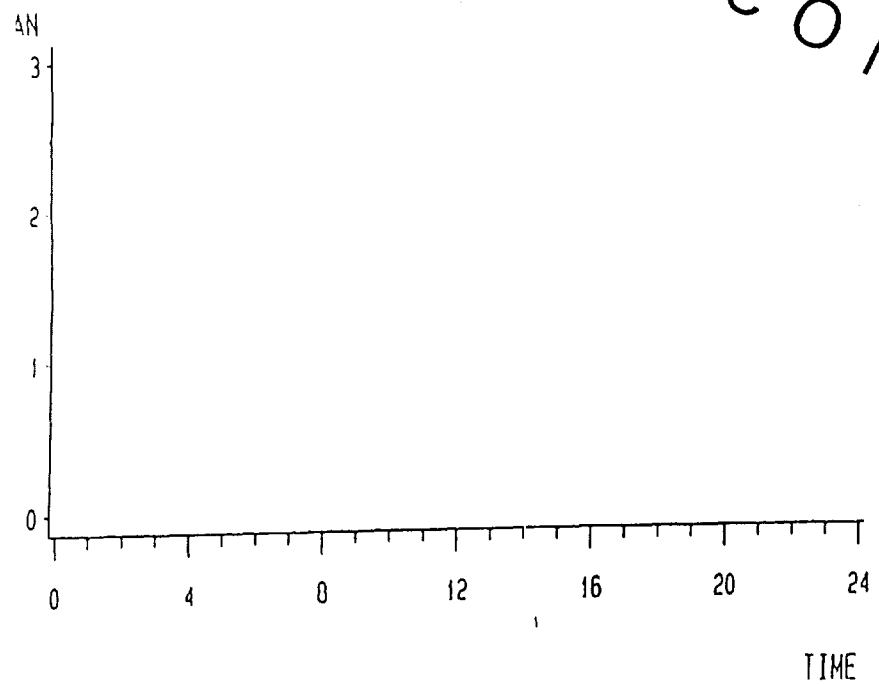
ARM	TINCUB	FORM	TIME	MSCORE	L*-VALUE
RIGHT	4 HRS	A	0	.	65.4240
RIGHT	4 HRS	A	1	0.03333	65.2240
RIGHT	4 HRS	A	3	0.00000	65.3907
RIGHT	4 HRS	A	5	0.03333	65.2073
RIGHT	4 HRS	A	7	0.00000	65.3107
RIGHT	4 HRS	A	21	0.03333	65.7327
RIGHT	4 HRS	A	24	0.00000	64.9993
RIGHT	4 HRS	B	0	.	65.4420
RIGHT	4 HRS	B	1	1.36667	66.6853
RIGHT	4 HRS	B	3	1.43333	66.9787
RIGHT	4 HRS	B	5	1.43333	66.9000
RIGHT	4 HRS	B	7	1.06667	66.7907
RIGHT	4 HRS	B	21	0.86667	66.9520
RIGHT	4 HRS	B	24	0.53333	65.7680
RIGHT	4 HRS	C	0	.	65.4247
RIGHT	4 HRS	C	1	0.60000	66.0747
RIGHT	4 HRS	C	3	1.36667	66.8900
RIGHT	4 HRS	C	5	2.00000	67.5207
RIGHT	4 HRS	C	7	2.00000	67.6813
RIGHT	4 HRS	C	21	1.13333	67.0767
RIGHT	4 HRS	C	24	0.83333	66.2293
RIGHT	4 HRS	D	0	.	65.3160
RIGHT	4 HRS	D	1	0.70000	66.2157
RIGHT	4 HRS	D	3	0.76667	66.1680
RIGHT	4 HRS	D	5	0.83333	66.2500
RIGHT	4 HRS	D	7	0.73333	66.1547
RIGHT	4 HRS	D	21	0.46667	66.1113
RIGHT	4 HRS	D	24	0.33333	65.1313
RIGHT	4 HRS	E	0	.	66.0040
RIGHT	4 HRS	E	1	0.06667	65.8027
RIGHT	4 HRS	E	3	0.03333	66.0947
RIGHT	4 HRS	E	5	0.03333	65.2643
RIGHT	4 HRS	E	7	0.00000	65.4913
RIGHT	4 HRS	E	21	0.00000	66.2900
RIGHT	4 HRS	E	24	0.00000	65.3800

STUDY 94-MCK-04
Mean response per form

ARM	TINCUB	FORM	TIME	MSCORE	L*-VALUE
LEFT	11 HRS	A	0	.	65.2047
LEFT	11 HRS	A	1	0.23333	65.5753
LEFT	11 HRS	A	2	0.10000	65.6127
LEFT	11 HRS	A	4	0.13333	65.2180
LEFT	11 HRS	A	6	0.40000	65.0873
LEFT	11 HRS	A	8	0.06667	65.0847
LEFT	11 HRS	A	10	0.00000	65.0293
LEFT	11 HRS	A	24	0.00000	65.5487
LEFT	11 HRS	B	0	.	65.3840
LEFT	11 HRS	B	1	2.16667	67.9040
LEFT	11 HRS	B	2	2.00000	67.7793
LEFT	11 HRS	B	4	1.93333	67.6053
LEFT	11 HRS	B	6	1.96667	67.1927
LEFT	11 HRS	B	8	1.66667	66.9447
LEFT	11 HRS	B	10	1.56667	66.6687
LEFT	11 HRS	B	24	0.60000	66.1107
LEFT	11 HRS	C	0	.	65.3207
LEFT	11 HRS	C	1	2.36667	68.0720
LEFT	11 HRS	C	2	2.23333	67.9833
LEFT	11 HRS	C	4	2.26667	67.7393
LEFT	11 HRS	C	6	2.10000	67.1813
LEFT	11 HRS	C	8	2.06667	67.4187
LEFT	11 HRS	C	10	2.10000	66.9953
LEFT	11 HRS	C	24	0.56667	66.3880
LEFT	11 HRS	D	0	.	64.7707
LEFT	11 HRS	D	1	1.43333	66.7227
LEFT	11 HRS	D	2	1.43333	67.0080
LEFT	11 HRS	D	4	1.13333	66.3880
LEFT	11 HRS	D	6	0.93333	66.3013
LEFT	11 HRS	D	8	0.93333	65.9073
LEFT	11 HRS	D	10	0.90000	65.7007
LEFT	11 HRS	D	24	0.46667	65.5047
LEFT	11 HRS	E	0	.	65.5093
LEFT	11 HRS	E	1	0.06667	66.0107
LEFT	11 HRS	E	2	0.00000	66.1433
LEFT	11 HRS	E	4	0.00000	65.3607
LEFT	11 HRS	E	6	0.40000	65.7700
LEFT	11 HRS	E	8	0.03333	65.6147
LEFT	11 HRS	E	10	0.03333	65.4260
LEFT	11 HRS	E	24	0.03333	65.9980

VISUAL SCORES

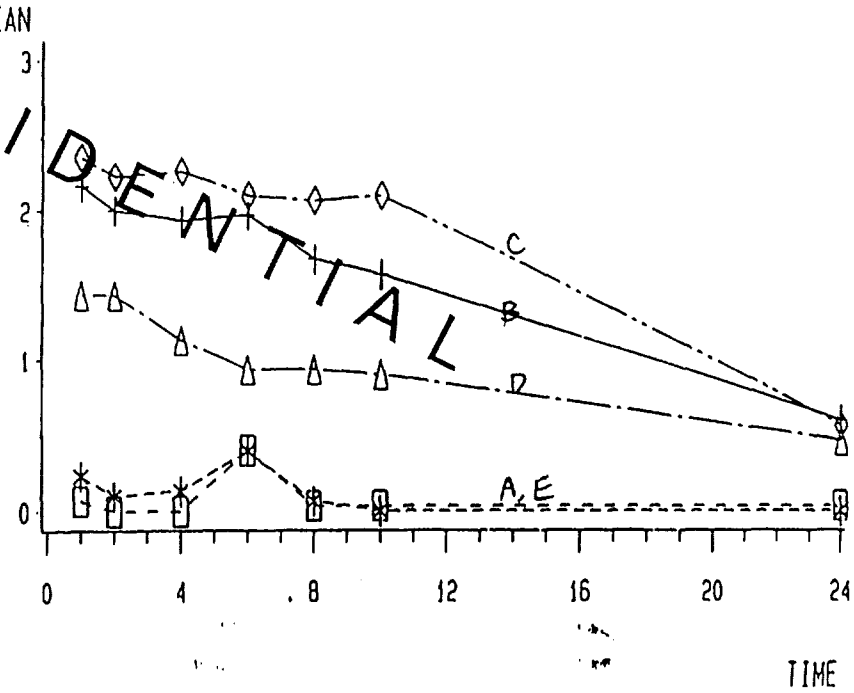
TINCUB=4 HRS



FORM *-*-* A +-+-+ B ◇-◇-◇ C Δ-Δ-Δ D □□□ E

VISUAL SCORES

TINCUB=11 HRS



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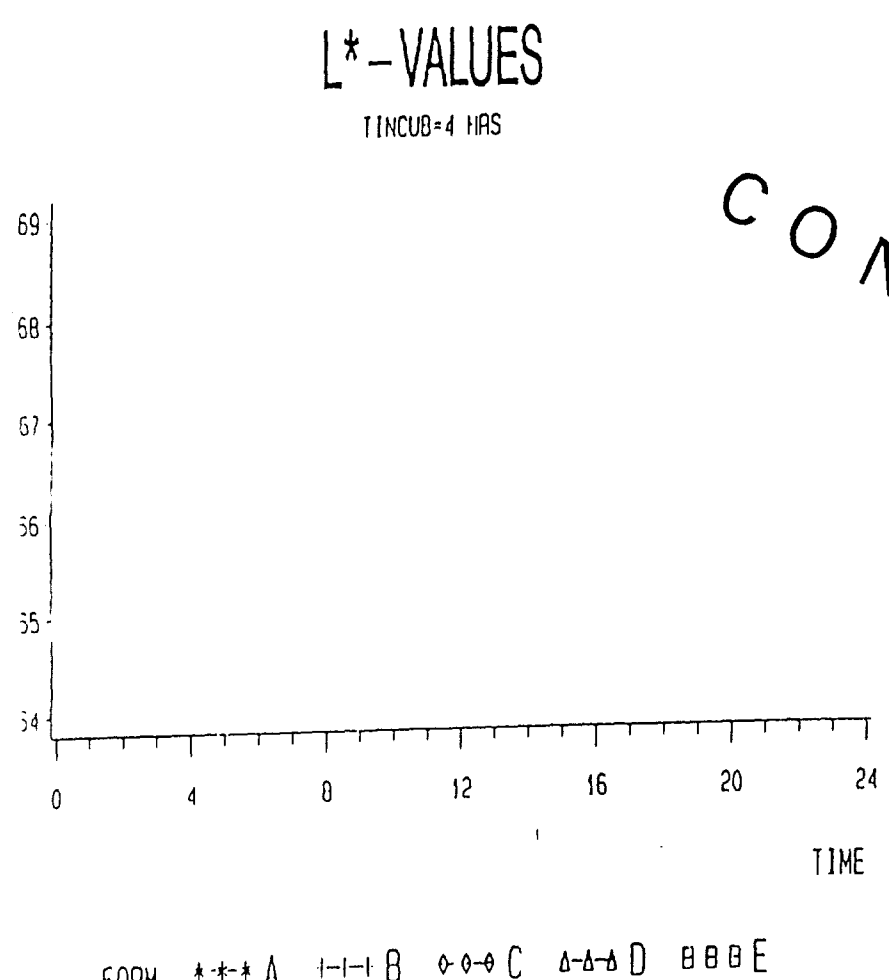
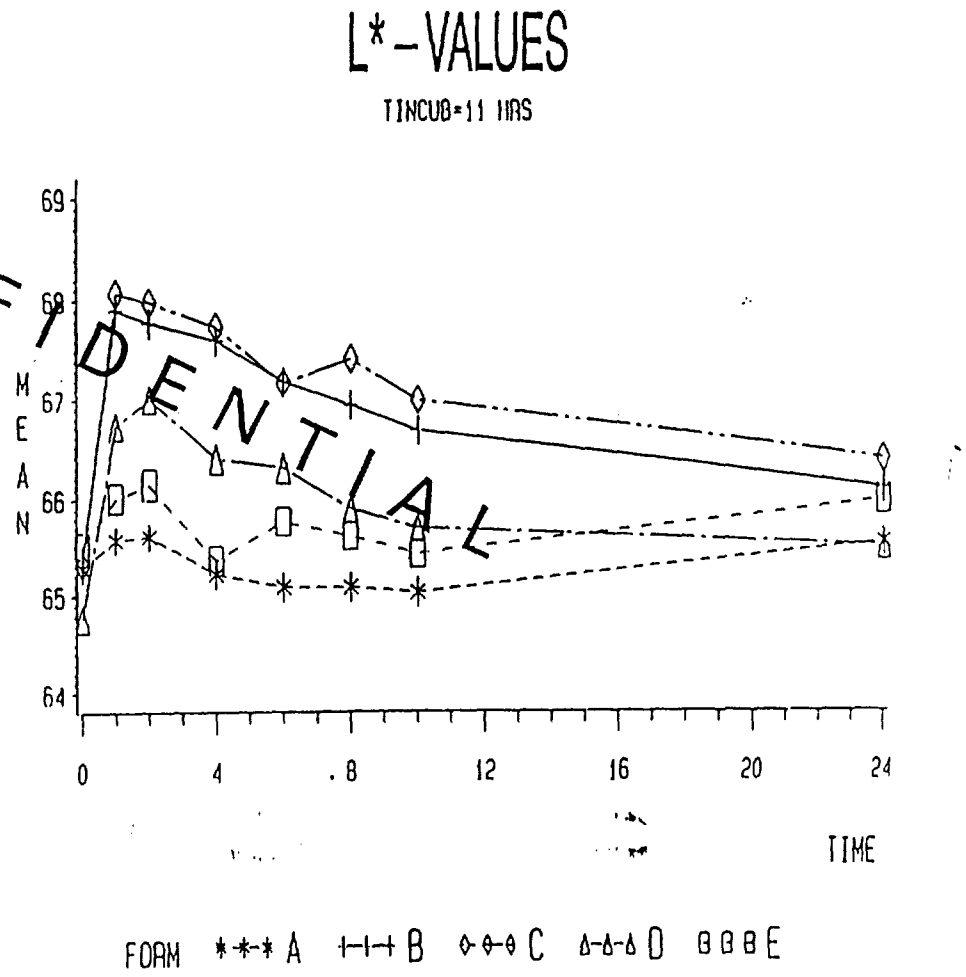




ADRENAL SUPPRESSION STUDIES:

1. A Comparative Study on the Adrenal Suppressive Effect of Locoid Lipocream Fatty Cream (0.1% Hydrocortisone-17-butyrate (Brocades Pharma)) and Elocon Fatty Cream (0.1% Mometasone Furoate (Schering)) (STUDY NO. 92-LOC-02)

INVESTIGATOR AND LOCATION:

OBJECTIVE:
To compare the effect of multiple dose treatment of Locoid Lipocream fatty cream with Elocon fatty cream (both under occlusion) on the adrenal function

TREATMENTS:
Treatment A: Locoid Lipocream Fatty Cream - 0.1% Hydrocortisone-17-butyrate (Brocades Pharma)
Treatment B: Elocon Fatty Cream - 0.1% Mometasone Furoate (Schering)

STUDY DESIGN:
This is an open label, randomized, two period crossover pharmacodynamic study with assessment of morning plasma cortisol and ACTH concentrations before, during and after treatments and the increase in plasma cortisol concentrations after intramuscular administration of Synacthen (0.25 mg/mL tetracosactide) before and during the treatments.

Twelve healthy male Caucasian volunteers between 18 and 45 years old participated and completed the study. On Days 3, 4, 5, 6 and 7 of each period, 16 grams of the test or reference cream was applied (at 8:00 pm) to the back, chest, belly and upper leg area of the skin at approximately 10 mg/cm^2. The cream was left on the skin under occlusion for 11 hours. Day 15 of period 1 is Day 1 of Period 2.

On Days 1 and 8 of each period, the subjects received 0.25 mg of tetracosactide i.m. (Synacthen test) at 10:00 am.

Blood sample collections -
For plasma cortisol levels: Samples were taken in the morning at 8:00, 8:30, 9:00, 9:30 and 10:00 (before i.m. injection of Synacthen) on Days 1, 8 and 15 (Period 1) and on Days 8 and 15 (Period 2). Aliquots of samples taken from the same subject on the same day were pooled.

For ACTH levels: Samples were taken at 8:00 am on Days 1, 8 and 15 (Period 1) and Days 8 and 15 (Period 2).

For Synacthen test (plasma cortisol levels after tetracosactide i.m.): On Days 1 and 8 of both periods, blood samples were taken before (at 10:00 am) and after (at 10:30 and 11:00 am) i.m. injection of Synacthen.

ASSAY:

RESULTS:

The mean plasma cortisol concentrations before treatment with the corticosteroids (Day 1) were:

Locoid Lipocream (Treatment A): 143.1 ± 36.3 $\mu g/L$

Elocon cream (Treatment B): 139.7 ± 36.9 $\mu g/L$

A significant decrease ($p=0.0001$) in plasma cortisol concentrations during treatment (Day 8) was observed for both treatments (mean conc.: 89.4 ± 39.0 $\mu g/L$ and 45.1 ± 23.4 $\mu g/L$, respectively). The decrease was significantly greater ($p=0.02$) with the Elocon cream than with the Locoid Lipocream. In both cases, the plasma cortisol levels returned to normal after treatment (Day 15), indicating the decrease of plasma cortisol concentrations during treatment was transient.

cortisol

day	A n	A arithmetic mean ($\mu g.L^{-1}$)	A SD ($\mu g.L^{-1}$)	B n	B arithmetic mean ($\mu g.L^{-1}$)	B SD ($\mu g.L^{-1}$)
1	12	143.1	36.3	12	139.7	36.9
8	12	89.4	39.0	12	45.1	23.4
15	12	143.0	23.1	12	142.1	27.5

The mean plasma ACTH concentrations before treatment with the corticosteroids (Day 1) were:
Locoid Lipocream (Treatment A): 9.3 ± 5.3 pmol/L
Elocon cream (Treatment B): 9.9 ± 5.5 pmol/L
There were no significant changes in the mean plasma ACTH levels during or after treatment with the corticosteroids.

ACTH

day	A n	A arithmetic mean ($pmol.L^{-1}$)	A SD ($pmol.L^{-1}$)	B n	B arithmetic mean ($pmol.L^{-1}$)	B SD ($pmol.L^{-1}$)
1	12	9.3	5.3	12	9.9	5.5
8	12	9.3	5.1	12	8.7	3.8
15	12	9.5	4.8	12	9.4	5.1

Synacthen test:
Prior to treatment with the corticosteroids (Day 1), the mean plasma cortisol concentrations immediately before the administration of Synacthen were:
Locoid Lipocream (Treatment A): 117.2 ± 35.2 $\mu g/L$
Elocon cream (Treatment B): 111.0 ± 31.3 $\mu g/L$
The mean plasma cortisol concentrations increased after i.m. administration of Synacthen to 193.3 ± 31.7 and 201.7 ± 34.9 $\mu g/L$, respectively, half hour after injection, and further to 228.7 ± 32.9 and 228.3 ± 38.9 $\mu g/L$, respectively, one hour after injection.

As stated above, plasma cortisol concentrations decreased during treatment with corticosteroids. Immediately before the administration of Synacthen, the mean plasma concentrations were:
Locoid Lipocream: 77.7 ± 40.1 $\mu g/L$
Elocon cream: 39.2 ± 25.5 $\mu g/L$
The mean concentrations increased after i.m. administration of Synacthen to 168.1 ± 31.6 $\mu g/L$ and 143.2 ± 37.7 $\mu g/L$, respectively, half hour after injection, and further to 193.8 ± 28.1 and 175.2 ± 37.0 $\mu g/L$, respectively, one hour after injection.

Blood Sample Collection Time	Plasma Cortisol Conc., μg/L	
	Locoid Lipocream	Elocon cream
Day 1 - prior to treatment & Synacthen i.m.		
Day 1 - prior to treatment & 0.5h after Synacthen i.m.		
Day 1 - prior to treatment & 1h after Synacthen i.m.		
Day 8 - during treatment & prior to Synacthen i.m.		
Day 8 - during treatment & 0.5h after Synacthen i.m.		
Day 8 - during treatment &1h after Synacthen i.m.		

The increase in the mean plasma cortisol concentrations one hour after the injection are listed in the table below and there are no significant difference ($p=0.62$) in the increase before and after treatment with Locoid Lipocream. Normally, it is expected to have an increase of at least μg/L within minutes and a concentration of greater than μg/L hour after injection. The sponsor considered that these results indicated no adrenocortical insufficiency had developed under the prescribed treatment.

	A		B	
	Δc_{before} ($\mu g.L^{-1}$)	Δc_{during} ($\mu g.L^{-1}$)	Δc_{before} ($\mu g.L^{-1}$)	Δc_{during} ($\mu g.L^{-1}$)
n	12	12	12	12
mean	111.4	116.1	117.3	135.9
SD	30.2	24.2	32.8	28.4

Adverse events: Mild skin irritations (e.g., erythema, burning and itching) were observed but both treatments were considered well tolerated.

COMMENTS:

1. The Locoid Lipocream used in the study was manufactured by If the sponsor intends to market the product manufactured at other sites, equivalence of the product to that manufactured by should be established..

2. Healthy subjects were used in the study. Since patients may have greater percutaneous absorption, the sponsor should conduct a study in patients.

3. Twelve subjects were included in the study. The appropriateness of this sample size was discussed with Dr. Rajagopalan Srinivasan, the supervisory statistician at HFD-540. The determination was based on a desirable mean plasma cortisol concentration of 181 μg/mL, and a standard deviation range of 28 to 35 μg/mL. It was found that

between 10 and 15 subjects are needed to give a 80% power for detecting a difference of μg/mL. Therefore, the number of subjects for this study was in the ballpark.

4. The validation of radioimmunoassay for cortisol was provided. The correlation coefficients for the calibration curves were acceptable but the parameters from the four-parameter logistic curve fitting was not indicated. In addition, the interference from momethasone was not tested.

Study #2. An Investigation into the Influence of Locally Applied Hydrocortisone 17-Butyrate Fatty Cream on the Serum Cortisol Level

A brief report of the study was provided. A portion of the study dealt with Locoid Lipocream. Three healthy male subjects participated in the study. The cream was applied to the skin of the whole body, except for the face, in two daily doses of 20 g, one in the morning and one in the evening, for 6 days. Blood samples were taken at 8:00 am. A trend towards a slight depression of the serum cortisol levels was noticeable but these remained within the normal range.

Comment: The report is very brief. The number of subjects (3) is probably too small for the purpose. The figure provided in this report has no legend and no standard deviation.

Study #3. Methylprednisolone Aceponate (MPA) - Use and Clinical Experience in Children (Journal of Dermatological Treatment (1992), 3, Suppl. 2, 27-29)

The publication as appeared in the journal was submitted. Twenty children with atopic dermatitis (age: 6 mo to 12 yrs) participated in the portion of the study that compared MPA with Locoid Lipocream. Each treatment was given to 10 of the children. Each patient was treated twice daily over a period of 7 days using a non-occlusive dressing. Blood samples were taken at 8:00 am before treatment and 3 days after last dose application. There was no significant difference in the plasma cortisol levels before μg/L) and after μg/L) the treatment with hydrocortisone butyrate fatty cream.

Comments:

1. The involved skin surface area in these children is not indicated, nor is the dose given to the children.
2. The effect of the corticosteroids on the serum cortisol level was evaluated by taking a blood sample 3 days after the last dose application. The cortisol level during treatment was not determined.

INDIVIDUAL DATA - ADRENAL SUPPRESSION STUDY

(STUDY NO. 92-LOC-02)

Appendix 6.2: **Demographic Characteristics of the Subjects**

Subject	Gender*	Age (y)	Weight (kg)	Height (cm)	Elbow Breadth (cm)	Frame Size**	Treatment sequence
Min							
Max							
Mean		23.3	71.8				
SD		6.4	6.8				

* m = male

** S = Small
M = Medium

*** Within % of the Index

Appendix 2.1: **Plasma Concentration Tables**
(cont.) Individual morning cortisol plasma concentrations as observed before, during and after application of corticosteroid containing preparations under occlusion for five consecutive nights (days 3, 4, 5, 6 and 7, each night for 11 h, 1 $g.dm^{-2}$) to 12 subjects
A = 16 g of Locoid Lipocream® fatty cream (0.1% hydrocortisone-17-butyrate)
B = 16 g of Elocon® fatty cream (0.1% mometasone furoate)
Subjects 01-12

A - cortisol

Day	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)
1						
8						
15						

Day	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)
1						
8						
15						

B - cortisol

Day	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)
1						
8						
15						

Day	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)
1						
8						
15						
23						

Note: values below the lower limit of quantitation (10.0 $\mu g.L^{-1}$) are between brackets

Appendix 2.1: **Plasma Concentration Tables**
(cont.) Individual morning ACTH plasma concentrations as observed before, during and after application of corticosteroid containing preparations under occlusion for five consecutive nights (days 3, 4, 5, 6 and 7, each night for 11 h, 1 $g.dm^{-2}$) to 12 subjects

A = 16 g of Locoid Lipocream® fatty cream (0.1% hydrocortisone-17-butyrate)
B = 16 g of Elocon® fatty cream (0.1% mometasone furoate)
Subjects 01-12

A - ACTH

Day	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)
1						
8						
15						

Day	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)
1						
8						
15						

B - ACTH

Day	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)
1						
8						
15						

Day	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)	Subject [redacted] Plasma concentration: ($pmol.L^{-1}$)
1						
8						
15						
23						

Note: values below the lower limit of quantitation (4.4 $pmol.L^{-1}$) are between brackets

Appendix 2.1: (cont.)

Plasma Concentration Tables

Individual morning cortisol plasma concentrations as observed during the Synacthen® test (0.25 mg tetracosactide i.m. on days 1 and 8) given before and after application of corticosteroid containing preparations under occlusion for five consecutive nights (days 3, 4, 5, 6 and 7, each night for 11 h, 1 $g.dm^{-2}$) to 12 subjects

A = 16 g of Locoid Lipocream® fatty cream (0.1% hydrocortisone-17-butyrate)

B = 16 g of Elocon® fatty cream (0.1% mometasone furoate)

Subjects 01-12

A - Synacthen®

Day	Scheme time (h)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)
1							
1							
1							
8							
8							
8							

Day	Scheme time (h)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)
1							
1							
1							
1							
8							
8							
8							

B - Synacthen®

Day	Scheme time (h)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)
1							
1							
1							
8							
8							
8							

Day	Scheme time (h)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)	Subject [redacted] Plasma concentration: ($\mu g.L^{-1}$)
1							
1							
1							
8							
8							
8							

Note: values below the lower limit of quantitation ([redacted] $\mu g.L^{-1}$) are between brackets

Appendix 2.3: **Pharmacodynamic Parameters**

Pharmacodynamic parameters Δc_{before} and Δc_{during} (Synacthen® test) as determined before and during application of corticosteroid containing preparations under occlusion for five consecutive nights (days 3, 4, 5, 6 and 7, each night for 11 h, 1 $g.dm^{-2}$) to 12 subjects

A = 16 g of Locoid Lipocream® fatty cream (0.1% hydrocortisone-17-butyrate)

B = 16 g of Elocon® fatty cream (0.1% mometasone furoate)

Subject	Sequence	A		B	
		Δc_{before} ($\mu g.L^{-1}$)	Δc_{during} ($\mu g.L^{-1}$)	Δc_{before} ($\mu g.L^{-1}$)	Δc_{during} ($\mu g.L^{-1}$)
n		12	12	12	12
mean		111.4	116.1	117.3	135.9
SD		30.2	24.2	32.8	28.4

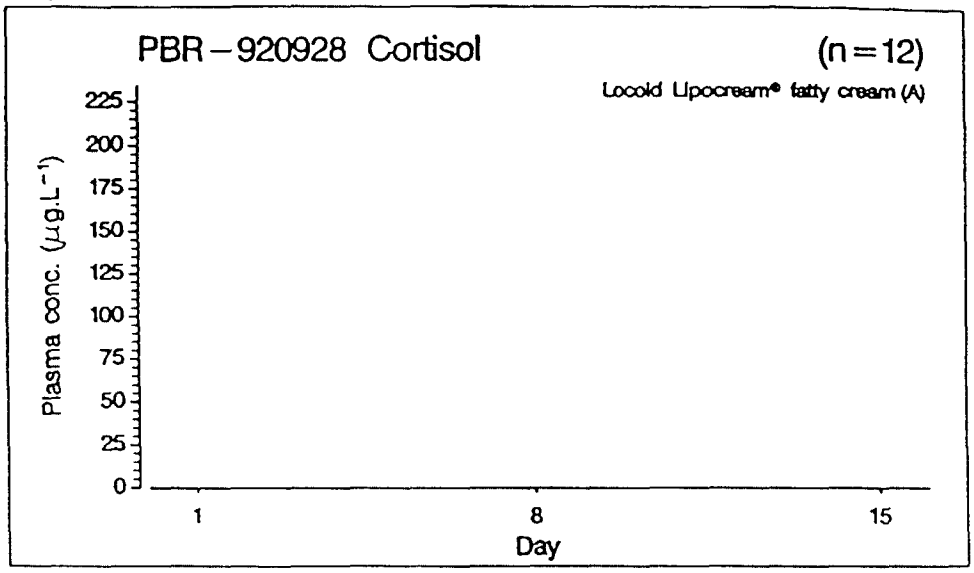
Appendix 2.2: **Diagrams of Plasma Concentrations**

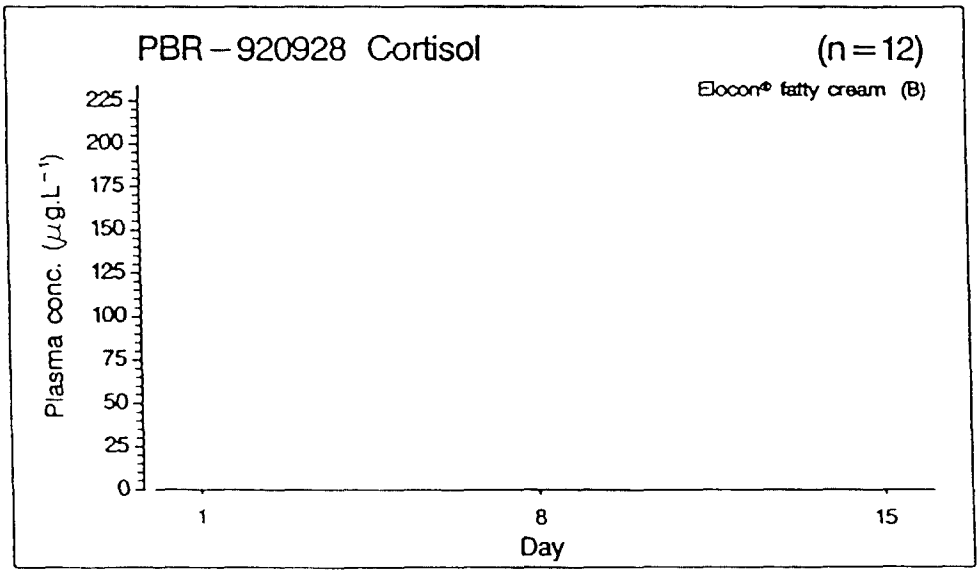
Diagrams of the cortisol morning plasma concentrations as observed before, during and after application of corticosteroid containing preparations under occlusion for five consecutive nights (days 3, 4, 5, 6 and 7, each night for 11 h, 1 $g.dm^{-2}$) to 12 subjects

A = 16 g of Locoid Lipocream® fatty cream (0.1% hydrocortisone-17-butyrate)

B = 16 g of Elocon® fatty cream (0.1% mometasone furoate)

Subjects 01-12





Appendix 2.2: (cont.)

Diagrams of Plasma Concentrations

Diagrams of the ACTH morning plasma concentrations as observed before, during and after application of corticosteroid containing preparations under occlusion for five consecutive nights (days 3, 4, 5, 6 and 7, each night for 11 h, 1 g.dm^{-2}) to 12 subjects

A = 16 g of Locoid Lipocream® fatty cream (0.1% hydrocortisone-17-butyrate)

B = 16 g of Elocon® fatty cream (0.1% mometasone furoate)

Subjects 01-12