

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** 21-159

**CLINICAL PHARMACOLOGY and**  
**BIOPHARMACEUTICS REVIEW(S)**



clinical pharmacology and biopharmaceutics information provided in the original NDA was found acceptable, and in the absence of any new information, the information provided in this resubmission is also acceptable from a clinical pharmacology and biopharmaceutics perspective. However, the applicant should adequately address the labeling comments on page 6.

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**3. Summary of CPB findings previously submitted and reviewed in original NDA**

The reports of two studies (201 and 202) and a Phase III study (3001) that included serum and urine ciclopirox level measurements in the ciclopirox shampoo were previously submitted and reviewed in the original NDA. A brief summary of the studies are discussed below:

### Study 201

This was a Phase II, open-label, single-center, non-randomized trial of efficacy, safety, and pharmacokinetics of ciclopirox 1% shampoo after single and repeated single dose treatment. Eighteen Caucasian patients (4 females and 14 males) aged between 22-65 years old, with a diagnosis of seborrheic dermatitis were treated with 5mL of Loprox shampoo (~ 50 mg of ciclopirox) twice a week for 4 weeks. Blood samples were collected on study Days 1 and 29, pre-dose and 0.5, 1, 2, 3, 6, 8, 12 and 24 hours after drug application. Blood Samples were also collected at Visits 4 and 5 to determine the trough levels of ciclopirox. Urine samples were collected on Days 1 and 29, before and 0-4, 4-8, 8-12 and 12-24 hours after drug application. Serum concentrations of total (free and conjugated ciclopirox glucuronide) ciclopirox were detectable in 9 serum samples (7 on Day 1, 2 on Day 29) in 6 out of 18 patients. Serum concentrations ranged from 10.3-13.2 µg/L measured on Day 1. No secondary pharmacokinetic parameters were evaluated because of the few measurable concentrations.

The total median amount of ciclopirox excreted in the urine during the 24 hours post-administration was 207.8 mcg (0.42% of the administered dose) on Day 1 and 172.8 mcg (0.35% of the administered dose) on Day 29. The maximum amount excreted was — (0.83% of dose) on Day 1 and — (0.74% of dose) on Day 29. The urine results are consistent with the serum findings with regards to lower systemic absorption on Day 29 as compared to Day 1 (possibly due to decreased skin inflammation/involvement). Also the urine results consistent with the serum findings indicate that no accumulation of ciclopirox occurred by Day 29.

### Study 202

This was a Phase II, open-label, multi-center, uncontrolled study evaluating the pharmacokinetics, efficacy and safety profile of ciclopirox 1% shampoo after exaggerated use at three centers in Germany. Twelve Caucasian patients (5 female and 9 males) aged between 18-58 years old, with a diagnosis of seborrheic dermatitis were treated daily for 29 days with 5 mL (~ 50 mg ciclopirox) of ciclopirox shampoo 1%. The shampoo was applied daily with a contact time of 3 minutes for the first 15 days and then 6 minutes for the following 14 days (Total = 29 days). Blood samples were collected on study Days 1, 15 and 29, pre-dose and 0.25, 0.5, 0.75, 1, 2, 4, and 6 hours after drug application. Urine samples were collected on Days 1, 15 and 29, pre-dose and 0-4, 4-6, 6-12 and 12-24 hours after drug application.

Serum concentrations of total (free and conjugated) ciclopirox were measurable in 9 of 12 patients on Day 1 (maximum value: — ), in 6 of 12 patients on Day 15 (max: — µg/L), and in 11 of 12 patients on Day 29 (max: — µg/L). No secondary pharmacokinetic parameters were evaluated because of the few measurable concentrations.

The total median amount of ciclopirox excreted in urine during the 24 hours post-administration period was 511.9 mcg (1.02 % of the administered dose) on Day 1, 477.5 mcg (0.96 % of the administered dose) on Day 15, and, 679.7 mcg (1.36 % of the administered dose), on Day 29. A Dunnett's one-tailed t-test was used to compare the fraction of dose of total ciclopirox excreted (%) on Day 1 with that of Day 15 and Day 29. This analysis showed that there were no statistically ( $p > 0.05$ ) significant ( $p = 0.2880$  [Day15 vs. Day1] and  $0.3741$  [Day 29 vs. Day 1]) differences between the fraction of dose excreted on Days 15 and 29 compared to Day 1. The maximum amounts excreted were — (3.13% of dose) on Day 1, — µg (1.55 % of dose) on Day 15, and — µg (1.96 % of dose) on Day 29. This data suggest that doubling the contact time increased (but did not double) the amount systemically absorbed and

therefore excreted. Serum and urinary excretion data on Days 1, 15, and 29 did not suggest accumulation of ciclopirox.

### Study No. 3001

This was a Phase III, double-blind, vehicle-controlled, multi-center study evaluating the efficacy and safety of ciclopirox 1% shampoo in the treatment and prophylaxis of seborrheic dermatitis/dandruff of the scalp at 45 centers in Europe. After a 2-week run-in period, 949 Caucasian patients (412 female and 537 male) aged between 18-88 years old with a diagnosis of seborrheic dermatitis of the scalp were treated once or twice weekly with 5-10 mL (depending on hair length) of ciclopirox 1% shampoo or with vehicle for 4 weeks in Segment A of the study. Four hundred and twenty eight Caucasian patients (184 female and 244 male) segment A responders (status, inflammation, scaling, itching scores each =1) were continued into Segment B. They were treated once a week or once every 2 weeks with ciclopirox 1% shampoo or with vehicle for 12 weeks. In addition to efficacy and safety measurements, blood and urine samples were collected at selected sites in England and Germany during Segments A and B to assess systemic concentrations of the ciclopirox. Blood and urine sampling for drug levels occurred for patients at selected centers at Visit 1 (screening), Visit 4 (end of Segment A/beginning of Segment B), and Visit 6 (end of Segment B). The safety and efficacy results of this study will not be discussed here.

A total of 629 serum samples were taken in the study. The total number of patients with quantifiable blood samples above LOQ from Segment A was 263 and for Segment B was 94. At the end of Segment A, total (free and conjugated) ciclopirox levels were measurable in 4 of 263 patients. Three of these patients had received ciclopirox 1% shampoo twice per week for 4 weeks and one had received once per week for 4 weeks. The serum levels ranged from \_\_\_\_\_

The highest value was found in a patient in the twice per week group. At the end of Segment B, total (free and conjugated) ciclopirox serum levels were measurable in 2 of 94 patients. One value \_\_\_\_\_, in a patient who had received ciclopirox 1% shampoo twice per week in Segment A and had received vehicle in Segment B, was considered an artifact by the applicant; the urine sample of the same patient was drug-free. The second value \_\_\_\_\_ occurred in a patient who had received ciclopirox 1% shampoo once per week in both segments of the study.

After 4 weeks of treatment (Segment A), 139 patients treated with ciclopirox 1% shampoo once or twice per week had measurable ciclopirox levels in their urine. In the twice per week group, the median amount of ciclopirox excreted was 240  $\mu\text{g}$  (0.48% of dose) and in the once per week group, the median amount excreted was 259  $\mu\text{g}$  (0.52% of dose). The maximum value found in one patient (once per week group) was \_\_\_\_\_ (4.54% of dose). Nine samples from 6 of 52 (11.5%) patients in the vehicle group had measurable urinary ciclopirox levels. The values measured were in the range of \_\_\_\_\_. The applicant stated that for one of these patients this was caused by a ciclopirox concomitant medication (Batrafen vaginal cream). The other of these findings was claimed to be due to possible interference by food and spices not controlled in the study.

After 12 weeks (3 months) of prophylactic treatment (Segment B), 36 patients treated with ciclopirox 1% Shampoo once per week or once every 2 weeks had measurable ciclopirox concentrations in their urine. In the once weekly group, the median amount of ciclopirox excreted was 242  $\mu\text{g}$  (0.48% of the administered dose) and in the once every two weeks group, the median amount excreted was 137  $\mu\text{g}$  (0.27% of the administered dose). Two out of 27

(11.1%) patients who received vehicle shampoo had ciclopirox in their urine. The applicant stated that it is possible that the small peaks observed in the chromatograms of these samples from vehicle patients were due to interference from unknown compounds such as food and spices not controlled during the study.

#### 4. Labeling Comments

##### Applicant's Proposed Label:

The applicant has proposed the following text to be included in the proposed package insert under the heading "Pharmacokinetics and Pharmacodynamics":

#### **CLINICAL PHARMACOLOGY**

##### **Pharmacokinetics and Pharmacodynamics**

**Reviewer's Revised Label:**

The proposed label should be rewritten as follows:

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics and Pharmacodynamics**

In a study in patients with seborrheic dermatitis of the scalp, application of 5mL ciclopirox shampoo 1% twice weekly for 4 weeks, with an exposure time of 3 minutes per application, resulted in detectable serum concentrations of ciclopirox in 6 out of 18 patients. The serum concentrations measured throughout the dosing interval on Days 1 and 29 ranged from 10.3 ng/mL to 13.2 ng/mL. Total urinary excretion of ciclopirox was less than 0.5 % of the administered dose.

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Abi Adebawale  
1/17/03 04:30:23 PM  
BIOPHARMACEUTICS

Dennis Bashaw  
1/28/03 10:28:57 AM  
BIOPHARMACEUTICS

**APPEARS THIS WAY  
ON ORIGINAL**



**Question Based Review of Ciclopirox Shampoo 1%**

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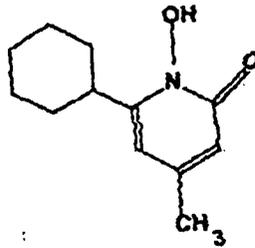
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### III. Ciclopirox

What is Ciclopirox and how does it work?

#### ***Physiochemical Properties and Mechanism of Action:***

Chemically Ciclopirox is a hydroxypyridone derivative, 6-Cyclohexyl-1-hydroxy-4-methyl-2-(1H) pyridone and an empirical formula of  $C_{12}H_{17}NO_2$ . The chemical structure is:



**Ciclopirox**

The molecular weight is ——— It is a white-to-slightly yellowish-white, odorless to almost odorless, crystalline powder. It is soluble in chloroform, dichloromethane, alcohol and ether and, slightly soluble in water. It has a pKa of 7.2.

Ciclopirox is a synthetic broad-spectrum antifungal agent. The proposed mechanism of action of Ciclopirox free acid and olamine salt is the inhibition of the growth of fungal pathogens, including *Pityrosporum ovale*, the suspected causative agent in seborrhoeic dermatitis (an inflammatory scaling disease of the scalp, face and occasionally other areas).

What is the proposed indication(s) and, dosing regimen for ciclopirox?

#### ***Indications:***

The proposed indications for Loprox<sup>®</sup> (ciclopirox) Shampoo 1% include the topical treatment ——— of seborrhoeic dermatitis of the scalp and ——— in adults.

#### ***Dosing regimen:***

The proposed dosing regimens are as follows:

***Treatment:*** Wet hair and apply 5ml (1 capful) or 10ml (long hair) to the scalp. Lather and leave on hair and scalp for 3 minutes and rinse off thereafter. Treatment should occur ——— twice per week for 4 weeks, with a minimum of 3 days between applications.

***Prophylactic:*** ?

#### IV. Formulation

Was the formulation used in each bio-study the to be marketed formulation?

The sponsor sent in a written confirmation on request from the FDA dated October 24<sup>th</sup> 1999 that stated that "the Biopharmaceutics/Pk investigations were performed on batches No. 8,18 and 19. The composition of these batches is identical with the composition of the future commercial batches".

Loprox® Shampoo (1%) was described by the sponsor as an almost colorless, slightly yellowish translucent solution of ciclopirox in a shampoo base containing sodium laureth sulphate, disodium laureth sulphosuccinate, \_\_\_\_\_, purified water, and sodium chloride. Each gram of Loprox® Shampoo (1%) contains 10 mg ciclopirox. A copy of the composition is inserted below:

	Components	1 g Shampoo [mg]
1.	Ciclopirox	10.0

5.	Sodium chloride	
6.	Purified water	

The content of sodium chloride in all the formulations used in all the studies however, were within the established limits.

Would the difference in formulation have an effect on the bioavailability of the drug product that could be clinically significant?

After consultation with the review chemist (Dr. M. Gautam-Basak), it was concurred that the slight variation in sodium chloride content, and deletion of the \_\_\_\_\_ would have very negligible effect on the final quality and bioavailability of the product.

**V. Application Overview**

What types of bioavailability and pk studies were included in this submission?

Included in the Human Pharmacokinetics and Bioavailability section are the results of two bioavailability Phase II studies (201 and 202) and a Phase III study (3001) conducted in Germany. All the studies included data on serum and urinary levels of total ciclopirox (free acid and conjugated). Two of the studies submitted (201 and 202) were considered pivotal and one (3001) was considered to be supportive by this reviewer.

**VI. Analytical Methods and Validation**

Were the assay methods used for the determination of ciclopirox in serum and urine validated?

The serum/urine samples collected in the pharmacokinetic studies submitted were analyzed for total ciclopirox (total and conjugated) by similar

The analytical sites appeared different although the principal scientist was the same. The sites were as follows: 1)

The methods used and the validation results obtained are summarized below.

**1. Sample Extraction Methods:**

## 2. *Validation Results of Assay Methods for Study Nos.201&202*

### 3 *Analytical Conclusions:*

The assay methods used for Study # 201 and 202 were validated with respect to linearity, precision and accuracy. The validation of the assay method for use in quantitating the samples from Study # 3001 also indicated that the method was reproducible and accurate.

From a clinical pharmacology and biopharmaceutical standpoint, the analytical methods and validation data included in this submission are acceptable.

## VII. Summary of BIO/PK Characteristics

What are the pharmacokinetic and bioavailability characteristics of ciclopirox after administration as a shampoo?

Due to the majority of samples having serum levels of ciclopirox below the LOQ in the three studies submitted no pharmacokinetic parameters were evaluable from the serum data. The systemic exposure evaluation was conducted mainly with the more quantifiable urine data. The applicant stated that based on a literature report<sup>1</sup> that 98% of ciclopirox is eliminated via the renal pathway, cumulated amount excreted in the urine is a direct measure of the fraction absorbed during the head washing procedure. The results of these studies are discussed below:

<sup>1</sup> Kellner H.-M., et al. *Arzneim-Forsch./Drug Res.* 31 (II), No.8a (1981) 1337-1353

### *Study #201*

This was a single-center, open-label study in which the applicant evaluated the serum and urine pharmacokinetics of ciclopirox 1% shampoo after single and repeated single dose (5ml (~50mg ciclopirox) twice weekly for 4 weeks) treatment of patients suffering from seborrhoeic dermatitis. Eighteen (18) Caucasian patients (4 female and 14 male) with

seborrhoeic dermatitis, mean age  $42 \pm 13$  (range 22-65) years old, mean weight  $74.4 \pm 9.4$  (range 61 – 98) Kg and, mean height  $173 \pm 9$  (range from 149 –187) cm, completed the study. The percentage of scalp area affected at baseline ranged from 20 – 30 % (1 patient), 30 – 50% (4 patients) and, 50-75% (8 patients) and, 75-100% (5 patients). Blood and Urine samples were collected before dosing and at intervals during 24 hours after dosing on days 1 and 29. Reproduced in the tables below are the summary results from this study, a copy of the study abstract sheet and detailed results are attached in the Appendix as pages 2 – 9.

**Serum:** Serum concentrations were quantifiable in only ~1.3% of the sample from 6/18 patients, a summary of the distribution is shown in the table below:

Table 2: Serum concentrations of total ciclopirox and frequency distributions

Day	No. of Samples (N = 6/18 patients)	Time (h)	Serum Concentration Range (ng/ml)
1	7/702	0.5-1.0	10.3 –13.2
29	2/702	0.5	—

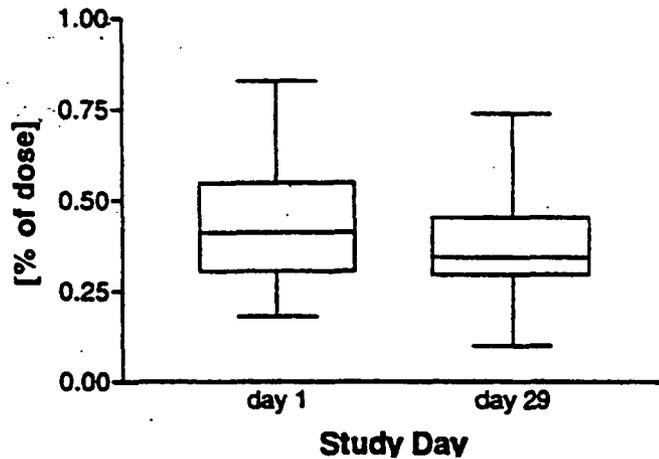
- The above table shows that serum concentrations of total ciclopirox (free and conjugated) above LOQ were quantifiable in only 9/702 (1.3%) samples (7 day 1 and 2 on day 29) in 6/18 patients with a maximum concentration of 13.2 ng/ml.
- The serum results also, suggested that there was probably a lower systemic absorption on day 29 as compared to day 1 (possibly due to decreased skin inflammation/involvement).

**Urine:**

Table 3: Urine total ciclopirox data

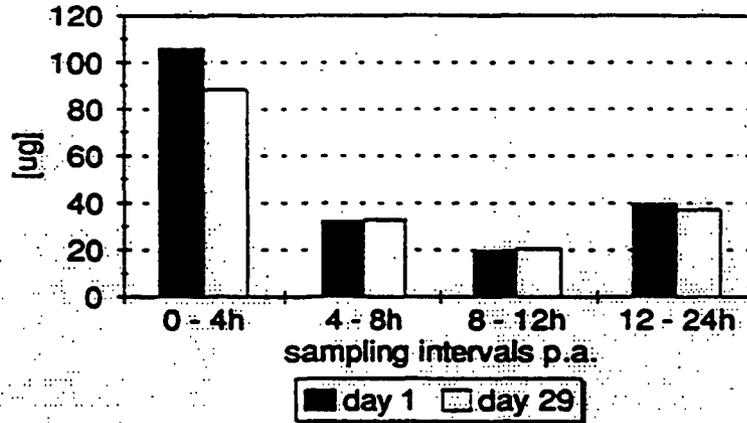
Study day	Mean (SD) Amount ( $\mu$ g) Excreted of Total Ciclopirox					Mean Cumulative amount Excreted ( $\mu$ g)	% of Dose excreted	Mean Geometric mean and 90% CI (day 1/day 29)
	0 h	0-4h	4-8h	8-12h	12-24h			
Day 1	<LOQ	123.1 (74.1)	35.6 (14.6)	18.6 (8)	43.6 (16)	220.9 (97.1)	0.44 (0.19)	
Day 29	3.5 (7.8)	92.3 (47.5)	38.6 (21.1)	22.3 (14.8)	37.9 (19.8)	192.2 (83.7)	0.38 (0.17)	86.67 (74.30-101.10 %)

- The cumulative amount excreted of total ciclopirox on day1 was  $220.9 \pm 97.1 \mu$ g (0.44  $\pm$  0.19 % of the dose) and on day 29 it was  $192.2 \pm 83.7 \mu$ g (0.38  $\pm$  0.17 % of the dose) suggesting that there was lower systemic absorption of about 13% on day 29 as compared to day 1 although the absolute difference was very small (box plot below illustrates this difference as the % of dose administered).



**Figure 1** Box plot of the cumulated amount of total ciclopirox as a percentage of dose excreted during 24 h p.a. on study days 1 and 29.

- The systemic absorption on day 29 as compared with day 1 were found not to be equivalent based on the 90% CI (74.30% -101.10% for day 29/day1) for urinary excretion of total ciclopirox which was outside the CI (80-125%) specified by the applicant.



**Figure 2** Bar graph of the median amounts of total ciclopirox excreted for day 1 and day 29 by the four different sampling times

- The above graph also shows that the greatest median amount was excreted during the 0-4h interval, and the least amount was excreted during the 8-12h interval.
- Similarly, the median (range) amounts of total ciclopirox excreted in the urine during 24h p.a. on day 1 [207.8 ( — ) µg and (0.42 ( — ) of administered dose] was higher than day 29 [172.8 ( — ) µg and 0.35 (0.1 – 0.74) % of administered dose].

- The median pH values for the sampling periods were between 5.77 – 6.49 on day 1 and 5.68 – 6.19 on day 29 (lowest 0 h and highest 4-8h). There did not appear to be any correlation between the amount excreted during a sampling time interval and the pH suggesting that urinary excretion of ciclopirox was not influenced by the changes in pH during the study period.
- The urine results are consistent with the serum findings with regards to lower systemic absorption on day 29 as compared with day 1 and, also indicated that no accumulation of ciclopirox occurred by day 29.

**Study #202**

This was a multi-center, open-label, uncontrolled study in which the applicant evaluated the serum and urine pharmacokinetics of ciclopirox 1% shampoo after exaggerated use with increasing contact time in patients suffering from seborrhoeic dermatitis. Five (5ml) of ciclopirox 1% shampoo (~ 50 mg of ciclopirox) was used daily with a contact time of 3 minutes for the first 15 days and then 6 minutes for the following 14 days (total = 29 days). Fourteen (14) Caucasian patients (5 female and 9 male) with seborrhoeic dermatitis, mean age 35 ± 12 (range 18-58) years old, mean weight 79.6 ± 10.4 (range 65 – 97) Kg and, mean height 175 ± 10 (range from 156 –189) cm were enrolled and, 12 patients completed the study. For the two dropouts the applicant stated that one was due to technical reasons not making the holter ECG evaluable and the other was due to ventricular tachycardia on day 15 of trial. The percentage of scalp area affected at baseline ranged from 20 – 30 % (1 patient), 30 – 50% (5 patients) and, 50-75% (6 patients). Blood and Urine samples were collected before dosing and at intervals during 6 hours (serum) and 24 hours (urine) after dosing on days 1, 15 and 29. Reproduced in the tables below are the summary results from this study, detailed results and a copy of the study abstract sheet and details are attached in the Appendix as pages 10 –21.

**Serum:** Serum concentrations of total ciclopirox (free and conjugated) ≥ LOQ were quantifiable in 9/12 patients (32.3 % of samples) on day 1, in 6/12 patients (18.8 % of samples) on day 15 and, in 11/12 patients (41.7 % of samples) on day 29. The serum concentrations were all below the LOQ after the 2 hour sampling time interval on days 1, 15 and 29. The maximum serum concentration was \_\_\_\_\_ measured on day 29 (see table below).

**Table 4: Serum total ciclopirox concentrations and frequency distributions**

Day	Contact time of shampoo (min)	No. of Samples	No. of patients	Time (h) after exposure with shampoo	Serum Ciclopirox Concentration Range (ng/ml)
1	3	31/96 (32.3%)	9/12	0.25-2.0	
15	3	18/96 (18.8%)	6/12	0.25-1.0	
29	6	40/96 (41.7%)	11/12	0.25-2.0	

- The serum results in the above table suggest that there was probably a higher systemic absorption on day 1 as compared to day 15 and, doubling the contact time (6 minutes) appeared to result in an increase in the systemic absorption by day 29.

Urine

Table 5: Urine total ciclopirox data

Study Day	Contact Time (min)	Mean (SD) Amount (µg) Excreted of Total Ciclopirox				Mean (SD) Cumulative amount Excreted (µg)	% of Dose
		0-4h	4-6h	6-12h	12-24h		
Day 1	3	345.4 (312.3)	53.8 (23.7)	94.7 (34.6)	87.8 (43.5)	581.6 (343.0)	1.16 (0.69)
Day 15	3	223.0 (59.3)	54.2 (20.1)	103.8 (29.1)	95.0 (61.1)	476.0 (129.3)	0.95 (0.26)
Day 29	6	330.8 (128.9)	65.8 (41.5)	107.6 (45.5)	135.1 (121.0)	639.3 (243.2)	1.28 (0.49)
<sup>1</sup> Geometric mean quotient and 90% CI for % of dose of total ciclopirox excreted							
Day 15/Day 1		0.8972 (65.6-122.8%) p = 0.2880 (NS)					
Day 29/Day 1		1.154 (84.4-158.0%) p = 0.3741 (NS)					

<sup>1</sup>Geometric mean quotient = 100\*geometric mean (day 15 or 29/day 1), <sup>2</sup>NS = not significant

The results in the above table indicate that

- The cumulative amount excreted of total ciclopirox on day 1 (581.6 ± 343.0 µg (1.16 ± 0.69 % of the dose)) and, on day 15 (476.0 ± 129.3 µg (0.95 ± 0.26 % of the dose)) suggested that there was lower systemic absorption of about 18 % on day 15 as compared to day 1.
- On the other hand the cumulative amount excreted of total ciclopirox on day 15 ((476.0 ± 129.3 µg (0.95 ± 0.26 % of the dose)) and, on day 29 (639.3 ± 243.2 µg (1.28 ± 0.49 % of the dose)) suggested that doubling the contact time increased (but did not double) the amount absorbed.
- Similarly, the median (range) cumulative amount excreted during 24h post administration of total ciclopirox on day 1 [511.9 (.....) µg (1.02 (0.4 – 3.1) % of the dose)], was higher than on day 15 [477.5 (.....) µg (0.96 (0.6 – 1.6) % of the dose)] and lower than on day 29 [679.7 (.....) µg (1.36 (0.6 – 2.0)% of the dose)]. Below are graphical representations of the median amounts excreted for the sampling time intervals.

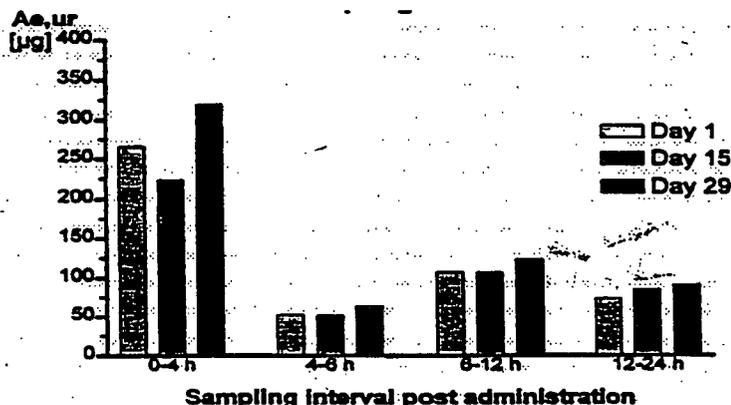
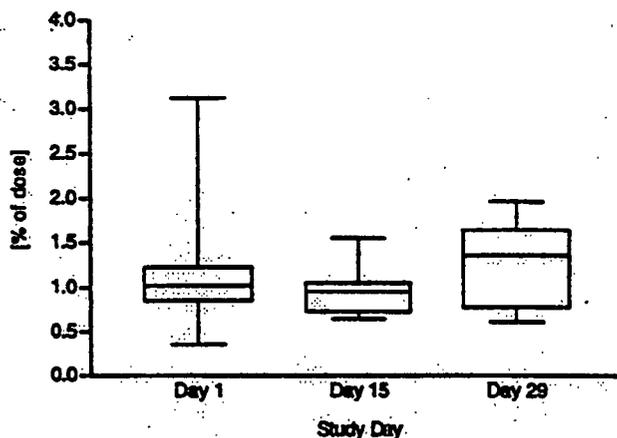


Figure 3 Bar graph of the median amounts of total ciclopirox (Ae<sub>ur</sub>) excreted for day 1 15 and 29 by the four different sampling times



**Figure 4** Box and whisker plot of the cumulated amount of total ciclopirox as a percentage of dose excreted during 24 h p.a. on study days 1, 15 and 29.

- The above plots further demonstrate that the systemic absorption on day 15 was marginally lower than the systemic absorption on day 1, but slightly higher on day 29.
- The median pH values for the sampling periods were between 5.68 – 6.72 on day 1, 5.75 – 6.53 on day 15 and, 5.40 – 6.58 on day 29, (lowest 0-4h and highest 6-12h). There did not appear to be any correlation between the amount excreted during a sampling time interval and the pH suggesting that urinary excretion of ciclopirox was not influenced by the changes in pH during the study period.
- The urine findings are consistent with the serum findings with regards to lower systemic absorption on day 15 as compared with day 1 and the slight increase on day 29.
- However, the statistical comparison of the fractions of dose [%] of topical ciclopirox excreted during 24 h p.a. on study days 1, 15 and 29, did not show significant differences between the three days.

#### **Study #3001**

This was a multi-center, multinational, 3 parallel groups randomized, double-blind study in which the applicant evaluated the efficacy and safety of ciclopirox 1% shampoo in the treatment of seborrheic dermatitis/dandruff of the scalp. Serum and urine concentrations of ciclopirox were monitored in patients at selected centers in England and Germany. There were two segments to the study (A (treatment) & B (prophylaxis)). Ciclopirox shampoo 5ml to 10ml (~ 50-100 mg of ciclopirox) depending on hair length, was administered as follows: *Segment A*: 1% Ciclopirox twice a week vs. 1% ciclopirox once a week vs. vehicle once or twice weekly for 4 weeks. *Segment B*: 1% Ciclopirox once a week vs. 1% Ciclopirox once every second week vs. vehicle every week or every second week for 12 weeks. Nine hundred and forty nine (949) Caucasian patients (412 female and 537 male) with seborrheic dermatitis of the scalp, with an age range from 18 – 88 years (median 38 years) were randomized into *segment A*. Four hundred and twenty eight (428) Caucasian patients (184 female and 244 male) *segment A* responders with an age range from 18 – 88 years (median 37 years) were continued into *segment B*.

Blood and Urine samples were collected before dosing (Visit1), final visit of segment A, end of 4 weeks (Visit 4) and, final visit of segment B, end of additional 12 weeks (Visit 6). Reproduced in the tables below are the summary results from this study, detailed results and a copy of the study abstract sheet are attached in the Appendix as pages 22 - 26.

**Serum:** A total of 629 serum samples were collected during the study. The total number of patients with blood samples from Segment A were 263 (104 Loprox<sup>®</sup> 2x/week, 106 Loprox<sup>®</sup> 1x/week and 53 vehicle) and for Segment B were 94 (32 Loprox<sup>®</sup> 2x/week, 31 Loprox<sup>®</sup> 1x/week and 31 vehicle). Serum concentrations of total ciclopirox (free and conjugated) above LOQ were quantifiable in 6/629 (~0.95%) samples in 4/210 patients at end of 4 weeks and 2/63 patients at end of additional 12 weeks treated with ciclopirox once or twice per week. Three of the patients in the segment A (4 weeks treatment) group had received ciclopirox shampoo 1% twice weekly and one had received ciclopirox shampoo 1% once weekly. In the segment B (12 week treatment) group one patient had received ciclopirox shampoo once weekly and the other patient had received vehicle shampoo (serum level considered artifact). The serum levels ranged between ———. The highest concentration was found in a patient in the twice per week segment A group.

The applicant stated that the serum concentrations found in one of the patients after 12 weeks of prophylactic treatment with the vehicle shampoo following treatment with ciclopirox 1% shampoo twice weekly for 4 weeks was an artifact because the urine sample of the same patient was drug free. The urine sample of the second patient who had measurable serum concentrations (not considered an artifact) was also drug free, so this argument although possible is not entirely correct.

**Urine** Reproduced in the table below are the results of the urine pharmacokinetic analysis which indicate that the % of the dose of ciclopirox excreted was also < 1 % for both the 4 week and 12 week treatment further demonstrating low systemic exposure.

Table 6:

Visit No. and dosing regimen	No. of patients with samples ≥ LOQ / No. of patients sampled	Range of Amount excreted (µg)	Median Amount Excreted (µg)	Mean (SD) Amount Excreted (µg)	% of Dose <sup>1</sup>
<b>4 (after 4 weeks treatment) Segment A</b>					
Ciclopirox twice weekly	75/98 (77%)		240.1	359.1 (359.5)	0.48, <b>0.72</b>
Ciclopirox once weekly	64/102 (63%)		259.0	421.0 (454.2)	0.52, <b>0.84</b>
Vehicle Shampoo	6/52 (12%)		34.6	36.9 (12.5)	NA
<b>6 (after an additional 12weeks) Segment B</b>					
Ciclopirox once weekly	18/31 (58%)		241.7	350.8 (360.7)	0.48, <b>0.70</b>
Ciclopirox once every second week	18/29 (62%)		137.2	258.1 (275.2)	0.27, <b>0.52</b>
Vehicle Shampoo	2/27 (7.4%)		90.8	90.8 (109.4)	NA

<sup>1</sup>% Dose of median in Bold and of mean in Bold Italics

The results in the above table indicate that:

- The urinary data results although supportive in terms of demonstrating low systemic levels of ciclopirox, are more suggestive than definitive due to the extremely high variability (greater than obtained with study #'s 201 and 202) associated with the parameters as reflected in the standard deviation and the range.
- Nine samples from 6/52 patients in the vehicle group after 4 weeks treatment and 2/27 patients in the vehicle group after 12 weeks of treatment had measurable urinary ciclopirox levels. The applicant stated that for one of these patients in the 4 week treatment group this was caused by a ciclopirox concomitant medication (Batrafen vaginal cream) and, that the other of these findings was probably due to interference by food and spices not controlled in this study.

Would ciclopirox accumulate during clinical use as the shampoo and, what levels of systemic exposure would be expected?

Based on the results of the three pharmacokinetic studies, there was negligible accumulation of ciclopirox during clinical use as the shampoo. In study 201, the serum findings were consistent with the urine findings in that both suggested that there was possibly a lower systemic absorption of ciclopirox on day 29 as compared with day 1 indicating that there was negligible accumulation of ciclopirox by day 29. This was further demonstrated in study 202 in which the serum and urine results also suggested that negligible accumulation of ciclopirox occurred by day 29. Also in study 3001 the serum and urine data suggested that there was a very little reduction in systemic absorption after an additional 12 weeks of treatment once weekly as compared to after 4 weeks of treatment once weekly.

The maximum serum ciclopirox concentration observed was 39 ng/ml from the three human studies data submitted in this application. According to the pharmacologist (Dr. M. Kumar) of HFD-540, systemic toxicity has not been observed in any of the non-clinical topical studies but have been observed in oral studies in rats and dogs. For oral doses, the NOEL in both rats and dogs was 10 mg/kg. Oral doses of 30 mg/kg and higher caused mortality and degenerative changes (especially heart and liver). The serum concentrations of ciclopirox measured at the NOEL ranged between \_\_\_\_\_ in rats and dogs and the serum drug levels associated with the systemic toxicity at 30 mg/kg/day ranged between \_\_\_\_\_. This maximum serum ciclopirox concentration observed in the 3 studies submitted was 72 – 90 times lower than the serum level observed at NOEL in rats and dogs and 126 – 4741 fold lower than the toxicological drug level observed in animal studies. Also the serum levels obtained with the vehicle shampoo due to the use of other topical ciclopirox containing products during the study were much lower than the toxicological levels obtained in animal studies.

### VIII. Conclusions

Based on the serum and urine findings of the three human pharmacokinetics and bioavailability studies included in this application, the maximum serum ciclopirox levels during clinical use as the shampoo was  $\leq 39$  ng/ml. This value is much lower than the

toxicological drug level (4,920 and 18,490ng/ml in rats and dogs) observed in animal studies after oral administration.

**IX. Labeling Comments**

1. Label

The proposed label included in the proposed package insert under the heading Pharmacokinetics and Pharmacodynamics should be rewritten as follows: (reviewer's recommended additions are identified by "shaded text" and deletions by "strike out"):

**Pharmacokinetics**

2. In future submissions if the applicant decides to specify median amounts or percentages in the label the range should also be specified so as to have the values within a meaningful context.

AA  
ISI  
07-28-00

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Abimbola O. Adebowale Ph.D.  
Office of Clinical Pharmacology /Biopharmaceutics  
Division of Pharmaceutical Evaluation III

RD/FT signed by Dennis Bashaw, Pharm.D.

S  
S/C/O

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CC:  
NDA 21-159  
HFD-540 (Div. File)  
HFD-540 (CSO/Lutwark)  
HFD-880 (Bashaw)  
HFD-880 (Lazor)  
HFD-880 (Adebowale)  
HFD-340 (Viswanathan)  
CDR: ATTN: Barbara Murphy

**APPENDIX**

**APPEARS THIS WAY  
ON ORIGINAL**

NDA 21159

*A table of the Results of the Validation Parameters for Studies # 201 & 202*

Validation Parameters	Serum	Urine
Range		
Specificity	N	
Linearity		
Precision		
Accuracy		
Sensitivity		
Retention times	Ciclopirox-methyl derivative ~ 5.8 mins Internal Standard Methyl derivative ~ 9.3 mins	Ciclopirox-methyl derivative ~ 5.9 mins Internal Standard Methyl derivative ~ 9.6 mins
Stability	Ciclopirox unconjugated and glucuronide were found to be stable (< 10% change in concentration) @ 23°C and 37°C after 6 & 24 hrs light protected storage, 3 freeze thaw cycles and, after storage @ <-15°C for 1.5yrs.	

Table 3: In study validation for study # 3001

	Serum			Urine		
	Range (ng/ml)	Precision (%CV)	Accuracy (%CV)	Range (ng/ml)	Precision (%CV)	Accuracy (%CV)
Calibration standards						
QC						

Study Abstract Sheet

NDA #: 21-159

Title: Study on the serum and urine pharmacokinetics, safety and efficacy of ciclopirox 1% shampoo after single and repeated single dose treatment of patients suffering from seborrhoeic dermatitis

Study No: HOE296B/2/D/201/SE Volume: 1.9

Investigator:

Study Center:

Study Date: 10<sup>th</sup> April, 1995 to 14<sup>th</sup> August 1995

Phase: II

Objectives: *Primary:* To determine the pharmacokinetic characteristics of ciclopirox after single and repeated single dosing of 5 ml 1 % shampoo in patients with seborrhoeic dermatitis. (2) To measure the urinary excretion of total ciclopirox during 24h after single and repeated single dose treatment.

*Secondary* To evaluate the efficacy of ciclopirox treatment in seborrhoeic dermatitis by assessment of changes in scaling, itching, inflammation, area affected and additional description (moistening, pustules, scratch marks). (2) To evaluate the safety by assessing local reactions, hematology, clinical chemistry, urinalysis and adverse events.

Formulations: HOE296B Ciclopirox Shampoo 1%; batch No. 1-263 (Hoechst Batch No. 8) and, Placebo Shampoo without ciclopirox; batch No. 1-263 (Hoechst Batch No. 5)

Study Design: Single Center, Open-label, Single and Repeated Single dose study

Treatments: 5ml (~ 50 mg of ciclopirox) was used twice weekly for 4 weeks. For daily use during the run-in phase as well as during treatment phase (on no treatment days) the placebo shampoo was used.

Subjects: Eighteen (18) Caucasian patients (4 female and 14 male) with seborrhoeic dermatitis, mean age  $42 \pm 13$  (range 22-65) years old, mean weight  $74.4 \pm 9.4$  (range 61 – 98) Kg and, mean height  $173 \pm 9$  (range from 149 – 187) cm, completed the study (of the 20 included). The applicant stated that for the 2 dropouts, one was because it was impossible to insert a venous cannula for blood sampling into the forearm, and the other was because of a concomitant bronchitis that required treatment. The percentage of scalp area affected at baseline ranged from 20 – 30 % (1 patient), 30 – 50% (4 patients) and, 50-75% (8 patients) and, 75-100% (5 patients).

Assay:

Methods	Sensitivity (LLOQ)	Precision	Accuracy

PK Sampling:

Biological Fluid	Sampling times
Serum (12 ml)	Day 1: pre-dose, 0.5, 1, 2, 3, 6, 8, 12 and 24 hrs p.a. Day 18 and 25 : 1 blood sample Day 29: same as day 1
Urine	Day 1: pre-dose, 0-4, 4-8, 8-12 and 12-24 h p.a. Day 29: same as day 1

Data Analysis:

*Pk Analysis:* Due to a large number of serum concentrations of total (free and conjugated) ciclopirox below LOQ, an evaluation of pharmacokinetic characteristics based on serum concentrations was not performed. For urine the concentrations of total ciclopirox and the corresponding volumes excreted during the sampling periods were calculated to determine the percentage of dose excreted in 24 hours.

*Statistical Analysis:* The cumulated amounts of total ciclopirox excreted in the urine on study days 1 and 29 were compared after log-transformation and equivalence was tested for by calculating the 90% confidence interval (criteria between 80-125%)

Results:

- *Serum:* Serum concentrations of total ciclopirox (free and conjugated) above LOQ were quantifiable in 9/702 samples (7 day 1 and 2 on day 29) in 6/18 patients. No pharmacokinetic parameters were evaluated from the serum data due to insufficient data points. Reproduced in the table below is a summary of the frequency distribution and concentration ranges of measured serum concentrations of total ciclopirox

Day	No. of Samples (N = 6/18 patients)	Time (h)	Serum Concentration Range (ng/ml)
1	7/702	0.5-1.0	
29	2/702	0.5	

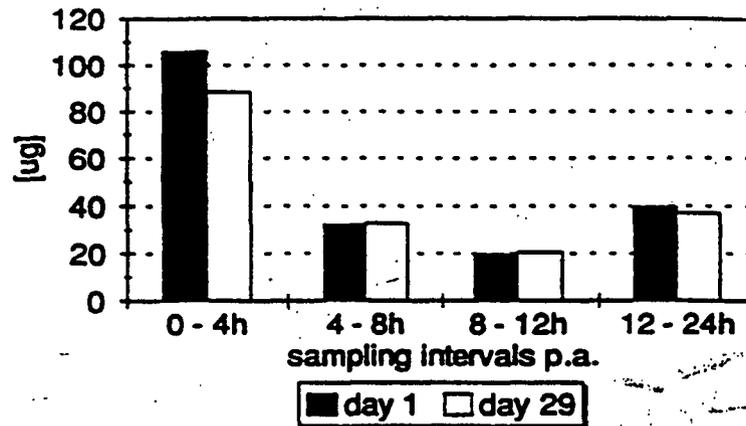
- The serum results also, suggested that there was probably a lower systemic absorption on day 29 as compared to day 1.

*Urine* Reproduced in the table below are the results of the urine pharmacokinetic analysis.

Study day	Mean (SD) Amount ( $\mu\text{g}$ ) Excreted of Total Ciclopirox					Mean Cumulative amount Excreted ( $\mu\text{g}$ )	% of Dose	Mean Geometric mean and 90% CI (day 1/day 29)
	0 h	0-4h	4-8h	8-12h	12-24h			
Day 1	<LOQ	123.1 (74.1)	35.6 (14.6)	18.6 (8)	43.6 (16)	220.9 (97.1)	0.44 (0.19)	
Day 29	3.5 (7.8)	92.3 (47.5)	38.6 (21.1)	22.3 (14.8)	37.9 (19.8)	192.2 (83.7)	0.38 (0.17)	86.67 (74.30-101.10 %)

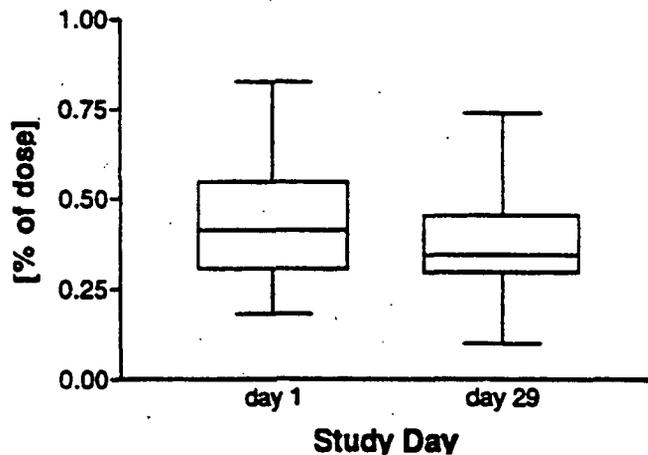
The results in the above table indicate that

- The cumulative amount excreted of total ciclopirox on day1 was  $220.9 \pm 97.1 \mu\text{g}$  ( $0.44 \pm 0.19$  % of the dose) and on day 29 it was  $192.2 \pm 83.7 \mu\text{g}$  ( $0.38 \pm 0.17$  % of the dose) suggesting that there was lower systemic absorption of about 13% on day 29 as compared to day 1.
- The lower systemic absorption on day 29 as compared with day 1 was further demonstrated by the 90% CI (74.30% -101.10% for day 29/day1) for urinary excretion of total ciclopirox which was outside the CI (80-125%) criteria specified by the applicant for equivalence.
- The urine results are consistent with the serum findings with regards to lower systemic absorption on day.29 as compared with day 1.
- The serum and urine results also indicate that no accumulation of ciclopirox occurred by day 29.
- Similarly, the median (range) amounts of total ciclopirox excreted in the urine during 24h p.a. on day 1 [207.8 ( )  $\mu\text{g}$  and (0.42 ( ) of administered dose] was higher than day 29 [172.8 ( )  $\mu\text{g}$  and 0.35 (0.1 – 0.74) % of administered dose)].



**Figure 1** Bar graph of the median amounts of total ciclopirox excreted for day 1 and day 29 by the four different sampling times

- The above graph also shows that the greatest median amount was excreted during the 0-4h interval, and the least amount was excreted during the 8-12h interval.



**Figure 2** Box plot of the cumulated amount of total ciclopirox as a percentage of dose excreted during 24 h p.a. on study days 1 and 29.

- The above graphs further demonstrate that the systemic absorption on day 29 was lower than the systemic absorption on day 1.
- Also the median pH values for the sampling periods were between 5.77 – 6.49 on day 1 and 5.68 – 6.19 on day 29, being fairly consistent imply that there were no extremely outlying pH values influencing urinary excretion of ciclopirox

**Safety:** Applicant reported that only 2 adverse events (earache and bronchitis) which were both not drug related occurred during the study period. (This is to be confirmed by the medical reviewer)

**Conclusions:**

- Following single and repeated single systemic administration of ciclopirox 1% shampoo to patients with seborrhoeic dermatitis serum concentrations were measurable in 6 out of 18 patients (7 day 1 and 2 on day 29) with a maximum serum concentration of —. The serum findings were consistent with the urine findings in that 0.44% of the dose administered was excreted on day 1 over a 24 hour period and 0.38 % was excreted over the same period on day 29.
- The serum and urine findings demonstrated that there was possibly a higher systemic absorption of ciclopirox on day 1 as compared with day 29 and that there was negligible accumulation.

PHARMACOKINETICS SERUM

TREATMENT: CICLOPIROX 1 & SHAMPOO AND PLACEBO

	Study Day 1		Study Day 29	
	Noni- nal Time HH.HH	Total Ciclo- pirox µG/L	Noni- nal Time HH.HH	Total Ciclo- pirox µG/L
Patient no.				
001				
002				
003				
004				
005				
006				
007				
208				
009				
010				
011				
012				
013				
014				
015				
016				
017				
018				
100*				

LOQ (LIMIT OF QUANTITATION):  
\* = DROP OUT.

ng/ml

TABLE 1: SERUM CONCENTRATIONS OF TOTAL CICLOPIROX.

Sponsor Code: HOE296B/2/D/201/SE  
 Code : ACD 9401

INN: Ciclopirox  
 September 1995

Subj. No.	Ae(ur,24 h) [ug]	Ae(ur,24 h) [%]
001		
002		
003		
004		
005		
006		
007		
208		
009		
010		
011		
012		
013		
014		
015		
016		
017		
018		
MEAN	220.923	0.4418
SDEV	97.067	0.1941
GEO. MEAN	201.013	0.4020
DISPERS.	1.577	1.5768
LOW. CON.		
UPP. CON.		
MEDIAN	207.839	0.4157
MIN		
MAX		
COUNT	18.000	18.0000

Table 22

Renal elimination of total ciclopirox following administration of HOE 296B (Shampoo 1%) on study day 1 (total dose: 5 ml = 50 mg Ciclopirox).

Cumulative amount of total ciclopirox excreted [ug] and [%] (% of dose).

Single Values, Arithmetic Means, Standard Deviations, Geometric Means, Dispersion Factors, 95% Confidence Limits of Geometric Mean, Medians, Minimum, Maximum and Number of Cases.

Sponsor Code: HOE296B/2/D/201/SE  
 Code : ACD 9401

INN: Ciclopirox  
 September 1995

Subj. No.	Ae(ur,24 h) [ug]	Ae(ur,24 h) [%]
001		
002		
003		
004		
005		
006		
007		
208		
009		
010		
011		
012		
013		
014		
015		
016		
017		
018		
MEAN	192.190	0.3844
SDEV	83.704	0.1674
GEO.MEAN	174.225	0.3484
DISPERS.	1.616	1.6156
LOW.CON.		
UPP.CON.		
MEDIAN	172.836	0.3457
MIN		
MAX		
COUNT	18.000	18.0000

Patient 003 and 007: no urine voided during sampling period 8-12 h p.a.

Table 23

Renal elimination of total ciclopirox following administration of HOE 296B (Shampoo 1%) on study day 29 (total dose: 5 ml = 50 mg Ciclopirox).

Cumulative amount of total ciclopirox excreted [ug] and [%] (% of dose).

Single Values, Arithmetic Means, Standard Deviations, Geometric Means, Dispersion Factors, 95% Confidence Limits of Geometric Mean, Medians, Minimum, Maximum and Number of Cases.

Sponsor Code: HOE296B/2/D/201/SE - 95 -  
Code: ACD 9401

Page 9

INN: Ciclopirox  
January 1997

Sponsor Code: HOE296B/2/D/201/SE INN: Ciclopirox  
Code: ACD 9401 September 1995

90% CONFIDENCE LIMIT AND TEST OF BIOEQUIVALENCE

Parameter	MS Error (ANOVA)	geo.mean 100*day 29 /day 1	lower limit	upper limit
Ae(ur,24 h)	0.070527	86.673507	74.303136	101.103362

Student's t for  $\alpha=0.05$  (one tailed) and DF=17 : 1.739607  
18 subjects

day 1: administration of 50 mg of  
HOE 296B (Shampoo 1%)  
(total dose: 5 ml = 50 mg Ciclopirox) on day 1  
day 29: administration of 50 mg of  
HOE 296B (Shampoo 1%)  
(total dose: 5 ml = 50 mg Ciclopirox) on day 29

Table 26

90% confidence limit for Ae(ur,24 h) [ug] of total Ciclopirox

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**Study Abstract Sheet**

**NDA #:** 21-159

**Title:** Study on the serum and urine pharmacokinetics, safety and efficacy of ciclopirox 1% shampoo after exaggerated use with increasing contact time in patients suffering from seborrhoeic dermatitis

**Study No:** HOE296B/2/D/202/SE **Volume:** 1.10-1.11

**Investigator:** \_\_\_\_\_

**Study Center:** \_\_\_\_\_

**Study Date:** 02 June 1997 to 21st September 1997

**Phase:** II

**Objectives:** *Primary:* To determine the serum concentrations and if possible the pharmacokinetic characteristics of total ciclopirox in patients with seborrhoeic dermatitis after single dosing of 1 % shampoo with 3 minutes contact time and after multiple dosing with 3 and 6 minutes contact time. 2) To measure the urinary excretion of total ciclopirox during 24h after single dosing of 1 % shampoo with 3 minutes contact time and after multiple dosing with 3 and 6 minutes contact time.  
*Secondary* To evaluate the efficacy of ciclopirox treatment in seborrhoeic dermatitis by assessment of status and change of seborrhoeic dermatitis A. Itching score, B. Scaling score, C. Inflammation score, sum of scores A-C and response rate based on score "Status of seborrhoeic dermatitis" at individual endpoint. 2) To evaluate the safety by assessing local reactions, hematology, clinical chemistry, urinalysis creatinine clearance, 12-lead ECG's, 24-h Holter recording and adverse events.

**Formulations:** HOE296B Ciclopirox Shampoo 1% ( \_\_\_\_\_ ); batch No. 1-263 (Hoechst Batch No. 18) and, \_\_\_\_\_ Shampoo for normal and oily hair in 400ml bottles (mild shampoo without anti-ptyrosporal activity).

**Study Design:** Multi Center, Open-label, uncontrolled with repeated measurements of serum concentrations (after single dosing with 3 minutes contact time and after multiple dosing with 3 as well as 6 minutes contact time).

**Treatments:** 5ml (~ 50 mg of ciclopirox) was used daily with a contact time of 3 minutes for the first 15 days and then 6 minutes for the following 14 days (total = 29 days). Medical staff administered the shampoo on days 1, 15 and 29. For daily use during the run-in phase as well as additional use during treatment phase, the \_\_\_\_\_ shampoo was used.

**Subjects:** Fourteen (14) Caucasian patients (5 female and 9 male) with seborrhoeic dermatitis, mean age  $35 \pm 12$  (range 18-58) years old, mean weight  $79.6 \pm 10.4$  (range 65 – 97) Kg and, mean height  $175 \pm 10$  (range from 156 –189) cm. 12 patients completed the study. For the two dropouts the applicant stated that one was due to technical reasons not making the holter ECG evaluable and the other was due to ventricular tachycardia on day 15 of trial. The percentage of scalp area affected at baseline ranged from 20 – 30 % (1 patient), 30 – 50% (5 patients) and, 50-75% (6 patients).

**Assay:**

Methods	Sensitivity (LLOQ)	Precision	Accuracy

**PK Sampling:**

Biological Fluid	Sampling times
Serum (12 ml)	Day 1: pre-dose, 0.25 0.5, 0.75 1, 2, 4 and 6 hr p.a. Day 15 and 29 : same as day 1
Urine	Day 1: pre-dose, 0-4, 4-6, 6-12 and 12-24 hr p.a. Day 15 and 29: same as day 1

**Data Analysis:** *Pk Analysis:* Due to a large number of serum concentrations of total (free and conjugated) ciclopirox below LOQ, an evaluation of pharmacokinetic characteristics based on serum concentrations was not performed. For urine the concentrations of total ciclopirox and the corresponding volumes excreted during the sampling periods were calculated to determine the percentage of dose excreted in 24 hours.

*Statistical Analysis:* The areas, maximum concentrations (days 1, 15 & 29) were log transformed and compared by one-sided Dunnett's t-test and also log transformed trough concentrations (days 15 & 29) were compared by a paired t-test. All statistical tests were conducted at the 5% level of significance.

**Results:** *Serum:* Serum concentrations of total ciclopirox (free and conjugated)  $\geq$  LOQ were quantifiable in (32.3%) on day 1 (18.8%) on day 15 and, (41.7%) on day 29 of samples. The serum concentrations were all below the LOQ after the 2 hour sampling time interval on days 1, 15 and 29. No pharmacokinetic parameters were evaluated from the serum data due to the large number of serum concentration samples below LOQ. Reproduced in the table below is a summary of the frequency distribution and

concentration ranges of measured serum concentrations of total ciclopirox (Copies of individual data are attached in the Appendix pages ).

Day	Contact time of shampoo (min)	No. of Samples	No. of patients	Time (h) after exposure with shampoo	Serum Ciclopirox Concentration Range (ng/ml)
1	3	31/96	9/12	0.25-2.0	—
15	3	18/96	6/12	0.25-1.0	—
29	6	40/96	11/12	0.25-2.0	—

- The serum results suggest that there was probably a higher systemic absorption on day 1 as compared to day 15 with the 3 minutes contact time.
- The serum results suggest that there was probably a slightly higher systemic absorption on day 29 as compared to day 1, probably due to the doubling of the contact time (to 6 minutes).

*Urine*

Reproduced in the table below are the results of the urine pharmacokinetic analysis. (Copies of individual data are included in the Appendix).

Study Day	Contact Time (min)	Mean (SD) Amount (µg) Excreted of Total Ciclopirox				Mean (SD) Cumulative amount Excreted (µg)	% of Dose
		0-4h	4-6h	6-12h	12-24h		
Day 1	3	345.4 (312.3)	53.8 (23.7)	94.7 (34.6)	87.8 (43.5)	581.6 (343.0)	1.16 (0.69)
Day 15	3	223.0 (59.3)	54.2 (20.1)	103.8 (29.1)	95.0 (61.1)	476.0 (129.3)	0.95 (0.26)
Day 29	6	330.8 (128.9)	65.8 (41.5)	107.6 (45.5)	135.1 (121.0)	639.3 (243.2)	1.28 (0.49)
<sup>1</sup> Geometric mean quotient and 90% CI for % of dose of total ciclopirox excreted Day 15/Day 1: 89.72 (66.6 - 122.3%) p = 0.2880 (NS) Day 29/Day 1: 115.4 (81.4 - 163.0%) p = 0.1740 (NS)							

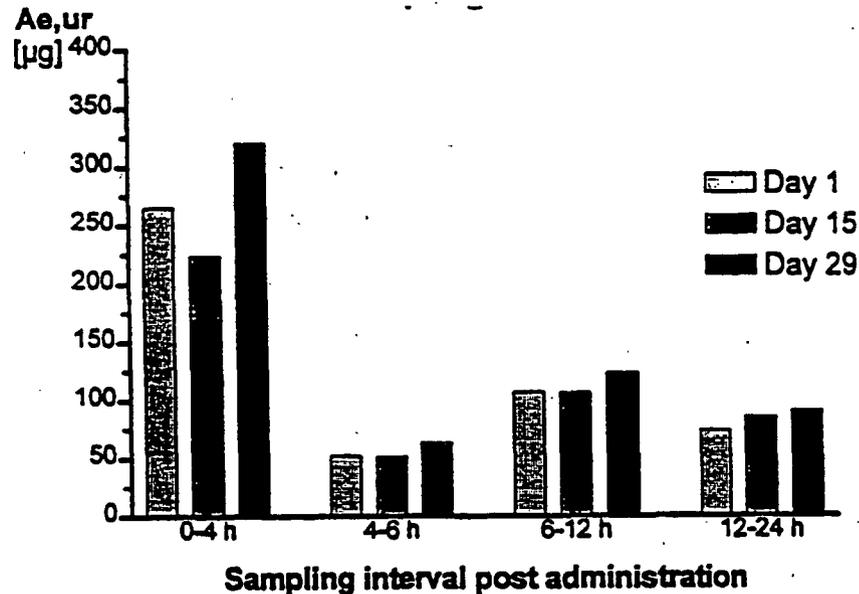
<sup>1</sup>Geometric mean quotient = 100 \* geometric mean (day 15 or 29/day 1)

<sup>2</sup>NS = not significant

The results in the above table indicate that

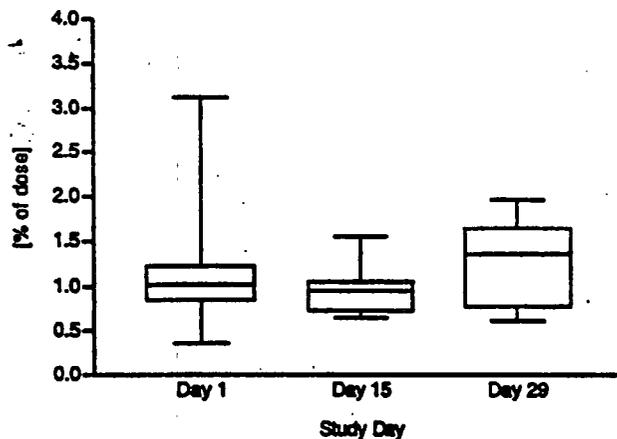
- The cumulative amount excreted of total ciclopirox on day 1 (581.6 ± 343.0 µg (1.16 ± 0.69 % of the dose)) and, on day 15 (476.0 ± 129.3 µg (0.95 ± 0.26 % of the dose)) suggested that there was lower systemic absorption of about 18 % on day 15 as compared to day 1.
- On the other hand the cumulative amount excreted of total ciclopirox on day 15 ((476.0 ± 129.3 µg (0.95 ± 0.26 % of the dose)) and, on day 29 (639.3 ± 243.2 µg (1.28 ± 0.49 % of the dose)) suggested that doubling the contact time increased (but did not double) the amount absorbed.

- The statistical comparison of the fractions of dose [%] of topical ciclopirox excreted during 24 h p.a. on study days 1, 15 and 29, did not show significant differences between the three days.
- The median pH values for the sampling periods were between 5.68 – 6.72 on day 1, 5.76 – 6.53 on day 15 and, 5.40 – 6.58 on day 29, (lowest 0-4h and highest 6-12h). The pH being fairly consistent suggested that the urinary excretion of ciclopirox was not influenced by the changes in pH during the study period.
- The urine results are consistent with the serum findings with regards to lower systemic absorption on day 15 as compared with day 1 and the slight increase on day 29.
- The serum and urine results also suggest that negligible accumulation of ciclopirox occurred by day 29.



**Figure 1** Bar graph of the median amounts of total ciclopirox ( $A_{e,ur}$ ) excreted for day 1 15 and 29 by the four different sampling times

- Similarly, the median (range) cumulative amount excreted during 24h p.a. of total ciclopirox on day 1 [511.9 ( — ) µg (1.02 (0.4 – 3.1) % of the dose)], was higher than on day 15 [477.5 ( — ) µg (0.96 (0.6 – 1.6) % of the dose)] and lower than on day 29 [679.7 ( — ) µg (1.36 (0.6 – 2.0)% of the dose)]. Above is a graphical representation of the median amounts excreted for the sampling time intervals.



**Figure 2** Box and whisker plot of the cumulated amount of total ciclopirox as a percentage of dose excreted during 24 h p.a. on study days 1, 15 and 29.

- The above plots further demonstrate that the systemic absorption on day 15 was lower than the systemic absorption on day 1, but slightly higher on day 29.

**Safety:** Applicant reported that only 4 adverse events (allergic conjunctivitis, upset stomach, non sustained ventricular tachycardia and lumbalgia) in 3 patients who were not drug related occurred during the study period. (This is to be confirmed by the medical reviewer)

**Conclusions:**

- Following single and multiple (with different contact times) systemic administration of ciclopirox 1% shampoo to patients with seborrhoeic dermatitis the maximum serum concentration was — (day 1), — (day 15) — (day 29). The serum findings were consistent with the urine findings in that ~1.16%, 0.95 % and 1.28 % of the dose administered respectively was excreted on days 1, 15 and 29 over a 24 hour period.
- The serum and urine findings suggested that there was possibly a higher systemic absorption of ciclopirox on day 1 as compared with day 15 suggesting that by day 15 skin conditions might have improved leading to reduced systemic absorption. On the other hand, data from days 15 and 29 suggested that doubling the contact time increased (but did not double) the amount absorbed. This was however complicated by possible continued improvement of skin conditions.
- The urinary excretion data however, indicated that there was no statistically significant difference in the fraction of dose excreted on days 1, 15 and 29 despite the doubled time of exposure.

Sponsor Code: HOE296B/2/D/202/SE 5  
Code: ACD 9402  
INN: Ciclopirox

July 1999  
Appendix 2

Time [h]:	0.00	0.25	0.50	0.75	1.00	2.00	4.00	6.00
Subj.No.								
001								
002 *								
003								
004 *								
005								
006								
007								
008 <J								
009								
010								
011								
012								
013								
014								
MEDIAN	.	7.8	13.7	14.7	12.5	.	.	.
MEAN	.	11.2	14.3	13.9	11.3	.	.	.
SDEV	.	7.7	9.1	7.9	6.9	.	.	.
CV%	.	69.1	63.2	56.8	61.1	.	.	.
GEO.MEAN	.	9.1	11.7	11.7	9.6	.	.	.
DISPERS.	.	1.9	2.0	1.9	1.8	.	.	.
MIN								
MAX								
COUNT	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0

\* : Drop out, not used for evaluation  
<10.0: below the limit of quantification  
n.s. : no sample

Table 2.1

Concentrations of total ciclopirox [ $\mu\text{g/L}$ ] following administration of HOE296B (Shampoo 1%) on study day 1 (total dose: 5 mL = 50 mg ciclopirox, contact time: 3 minutes).

Single values, Medians, Arithmetic Means, Standard Deviations, Coefficients of Variation, Geometric Means, Dispersion Factors, Minima, Maxima and Number of Cases:

No calculations performed if less than 1/2 of the individual concentrations are  $\geq 10$ . Concentrations  $< 10$  calculated as 5.

Handwritten signature or initials.

Sponsor Code: HOE296B/2/D/202/SE 6  
Code: ACD 9402  
INN: Ciclopirox

July 1999  
Appendix 2

Time [h]:	0.00	0.25	0.50	0.75	1.00	2.00	4.00	6.00
Subj.No.								
001								
003								
004 *								
005								
006								
007								
008								
009								
010								
011								
012								
013								
014								
MEDIAN	.	.	.	.	.	.	.	.
MEAN	.	.	.	.	.	.	.	.
SDEV	.	.	.	.	.	.	.	.
CV%	.	.	.	.	.	.	.	.
GEO.MEAN	.	.	.	.	.	.	.	.
DISPERS.	.	.	.	.	.	.	.	.
MIN	.	.	.	.	.	.	.	.
MAX	.	.	.	.	.	.	.	.
COUNT	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0

\* : Drop out, not used for evaluation  
<10.0: below the limit of quantification

Table 2.2

Concentrations of total ciclopirox [ $\mu\text{g/L}$ ] following administration of HOE296B (Shampoo 1%) on study day 15 (total dose: 5 mL = 50 mg ciclopirox, contact time: 3 minutes).

Single values, Medians, Arithmetic Means, Standard Deviations, Coefficients of Variation, Geometric Means, Dispersion Factors, Minima, Maxima and Number of Cases.

No calculations performed if less than 1/2 of the individual concentrations are  $\geq 10$ .

Sponsor Code: HOE296B/2/D/202/SE 7  
Code: ACD 9402  
INN: Ciclopirox

July 1999  
Appendix 2

Time (h):	0.00	0.25	0.50	0.75	1.00	2.00	4.00	6.00
Subj.No.								
001								
003								
005								
006								
007								
008								
009								
010								
011								
012								
013								
014								
MEDIAN			13.1	16.3	16.4	8.0		
MEAN			18.0	16.7	15.5	8.7		
SDEV			11.8	8.1	6.2	4.0		
CVA			65.8	48.3	39.9	45.5		
GEO. MEAN			14.6	14.6	14.0	7.8		
DISPERS.			2.0	1.8	1.7	1.6		
MIN								
MAX								
COUNT	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0

<10.0: below the limit of quantification

Table 2.3

Concentrations of total ciclopirox [ $\mu\text{g/L}$ ] following administration of HOE296B (Shampoo 1%) on study day 29 (total dose: 5 mL = 50 mg ciclopirox, contact time: 6 minutes).

Single values, Medians, Arithmetic Means, Standard Deviations, Coefficients of Variation, Geometric Means, Dispersion Factors, Minima, Maxima and Number of Cases.

No calculations performed if less than 1/2 of the individual concentrations are  $\geq 10$ . Concentrations < 10 calculated as 5.

Sponsor Code: HOE296B/2/D/202/SE 18  
 Code: ACD 9402  
 INN: Ciclopirox

July 1999  
 Appendix 3

Subj. No.	Ae(ur,24 h) [µg]	Ae(ur,24 h) [%]
001		
002 *		
003		
004 *	—	
005		
006		
007		
008		
009		
010	—	
011		
012		
013		
014		
<b>MEDIAN</b>	511.89	1.0238
<b>MEAN</b>	581.64	1.1633
<b>SDEV</b>	343.00	0.6860
<b>CV [%]</b>	58.97	58.9720
<b>GEO.MEAN</b>	514.24	1.0285
<b>DISPERS.</b>	1.66	1.6610
<b>MIN</b>		
<b>MAX</b>	—	
<b>COUNT</b>	12.00	12.0000

*Ciclopirox 1% Shampoo*  
*Study Report*

\*: Drop out, not used for evaluation

Table 4.7

Renal elimination of total ciclopirox following administration of HOE296B (Shampoo 1%) on study day 1 (total dose: 5 mL = 50 mg ciclopirox, contact time: 3 minutes).

Cumulative amount of total ciclopirox excreted [µg] and [%] (% of dose).

Single values, Medians, Arithmetic Means, Standard Deviations, Coefficients of Variation, Geometric Means, Dispersion Factors, Minima, Maxima and Number of Cases.

Sponsor Code: HOE296B/2/D/202/SE 19  
 Code: ACD 9402  
 INN: Ciclopirox

July 1999  
 Appendix 3

Subj. No.	Ae(ur, 24 h) [µg]	Ae(ur, 24 h) [%]
001		
003		
004		
005		
006		
007		
008		
009		
010		
011		
012		
013		
014		
-----		
MEDIAN	477.507	0.9550
MEAN	476.002	0.9520
SDEV	129.251	0.2585
CV [%]	27.153	27.1534
GEO. MEAN	461.356	0.9227
DISPERS.	1.293	1.2932
MIN		
MAX		
COUNT	12.000	12.0000

\*: Drop out, not used for evaluation

Table 4.8

Renal elimination of total ciclopirox following administration of HOE296B (Shampoo 1%) on study day 15 (total dose: 5 mL = 50 mg ciclopirox, contact time: 3 minutes).

Cumulative amount of total ciclopirox excreted [µg] and [%] (% of dose).

Single values, Medians, Arithmetic Means, Standard Deviations, Coefficients of Variation, Geometric Means, Dispersion Factors, Minima, Maxima and Number of Cases.

Sponsor Code: HOE296B/2/D/202/SE

20

July 1999

Code: ACD 9402

Appendix 3

INN: Ciclopirox

Subj. No.	Ae(ur, 24 h) [µg]	Ae(ur, 24 h) [%]
001		
003		
005		
006		
007		
008		
009		
010		
011		
012		
013		
014		
-----		
MEDIAN	679.722	1.3594
MEAN	639.334	1.2787
SDEV	243.153	0.4863
CV [%]	38.032	38.0322
GEO. MEAN	593.652	1.1873
DISPERS.	1.513	1.5129
MIN		
MAX		
COUNT	12.000	12.0000

Table 4.9

Renal elimination of total ciclopirox following administration of HOE296B (Shampoo 1%) on study day 29 (total dose: 5 mL = 50 mg ciclopirox, contact time: 6 minutes).

Cumulative amount of total ciclopirox excreted [µg] and [%] (% of dose).

Single values, Medians, Arithmetic Means, Standard Deviations, Coefficients of Variation, Geometric Means, Dispersion Factors, Minima, Maxima and Number of Cases.

Sponsor Code: HOE296B/2/D/202/SE 22  
Code: ACD 9402  
INN: Ciclopirox

July 1999  
Appendix 3

The SAS System

General Linear Models Procedure

Dunnett's One-tailed T tests for variable: LN\_FRACT

NOTE: This tests controls the type I experimentwise error for comparisons of all treatments against a control.

Alpha= 0.05 Confidence= 0.95 df= 22 MSE= 0.144994  
Critical Value of Dunnett's T= 2.017  
Minimum Significant Difference= 0.3135

Comparisons significant at the 0.05 level are indicated by '\*\*\*\*'.

DAY Comparison	Simultaneous Lower Confidence Limit	Difference Between Means	Simultaneous Upper Confidence Limit	p-Value
day 29 - day 1	-0.1699	0.1436	0.4571	0.3741
day 15 - day 1	-0.4220	-0.1085	0.2050	0.2880

day 1 : administration of HOE296B (Shampoo 1%) on study day 1  
(total dose: 5 mL = 50 mg ciclopirox, contact time: 3 minutes)  
 day 15: administration of HOE296B (Shampoo 1%) on study day 15  
(total dose: 5 mL = 50 mg ciclopirox, contact time: 3 minutes)  
 day 29: administration of HOE296B (Shampoo 1%) on study day 29  
(total dose: 5 mL = 50 mg ciclopirox, contact time: 6 minutes)

Table 5

Dunnett's one-tailed t-tests for log (ln) transformed fractions of dose of total ciclopirox excreted [%].

*Multiples comparisons against control*

Study Abstract Sheet

NDA #: 21-159

Title: A randomized, double-blind, multinational, multi-center study of the efficacy and safety of Ciclopirox shampoo in the treatment and seborrheic dermatitis/dandruff of the scalp

Study No: HOE296B/3001 Volume: 1.12

Investigator (s):

Study Center:

Study Date: 23<sup>rd</sup> April, 1997 to 22<sup>nd</sup> June, 1998

Phase: III

Objectives: *Primary:* Segment A: Efficacy of 1-% Ciclopirox shampoo in the therapeutic treatment of seborrheic dermatitis of the scalp  
Segment B: Efficacy of 1-% Ciclopirox shampoo in the prophylaxis of seborrheic dermatitis of the scalp in responders from Segment A.  
*Secondary:* Safety and Tolerability of 1-% Ciclopirox for the same indications.

Formulations: HOE296B (Ciclopirox) Shampoo 1% (Bactraban<sup>®</sup>/Loprox<sup>®</sup>; Batch No. 18, 90 ml bottles Ciclopirox Vehicle (Shampoo base) Batch No. 15 and. — Shampoo for normal and oily hair in 400ml bottles (mild shampoo without anti-pityrosporal activity).

Study Design: Multi Center, Multinational, 3 Parallel groups, Randomized, Double Blind study

Treatments: 5ml to 10ml (~ 50-100 mg of ciclopirox) depending on hair length as follows: *Segment A:* 1% Ciclopirox twice a week vs. 1% ciclopirox once a week vs. vehicle once or twice weekly for 4 wks. *Segment B:* 1% Ciclopirox once a week vs. 1% Ciclopirox once every second week vs. vehicle every week or every second week for 12 weeks. The patients applied all the medication themselves. During the run-in phase (at least twice weekly) as well as during treatment phase (on no treatment days) the — shampoo was used.

Subjects: *Segment A:* Nine hundred and forty nine (949) Caucasian patients (412 female and 537 male) with seborrheic dermatitis of the scalp, with an age range from 18 – 88 years (median 38 years) were randomized into segment A.  
*Segment B:* Four hundred and twenty eight (428) Caucasian patients (184 female and 244 male) segment A responders, with an age range from 18 – 88 years (median 37 years) were continued into segment B.

Assay:

Methods	Sensitivity (LLOQ)	Precision	Accuracy
---------	--------------------	-----------	----------

PK Sampling: monitored in patients at selected centers in

Biological Fluid	Sampling times
Serum (12 ml)	Visit 1 (before administration of the study drug), Visit 4 (final visit of Segment A, end of 4 wks) and visit 6 (final visit of Segment B, end of additional 12 wks)
Urine (10 ml)	Visit 1 (before administration of the study drug), Visit 4 (final visit of Segment A, end of 4 wks) and visit 6 (final visit of Segment B, end of additional 12 wks)

Results:

*Serum:* A total of 629 samples were collected during the study. Serum concentrations of total ciclopirox (free and conjugated) above LOQ were quantifiable in 6/357 (~1.7 %) patients (4/263 patients at end of 4 weeks and 2/94 patients at end of additional 12 weeks). Reproduced in the table below is a summary of the frequency distribution and concentration ranges of measured serum concentrations of total ciclopirox

Visit No.	No. of patients with samples $\geq$ LOQ / No. of patients sampled	No. of Patients (Dosing Regimen)	Serum Concentration Range (ng/ml)
1 (Screening)	0/272 (0%)	none	none
4 (after 4 weeks)	4/263 (1.5%)	3 (1% ciclopirox twice weekly) and 1 (1% ciclopirox once weekly)	—
6 (after 4+12weeks)	2/94 (1.1%)	1 (1% ciclopirox once weekly segments A & B) and 1 (vehicle segment B and ciclopirox twice per week in segment A)*	—

\*The applicant stated that this was an artifact, urine sample of the same patient was drug free.

- The serum concentration results suggest that there was a higher systemic absorption after 4 weeks of treatment once weekly as compared to after an additional 12 weeks of treatment once weekly.
- The applicant stated that the serum concentrations found in one of the patients after 12 weeks of prophylactic treatment with the vehicle shampoo following treatment with ciclopirox 1% shampoo twice weekly for 4 weeks was an artifact because the urine sample of the same patient was drug free. The urine sample of the second

patient who had measurable serum concentrations (not considered an artefact) was also drug free, so this argument although possible is not entirely correct based on the results.

Urine Reproduced in the table below are the results of the urine pharmacokinetic analysis. (Copies of individual data are included in the Appendix).

Visit No. and dosing regimen	No. of patients with samples $\geq$ LOQ / No. of patients sampled	Range of Amount excreted ( $\mu\text{g}$ )	Median Amount Excreted ( $\mu\text{g}$ )	Mean (SD) Amount Excreted ( $\mu\text{g}$ )	% of Dose <sup>1</sup>
<b>4 (after 4 weeks treatment) Segment A</b>					
Ciclopirox twice weekly	75/98 (77%)		240.1	359.1 (359.5)	<b>0.48, 0.72</b>
Ciclopirox once weekly	64/102 (63%)		259.0	421.0 (454.2)	<b>0.52, 0.84</b>
Vehicle Shampoo	6/52 (12%)		34.6	36.9 (12.5)	NA
<b>6 (after an additional 12 weeks) Segment B</b>					
Ciclopirox once weekly	18/31 (58%)		241.7	350.8 (360.7)	<b>0.48, 0.70</b>
Ciclopirox once every second week	18/29 (62%)		137.2	258.1 (275.2)	<b>0.27, 0.52</b>
Vehicle Shampoo	2/27 (7.4%)		90.8	90.8 (109.4)	NA

<sup>1</sup>% Dose of median in Bold and of mean in Bold

The results in the above table indicate that:

- The cumulative amount excreted of total ciclopirox after 4 weeks of treatment in patients who were administered ciclopirox shampoo 1% twice weekly ( $359.1 \pm 421.0 \mu\text{g}$  (~0.72 % of the dose)) was less than those administered once weekly ( $421.0 \pm 454.2 \mu\text{g}$  (~0.84 % of the dose)) suggesting possible skin improvement with increase in frequency of use resulting in lower systemic absorption.
- On the other hand the cumulative amount excreted of total ciclopirox after an additional 4 weeks of treatment in patients who were administered ciclopirox shampoo 1% once weekly ( $350.8 \pm 360.7 \mu\text{g}$  (~0.70 % of the dose)) was greater than those administered once every two weeks ( $258.1 \pm 275.2 \mu\text{g}$  (~0.52 % of the dose)) suggesting possible skin improvement with increase in duration but not frequency of use, resulting in lower systemic absorption.
- These results are however more suggestive than definitive because the variability associated with these urinary data parameters are much higher than obtained with Study #'s 201 and 202 as reflected in the standard deviation.
- Nine samples from 6/52 patients in the vehicle group after 4 weeks treatment and 2/27 patients in the vehicle group after 12 weeks of treatment had measurable urinary ciclopirox levels. The applicant stated that for one of these patients in the 4 week treatment group this was caused by a ciclopirox concomitant medication (Batrafen vaginal cream). The other of these findings

was probably due to interference by food and spices not controlled in this study.

- The serum and urine data obtained with the vehicle shampoo indicate that concomitant use of other topical ciclopirox containing products with ciclopirox shampoo will probably cause an increase in the serum drug levels, and could be a safety concern.

Safety: For safety considerations, we may need to consider patients applying various Loprox products for various dermatological conditions leading to higher serum ciclopirox concentrations than when one product alone is applied.

Conclusions:

- Serum drug levels were only quantifiable in about 2 % of the samples collected, further supporting very low systemic exposure.
- The % of the dose of ciclopirox excreted was also < 1 % for both the 4 week and 12 week treatment further demonstrating low systemic exposure.
- The urinary data results although supportive in terms of demonstrating low systemic levels of ciclopirox, are more suggestive than definitive due to the extremely high variability associated with the parameters.

**APPEARS THIS WAY  
ON ORIGINAL**

Table 9.1.1: HOE 296 in Serum - individual cases  
(all patients from segment A and B from which blood samples were taken)

(LOQ = )

Centre	Patient	Treatment Segment A	Treatment Segment B	Visit	Value [ng/ml]
101	27	Ciclopirox 1x/w		4	
105	37	Ciclopirox 2x/w		4	
	44	Ciclopirox 2x/w		4	
112	22	Ciclopirox 2x/w		4	
113	16	Ciclopirox 2x/w	Vehicle shampoo	6	
206	3	Ciclopirox 1x/w	Ciclopirox 1/w	6	

Total number of patients with blood samples

Screening: 282

Visit 4 (segment A): 263 (104 Cicl. 2 x/w, 106 Cicl. 1 x/w, 53 Vehicle)

Visit 6 (segment B): 94 (32 Cicl. 1 x/w, 31 Cicl. 1 x/2 w, 31 Vehicle)

Note: The drug level measured for patient 16, centre 113 is an artefact.  
The urin sample of the same patient was drug free.

APPEARS THIS WAY  
ON ORIGINAL