Rapport de recherche N°9705

Etude de bioéquivalence d'une administration orale d'un comprimé d'Androcur 100 versus 2 comprimés d'Androcur 50 chez 36 volontaires

Total no. of pages: 35
Date: 09 Jul 1992

Fly Sheet 1

Bioequivalence Trial of Oral Administration of ANDROCUR 100 mg Tablets as Compared to Two ANDROCUR 50 mg Tablets in 36 Young Men

Segment: Oncology	All records and specimens are in the archives of the: Institut für Humanpharmakologie Institut für Pharmakokinetik Institut für Biometrie
Study number: ME 91089 KI 92046	Studies were carried out: from Oct. 1991 to Nov. 1992
ZK number: 9471	Generic name: Cyproterone acetate
SH number: T 548 A, 8.0714-50 MG	Clinical trial phase: I

Purpose of the study

Cyproterone acetate (CPA) is a well known steroid hormone with progestogenic and antiandrogenic properties which is used in various indications, prostate carcinoma being one of them. The commercial preparation (ANDROCUR 50) contains 50 mg CPA/unit. Daily dosages lie between 100 and 200 mg for castrated patients, and between 200 and 300 mg for patients who are not castrated. In order to facilitate treatment and to increase compliance, a new preparation containing 100 mg CPA/unit had been developed. The present study in 36 male volunteers (randomized, cross-over) was carried out in order to examine the bioequivalence of both preparations.

Fly Sheet 2: Summary of the report

Design:

The trial was conducted as an open randomized, intra-individual comparison with two treatments and two sequences (A/B and B/A):

- Treatment A: One tablet of ANDROCUR 100 mg
- Treatment B: Two tablets of ANDROCUR 50 mg

Thirty-six healthy young male volunteers participated in the study and each volunteer was given both treatments. Between the treatments there was a wash-out period of 21 days. The volunteers were randomly allocated to one of the two sequences.

Material and methods:

After each treatment, blood was drawn and serum was prepared at the following time points: prior to drug administration (0 h) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120 h after drug intake.

Serum was kept deep frozen at -20°C until analysis. The concentration of CPA in the serum samples was measured by means of a specific GC/MS method with a lower limit of quantification of 0.5 ng/ml.

Target variables for the assessment of bioequivalence were: C_{max}, t_{max}, AUC(0-120h) and AUC.

Results:

The pharmacokinetic parameters of CPA which were determined following the administration of 1 tablet of ANDROCUR 100 and two tablets of ANDROCUR 50, respectively, are summarized in Table 1. No sequence effect was observed. Both preparations were found to be bioequivalent with respect to the main target variables AUC(0-120h) and AUC. However, based on log transformed data, for the target variables t_{max} and C_{max} the 90 % confidence limits were slightly outside the range of 80 % to 125 %. For t_{max}, the observed range was 88 % to 127 % and for C_{max} the range was between 69 % and 95 %.

Fly Sheet 2: Summary of the report (continued)

Table 1: Pharmacokinetic parameters of CPA (mean ± S.D.) obtained from 35 healthy young men who received a single tablet of ANDROCUR 100 and two tablets of ANDROCUR 50 in a randomized sequence. There was a wash-out phase of 21 days between two treatments.

Parameter		ANDROCUR 100 (1 tablet)	ANDROCUR 50 (2 tablets)
C_{max}	[ng/ml]	241.7 ± 114.9	285.6 ± 105.2
t_{max}	[h]	2.8 ± 1.1	2.6 ± 1.1
$t_{½}$	[h]	42.8 ± 9.7[1]	43.9 ± 12.8
AUC(0-120h)	[ng · ml^{-1} · h]	5646.3 ± 1682.2	5840.1 ± 1553.2
AUC	[ng · ml^{-1} · h]	6557.5 ± 2167.5	6861.7 ± 2078.8

Both formulations were well tolerated with no serious adverse events observed.

Conclusions:

- With regard to the extent of absorption, one tablet of ANDROCUR 100 is bioequivalent to two tablets of ANDROCUR 50.

- Minor differences between both preparations with regard to the rate of absorption are of no clinical relevance.

- ANDROCUR 100 tablets can be used instead of ANDROCUR 50 in clinical therapy

[1] n=36

Fly Sheet 3: Signatures

We declare that to the best of our knowledge this study was conducted in compliance with GCP-standards (see foot notes). No deviations were identified which affect the quality and integrity of the study or the interpretation of the results in this report.

Institut für Biometrie Head: Signature, date 6.11.92	**Institut für Pharmakokinetik** Head: Signature, date Sept. 3, 1992	**Institut für Humanpharmakologie** Head: Signature, date 7.10.92
Fachgebiet Biostatistik Head: Signature, date 6.11.92	**Fachgebiet Sexualsteroide und Massenspektrometrie Pharmakokinetik** Head: Signature, date 1992	**Fachgebiet Herz-Kreislauf, Diagnostik, Zentrallabor Humanpharmakologie.** Head: Signature, date 6.10.92
Head: Signature, date	Head: Signature, date	**Laboratorium Pharmakokinetik Humanpharmakologie** Head: Signature, date 6.10.92

Responsible for: Statistical analyses/report Name: Signature, date 05.11.92	Responsible for: Kinetic analyses/report Name: Signature, date .1992	Responsible for: Study director, report Name: .7.92 Signature, date
Responsible for: Name: Signature, date	Responsible for: Name: Signature, date	Responsible for: Name: Signature, date
Responsible for: Name: Signature, date	Responsible for: Name: Signature, date	Responsible for: Name: Signature, date

Fly Sheet 4: Pharmaceutical data

Data on test article(s) and formulation(s)

Batch number and stability of test article(s) and/or tested formulations

Substance:
Cyproterone acetate
U No.: 28046475/28046543

Formulation:
Lot No
U N

Manufacturer of test article(s):
Schering AG, Berlin

Manufacturer of formulation of test article(s):
Schering AG, Berlin, Dept. Galenik

Formulation (if SH formulations are used, state SH number):
SH T 548: tablet with 100 mg cyproterone acetate

Data on control article(s) and -preparation(s)

Generic name, ZK number, batch number and stability of control article(s) and/or commercial preparation(s):
Substance: Cyproterone acetate,
Formulation

Manufacturer of control article(s):
Schering AG, Berlin

Manufacturer of formulation of control article(s):
Schering AG, Berlin

Formulation (if commercial preparations are used, state trade name):
SH 8.0714-50 MG (ANDROCUR 50 MG): tablet with 50 mg cyproterone acetate

Fly Sheet 5: Chemical data

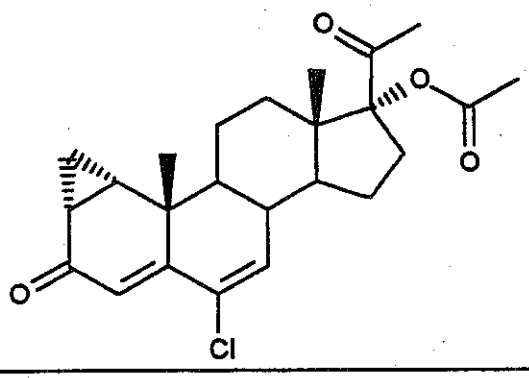
Chemical name (IUPAC):

17-Acetoxy-6-chloro-1α,2α-methylene-4,6-pregnadiene-3,20-dione

ZK number:
9471

Generic name:
Cyproterone acetate

Structural formula:



Fly Sheet 6: Quality Assurance Statement

Study number:
91089

Protocol and conduct of this study have been subject to periodic auditing by the Quality Assurance Unit to ensure that the trial has been performed and the data have been generated in compliance with Good Clinical Practice (GCP). The dates of periodic auditings are given below.

Date of QAU audits	Date of Report to Management
19.09.91	19.09.91
10.10.91	10.10.91
16.10.91	16.10.91
14.09.92	30.09.92
10.11.92	10.11.92

The reported results have been audited by the QAU to ensure the compliance with GCP.

Signature, Manager Quality Assurance Unit, Date

11.11.92

Table of Contents

Appendices V - VIII are available upon request in Institut of Humanpharmacology

1. Introduction

Cyproterone acetate (CPA) is a steroid hormone with anti-androgenic properties, which is used in the treatment of prostate carcinoma. The commercial preparation ANDROCUR contains 50 mg CPA. Daily dosages lie between 100 and 200 mg for castrated patients, and between 200 and 300 mg for patients who are not castrated.

To ease intake of the substance and to improve patient "compliance", a new ANDROCUR tablet has been developed, which contains 100 mg CPA.

In earlier pharmacokinetic studies, a radioimmunoassay was used to determine the plasma level of CPA. Although this method is very sensitive, the detection limit is approx. 50 pg/ml, it is not entirely specific, the RIA shows cross-reactions (approx. 20%) with the main metabolite 15ß-hydroxy cyproterone acetate.

Because of this, the HPLC method was used in later trials as a new analytical technique which allowed for the simultaneous measuring of CPA and 15ß-hydroxy cyproterone acetate levels. The AUC values which were compiled using the HPLC method were approx. 50% lower than those obtained using the RIA method. Because the HPLC method had a comparatively higher detection limit of 50 ng/ml, it was only used with high dosages of CPA.

A trial examining the bioequivalence of 100 mg tablets of ANDROCUR as opposed to two 50 mg tablets of ANDROCUR had already been conducted with 17 men. The HPLC method was used for determination of CPA levels.

The main criterion for bioequivalence is the area under the curve (AUC) and the time (t_{max}) and the height (C_{max}) of the maximum serum level. The trial results showed that the test power to show bioequivalence was too low according to the definition of the registration authorities (German Federal Health Office). The cause was the unexpectedly large degree of intra-individual variance in the AUC values of CPA, which possibly had methodological reasons.

The aim of the planned trial was to reexamine the bioequivalence of the new ANDROCUR 100 preparation compared to the commercially available preparation ANDROCUR 50 with a higher number of cases and using a more sensitive detection method (GC/MS) to test for CPA. The required group size (n= 36 men) was statistically calculated.

A list of trial-relevant data used, e.g. PH Research Reports, historic and bibliographic data, can be found in the trial documentation.

1.1 Trial aim and hypotheses

Trial aim:

Trial of the bioequivalence of ANDROCUR 100 mg and ANDROCUR 50 mg formulation by determination of the pharmacokinetic parameters - AUC(0 - 120 h), AUC, C_{max}, t_{max} - of the active ingredient cyproterone acetate. With respect to the extent of bioavailability, equivalence for AUC (0 - t_{last}) and AUC has to be shown. In the present study, t_{last} was 120 h post dose.

Trial hypothesis:

One tablet of ANDROCUR 100 mg and two tablets of ANDROCUR 50 mg are bioequivalent.

The main and accompanying parameters are detailed in section 2.5 (Biometric Planning and Evaluation.)

1.2 Design

The trial was conducted as an open randomized, intra-individual comparison with two treatments. The two treatments were 1 x 1 tablet ANDROCUR 100 mg and 1 x 2 tablets ANDROCUR 50 mg. Every volunteer was given both treatments (n = 36, 4 blocks of 9 volunteers). The treatments were given at 21 day intervals. The duration of the trial after each treatment was 5 days.

2. Methods

2.1 Volunteers

Table 1: Demographic data of the volunteers

NUMBER	INITIALS	AGE(y)	WEIGHT(kg)	HEIGHT(cm)	BS(m^2)	GENDER	TREATMENTS
1	:	28	89.0	189.0	2.15	m	ALL
2	:	28	74.0	186.0	1.97	m	ALL
3	:	30	68.0	176.0	1.82	m	ALL
4	:	24	98.0	185.0	2.22	m	ALL
5	:	29	83.0	184.0	2.05	m	ALL
6	:	26	76.0	193.0	2.02	m	ALL
7	:	31	71.0	178.0	1.87	m	ALL
8	:	38	76.0	174.0	1.91	m	ALL
9	:	41	75.0	175.0	1.90	m	ALL
10	:	24	83.0	184.0	2.05	m	ALL
11	:	36	103.0	189.0	2.30	m	ALL
12	:	41	77.0	179.0	1.95	m	ALL
13	:	29	76.0	185.0	1.97	m	ALL
14	:	21	55.0	166.0	1.60	m	ALL
15	:	30	84.0	192.0	2.11	m	ALL
16	:	31	76.0	179.0	1.94	m	ALL
17	:	28	75.0	180.0	1.93	m	ALL
18	:	24	71.0	177.0	1.87	m	ALL
19	:	25	71.0	186.0	1.92	m	ALL
20	:	31	83.0	183.0	2.04	m	ALL
21	:	35	67.0	175.0	1.81	m	ALL
22	:	28	70.0	181.0	1.88	m	ALL
23	:	22	63.0	177.0	1.77	m	ALL
24	:	29	110.0	203.0	2.46	m	ALL
25	:	30	78.0	180.0	1.97	m	ALL
26	:	39	66.0	182.0	1.83	m	ALL
27	:	23	67.0	184.0	1.86	m	ALL
28	:	43	76.0	171.0	1.89	m	ALL
29	:	26	75.0	182.0	1.94	m	ALL
30	:	34	76.0	190.0	2.00	m	ALL
31	:	38	80.0	176.0	1.97	m	ALL
32	:	43	88.0	186.0	2.12	m	ALL
33	:	32	98.0	192.0	2.27	m	ALL
34	:	26	73.0	183.0	1.93	m	ALL
35	:	24	74.0	173.0	1.88	m	ALL
36	:	28	82.0	196.0	2.11	m	ALL
	MEAN	30.4	78.0	182.5	1.98		
	+/-STD	6.1	11.2	7.5	0.16		

2.1.1 Inclusion criteria

Volunteers who took part in the trial met the following criteria:

- Age: 20-45 years
- Sex: male
- Body weight could not exceed or fall below the following value:

  Height in cm minus 100= weight in kg +/- 20%
- Physical condition: The volunteers were in good physical condition. This was determined through the physical and laboratory examinations and the anamnesis.
- belonging to a specific ethnic group was unimportant

2.1.2 Exclusion criteria

Volunteers were restricted from the trial according to the following criteria:

- Volunteers with azoospermia (with the exception of those who were sterilized)
- Volunteers who were Hepatitis antigen carriers (HBsAG or Hepatitis B test), or HIV positive
- Volunteers who, within one week before the beginning of the trial, had used systemic or local medication, which could have interfered with or influenced the trial aim
- Volunteers whose anamnesis suggested drug or alcohol abuse
- Volunteers on special or exclusive diets, e.g. strict vegetarian, low calorie diet
- Volunteers with known allergic reactions to cyproterone acetate or to components of the galenic preparation
- Volunteers with an anamnesis of severe, acute gastrointestinal illness within 30 days before trial begin
- Volunteers with previous or current thrombembolic processes
- Volunteers whose absorption, distribution and excretion of medication was assumed to be abnormal, due to a history of or current symptoms in the gastrointestinal tract, liver, kidneys, or endocrinic, respiratory or circulatory systems
- Volunteers whose absorption, distribution and excretion of medication was assumed to be abnormal, due to the presence of glaucoma, of changes in the blood, or changes in the peripheral or central nerves.
- Volunteers who had been severely ill within the four weeks preceding the beginning of the trial
- Volunteers who had undergone severe physical duress within 14 days before the beginning of the trial
- Volunteers who, in the opinion of the clinical trial director or the initial examination physician, should not have participated in the trial

2.1.3 Restrictions During The Trial

- Smoking — not permitted
- Alcohol consumption — not permitted
- Physical activity — strenuous physical activity was not permitted during the trial
- Additional therapy — not permitted
- Standardized food and beverages had to be consumed on treatment days.

2.1.4 Pre-trial examinations[2]

Before the beginning of the trial, an HIV- and HBsAG-test (the HIV- and HBsAG-test were to be no older than 3 months) and a drug screening[3] test were performed if necessary.

Within 3 weeks before the beginning of the trial, every volunteer underwent an internal and laboratory examination. A spermiogram was also performed on each volunteer.[4]

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[2]The following parameters will be screened as part of the **initial** and **final** volunteer examinations.

Hematology and Clinical chemistry:

alpha-Amylase	Urea	Cholesterol
LDH	Electrophoresis	Triglycerides
Alkaline phosphatase	Total protein	Blood sugar
Gamma-GT	Calcium	Urine status:
GOT	Chloride	- Urobilinogen
GPT	Potassium	- Erythrocytes
Cholinesterase	Sodium	- Hemoglobin
LAP	Quick	- Protein
Total bilirubin	Fibrinogen	- Ketones
Creatinine	PTT	- Bilirubin
Anorganic phosphate	Total blood count	- Nitrate
Uric acid	Total iron	- Glucose

Volunteers will be informed of any and all deviations of a pathological nature, and instructed to contact their personal physician. Volunteers are excluded from participation whenever lab findings, in medical opinion, suggest disease

All necessary examinations will be performed by
Hämatologie will be analyzed

[3]The *drug screening* included **cannabinoids, opiates, amphetamines, barbiturates, cocaine, benzodiazepine und methadone.**

The evaluations were performed by the

*The MDL as well as

d in external quality controls.

[4]The spermiogram was conducted in t

2.1.5 Post-Trial Examinations

The chemical analyses were repeated at the latest one week following the end of the trial and a spermiogram was performed within two weeks of the trial end. A final internal examination was not necessary.

2.1.6 Blood sampling, blood loss

The total amount of blood drawn during the 27 day trial was 192 ml, as well as 40 ml for the pre-trial and post-trial examinations.

2.1.7 Probation

Volunteers were not to participate in further trials within 1 month following individual trial completion.

2.1.8 Standard volunteer stipulations

2.1.8.1 Volunteer information

Each volunteer received oral and written information (General Volunteer Information). Each volunteer who participated in the trial received oral clarification of the trial; he also received a printed copy of Specific Volunteer Information as well as a copy of his signed consent form. Volunteers were given an updated copy of General Volunteer Information upon request.

Volunteer selection took place in accordance with the revised Helsinki Declaration, 1989 Hong Kong amendment and §§40/41 of the German Drug Law.

Volunteers were randomly selected from the Central Volunteer File according to established inclusion and exclusion criteria, then called or written to.

2.1.8.2 Volunteer insurance

Volunteers were insured in accordance with German Drug Law. Volunteer insurance was arranged by [redacted] the basis of an "Application for the Execution of a Clinical Trial" (number of volunteers). The insurer was [redacted]

2.2 Treatment and randomization

2.2.1 Trial preparation data

Manufacturer	Schering AG
Trade name	not applicable
ZK-No.	9471
SH-No.	T 548 A
Generic name	Cyproterone acetate
Chemical name	17-Acetoxy-6-chloro-1α,2α-methylene-4,6-pregnadiene-3,20-dione
Drug form	tablet
Concentration	100 mg
Unit dose	100 mg
Radioactive unit dose	not applicable
Packaging	glass jar
Specific Galenic data	none
Labelling[5]	Verum Prüfarz 1 Tablette zum Einnehmen Schering AG, Berlin/Bergkamen Zur klinischen Prüfung bestimmt/For clinical tests
Storage	Trial preparations were stored in a safe place at room temperature.
Return	The use and location of test preparations was documented. All containers, including left-over test preparations\containers, were turned over to ZV-Lagerverwaltung for disposal at the end of the trial. The whereabouts of missing containers/test preparations were explained in writing.

Exp. date 2.[illegible]
Trial director. . . . .
1 tablet for internal use
Schering AG, Berlin/Bergkamen
For clinical trials only

2.2.2 Control preparation data

Manufacturer	Schering AG
Trade name	ANDROCUR
ZK-No.	9471
SH-No.	8.0714-50 MG
Generic name	Cyproterone acetate
Chemical name	17-Acetoxy-6-chloro-1α,2α-methylene-4,6-pregnandiene-3,20-dione
Drug form	tablet
Concentration	50 mg
Unit dose	50 mg
Radioactive unit dose	not applicable
Packaging	glass jar
Specific Galenic data	none
Labelling[6]	Verw. bis Prüfarzt: 2 Tabletten zum Einnehmen Schering AG, Berlin/Bergkamen Zur klinischen Prüfung bestimmt/For clinical tests
Storage	Control preparations were stored in a safe place at room temperature.
Return	The use and location of control preparations was documented. All containers, including left-over control preparations/containers, were turned over to ZV-Lagerverwaltung for disposal at the end of the trial. The whereabouts of missing containers/control preparations were explained in writing.

Exp. date :
Trial director:
2 tablets for internal use
Schering AG, Berlin/Bergkamen
For clinical trials only

2.2.3 Treatment schedule

Treatment A: one tablet SH T 548 A at 100 mg

Treatment B: two tablets SH 8.0714-50 MG at 50 mg each

The two treatments were given to the volunteers in the morning as of 8:00. They were taken on an empty stomach with 100 ml of non-carbonated mineral water.

Administration/treatment was performed under the supervision of a member of the trial staff. This staff member assured and documented that the volunteers received treatment as planned.

The trial substances were applied at 21 day intervals.

2.2.4 Randomization

The randomization list was prepared by the Institut für Biometrie (Dr. [redacted]

The trial consisted of a treatment group with 36 participants (2 double blocks of 9 volunteers).

Volunteers 1 - 9 were treated on the first trial day (block 1), volunteers 10 - 18 on the second trial day (block 1), volunteers 19 - 27 on the third trial day (block 2) and volunteers 28 - 36 on the fourth trial day (block 2) of each treatment.

Table 2: Randomization list[7]

Volunteer	Order of Treatments		Block
1	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
2	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
3	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
4	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
5	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
6	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
7	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
8	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
9	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
10	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
11	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
12	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
13	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
14	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
15	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
16	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
17	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
18	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
19	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
20	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
21	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
22	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
23	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
24	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
25	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
26	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
27	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
28	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
29	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
30	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
31	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
32	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
33	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
34	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
35	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
36	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2

[7] Explanation:

Block: 1 = Block 1, 2 = Block 2

Treatment: 1 = 1x100MG , 2 = 2 x 50MG

Order: 1 = 1 x 100MG / 2 x 50MG; 2 = 2 x 50MG / 1 x 100MG

2.3 Research methods

2.3.1 Methods to insure volunteer safety

Laboratory-chemical "safety" parameters were not determined because there was ample data available as to the safety and tolerance of the active ingredient cyproterone acetate since it had been introduced in 1973 and had been used since as an antiandrogen.

The volunteers were asked how they were feeling before each of the two treatments.

They were asked to immediately inform the trial personnel of any concomitant events ("adverse events") during the entire trial. Every event reported by a volunteer who was undergoing treatment was entered on data record forms:

volunteer

treatment

reported event

beginning (day/hour/minute after administration of the trial substance)

duration (day/hour/minute after administration of trial substance)

intensity[8]

correlation to trial substance[9]

2.3.1.1 Drug screening during treatment

Drug screening was performed before every treatment (test point 1). The same drugs were screened for as those during the pre-trial examination.

2.3.2 Analytical methods

At specific times 6 ml of blood (2.5-3 ml serum)[10] were drawn and centrifuged after one-half hour, the collected serum was frozen until it was analyzed.

The concentrations of CPA in the serum samples were analyzed by a specific GC/MS method. All analyses were performed by

Sample preparation:

In each case (clinical samples, standards and quality control samples), 1 ml of serum was transferred into a round bottom, screwcap vial. After the addition of 25 µl of internal standard solution of 2 µg/ml chlormadinone acetate in methanol, corresponding to 50 ng, and 0.2 ml

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[8] 1 = mild; 2 = moderate; 3 = severe

[9] 1 = none; 2 = possible; 3 = definite

[10] only at test point 1 was 12 ml of blood (at least 5 ml of serum) drawn

0.1 N NaOH, the samples were extracted with 6 ml of cyclohexane/i-butanol (98.5/1.5; v/v). After centrifugation (10 min, 5000 rpm), the organic phase was transferred to a conical glass tube and stored in a refrigerator at about 4°C until measurement.

Preparation of the calibration samples:

Calibration samples were prepared by spiking pooled blank serum with a solution diluted from a methanolic stock solution, containing CPA at a concentration of 100 ng/µl and a subsequent serial dilution of this pool with blank serum. The final concentrations were 500, 200, 100, 50, 20, 10, 5, 2, 1 and 0.5 ng/ml serum.

Sample analysis:

Just prior to measurement, the organic extracts of the samples were removed from the refrigerator and evaporated under a stream of nitrogen while being kept in a heater at 40-50°C. The dry residue was reconstituted in 100 µl of ethylacetate and 1-2 µl of this solution were injected into the GC at 100°C oven temperature.

The GC/MS analysis was performed on a Finnigan MAT 4021 GC/MS system. A fused silica open tubular capillary column of cross-linked methyl siloxane type was used for GC-separation. The MS was operated in the negative ion chemical ionization mode with methane as reagent gas. Selected ion monitoring was performed for m/z 356, the base peak of CPA and m/z 344, the base peak of the internal standard. Both fragments correspond to a loss of acetic acid from the molecular ion. Data acquisition and integration of the peak areas were achieved using the standard Finnigan selected ion recording software (INCOS).

GC-conditions:

Capillary column:	DB 1; 10 m; i.d. = 0.32 mm [illegible]
	film thickness = 0.25 µm
Injector temp.:	260°C
Transfer line temp.:	300°C
Oven temp.:	0.5 min at 100°C
	from 100°C - 200°C at a rate of 49°C/min;
	from 200°C - 300°C at a rate of 25°C/min, 4 min at 300°C
Injection mode:	cold injection, splitless at 100°C
Carrier gas:	helium

Quality control:

Four different concentrations of CPA (300, 30, 3 and 1.5 ng/ml) were prepared by spiking pooled blank serum with a methanolic solution of CPA. The serum samples were extracted

and measured in sequences. One sequence consisted of the samples obtained from one subject following the two treatments, one set of calibration samples (0.5 -500 ng/ml) and 8 quality control samples (1.5, 3.0, 30 and 300 ng/ml in duplicate). The quality control samples were regularly distributed within the sequence, the standard curve was measured in the middle of the sequence.

Evaluation:

The internal standard method was used for evaluation. The peak areas of the analyte and the internal standard were calculated by the INCOS data system. The calibration curves were calculated (LAB CAL software, linear regression with 1/x weighting) from the peak area ratios CPA/internal standard and the nominal CPA concentrations. CPA concentrations (ng/ml) in clinical samples and quality control samples were calculated by interpolating the peak area ratios from the corresponding calibration curve. All values below the lower limit of quantification (0.5 ng/ml) were set to zero.

Assay quality:

The standard curves were linear in the measured range of 500 - 0.5 ng/ml and the lower limit of quantification was 0.5 ng/ml. During the study, 22 series of serum calibration and quality control samples were analyzed. The data for precision and accuracy are presented in Table 3.

Table 3: Quality control data for the analysis of CPA in serum samples

nominal conc.	[ng/ml]	300	30	3.0	1.5
n		41	41	40	41
mean	[ng/ml]	309.57	30.46	2.82	1.46
S.D.	[ng/ml]	25.78	3.49	0.24	0.21
accuracy	[%]	103.19	101.52	93.90	97.49
C.V.	[%]	8.33	8.19	8.36	14.48

2.3.3 Pharmacokinetic evaluation

The following pharmacokinetic parameters were derived from the CPA concentrations measured after each of the two treatments: C_{max}, t_{max}, AUC(0-24h), AUC(0-120h), AUC, $t_{½}$, MRT, CL and V_Z[11]. For the assessment of bioequivalence between the two formulations, only C_{max}, t_{max}, AUC(0-120h) and AUC were used as target variables in the biometrical evaluation.

[11] $t_{½}$, MRT, CL and V_Z additional to trial protocol

C_{max} and t_{max} were obtained directly from the measured CPA concentrations in the serum. When more than one maximum occurred in the drug level time course, the first one was chosen. The area under the curve was calculated according to the linear trapezoidal rule. The AUC was calculated according to the following equation:

$$AUC = AUC(0\text{-}120h) + C_{120h}/\lambda_z$$

with C_{120h} as the concentration at the last data point and λ_z as the terminal disposition rate constant. The terminal rate constant (λ_z) of the disposition of the drug in serum was calculated by means of regression analysis of the perceivable linear part of the curve in a semilogarithmic plot (λ_z: slope of the regression line).

The terminal half-life $t_{½}$ was calculated according to:

$$t_{½} = \ln 2/\lambda_z$$

The mean residence time of CPA was calculated from the ratio of the area under the moment curve (AUMC) and the AUC value:

$$MRT = AUMC\ (0 - 120\ h)/AUC\ (0 - 120\ h)$$

Total clearance (CL) was calculated according to:

$$CL/f = D/AUC$$

with f being the bioavailability (for CPA close to one) and D the dose administered. The volume of distribution (V_z) was calculated according to:

$$V_z = CL/\lambda_z$$

The pharmacokinetic parameters were calculated model-independent using the program TopFit, PC version 2.0 .

Evaluation of pharmacokinetic data was performed for all participants where a complete drug level - time course was obtained after the administration of either the reference or the test

preparation. For the bioequivalence testing, only those participants were considered, where a complete drug level - time ccurve was obtained after the administration of both preparations.

2.3.4 Analysis overview table

Table 4: List of selected items for treatments A and B

ITEM	PARAMETER METHOD	UNIT	RANGE FROM	RANGE TO
C309	CYPROTERONE-ACETATE; SERUM, GC/MS GC/MS	ng/ml		
H011	BLOOD SAMPLING 0: NOT DONE, 1: DONE	SCORE INDEX	0	1
H001	DRUG ADMINISTRATION P.O. 0: NOT ADMINISTERED; 1: ADMINISTERED	SCORE INDEX	0	1
A401	AMPHETAMINE; URINE ENZYME-IMMUNO-ASSAY	ug/ml	0	0.3
A402	BARBITURATE; URINE ENZYME-IMMUNO-ASSAY	ug/ml	0	0.3
A403	BENZODIAZEPINES; URINE ENZYME-IMMUNO-ASSAY	ug/ml	0	0.3
A404	CANNABINOIDS; URINE ENZYME-IMMUNO-ASSAY	ng/ml	0	50
A405	COCAINE; URIN ENZYME-IMMUNO-ASSAY	ug/ml	0	0.3
A406	OPIATES; URINE ENZYME-IMMUNO-ASSAY	ug/ml	0	0.3
A407	METHADONE; URINE ENZYME-IMMUNO-ASSAY	ug/ml	0	0.3

2.3.5 Methods and scheduling

Table 5: Study outline of targets and test points

			TESTTIME->													
			DAY------>	0	0	0	0	0	0	0	0	0	1	2	3	4	5
			HOUR----->	0	0	1	1	2	3	4	6	8	12	0	0	0	0
			MINUTE--->	0	30	0	30	0	0	0	0	0	0	0	0	0	0
			SECOND--->	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TG	ITEMNAME	ITEM	TESTPOINTS:														
A,B	CYPROTERONE-ACETATE;SERUM	C309	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
A,B	BLOOD SAMPLING	H011	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
A,B	DRUG ADMINISTRATION P.O.	H001	1														
A,B	AMPHETAMINE; URINE	A401	1														
A,B	BARBITURATE; URINE	A402	1														
A,B	BENZODIAZEPINES; URINE	A403	1														
A,B	CANNABINOIDS; URINE	A404	1														
A,B	COCAINE; URIN	A405	1														
A,B	OPIATES; URINE	A406	1														
A,B	METHADONE; URINE	A407	1														

2.4 Daily schedule

2.4.1 Volunteer accommodations (see also daily schedule chart)

Overnight stay:	before treatment days (day -1)
Daytime accommodations:	a maximum of 13 hours on treatment days (day 0)
	a maximum of 1 hour on examination days (days 1-5)

2.4.2 Volunteer care

On the treatment days (day 0), the volunteers received a light breakfast as of 10:00: 2 rolls, 40 g butter, 25 g sausage, 25 g jelly, 250 ml coffee substitute

As of 12:00 a standard lunch (frozen food: beef roll-up, red cabbage, potatoes), as well as 200 ml fruit yogurt and 250 ml non-carbonated water were served.

At 16:00 the volunteers received "afternoon coffee": 1 piece of fruit cake, 250 ml coffee substitute.

As of 19:00 dinner was offered: 3 slices of bread, 40 g butter, 75 g cold cuts, tomatoes/cucumbers/green pepper slices, 250 ml non-carbonated water).

2.4.3 Additional information

The 36 volunteers in a treatment group were treated in four blocks of nine participants on four consecutive days.

The nine volunteers in one block arrived around 21:00 on the evening prior to the treatment days (day -1) at Human Pharmakology and spent the night there (no food or drink after 22:00.).

On the following morning (7:00) they went to the trial unit. The volunteers were asked how they were feeling. They emptied their bladders. A drug test was carried out on the urine sample. An indwelling cannula was placed in a forearm vein and a blood sample was drawn for the determination of pre-treatment values.

The trial substance was applied to the volunteers between 8:00 and 8:30. The nine volunteers were treated at two minute intervals.

After this, blood samples were drawn for a period of 12 hours. After the final sample the volunteers were dismissed.

The volunteers appeared in the trial unit as of 7:30 on the five following examination days. They were asked how they were feeling. As of 8:00 a blood sample was drawn.

2.4.4 Daily schedule

Table 6: Daily schedule chart

Day	Test point	Time after administration	Real time	Measure
-1			21:00	volunteer arrival overnight stay
0	1		as of 7:00	urine (drug test), indwelling cannula, blood sample, questioning
			8:00	began administration of trial substance to first volunteer
	2	30 minutes	8:30	blood sample[12]
	3	60 minutes	9:00	blood sample
	4	90 minutes	9:30	blood sample
	5	2 hours	10:00	blood sample, followed by standard breakfast
	6	3 hours	11:00	blood sample
	7	4 hours	12:00	blood sample, followed by standard lunch
	8	6 hours	14:00	blood sample
	9	8 hours	16:00	blood sample, followed by "afternoon coffee"
			19:00	standard dinner
	10	12 hours	20:00	blood sample, followed by dismissal of volunteers
1			as of 7:30	volunteer arrival, questioning
	11	24 hours	8:00	blood sample
2			as of 7:30	volunteer arrival, questioning
	12	48 hours	8:00	blood sample
3			as of 7:30	volunteer arrival, questioning
	13	72 hours	8:00	blood sample
4			as of 7:30	volunteer arrival, questioning
	14	96 hours	8:00	blood sample
5			as of 7:30	volunteer arrival, questioning
	15	120 hours	8:00	blood sample

[12] from first volunteer

2.5 Biometric planning and evaluation

2.5.1 Target parameters

The main target criterion for bioequivalence was the area under the concentration time curve AUC(0-120h) of cyproterone acetate. Additional target criteria were the maximal achieved serum level (C_{max}) and the time of the highest serum level (t_{max}).

2.5.2 Statistical evaluation

Method

For each response variable (C_{max}, t_{max}, AUC(0-120h), AUC) the sequence effect, the treatment effect, and their standard errors were calculated from the logarithmically transformed data. The treatment effects were estimated from the intraindividual differences, which were calculated by substracting the values of the second period from those of the first period.

Each sequence effect was tested with a two-sided t-test (α = 5%). For each response variable the hypothesis

H_0: One tablet of Androcur100 and two tablets of ANDROCUR50 are not bioequivalent

was tested against their alternative

H_1: One tablet of ANDROCUR100 and two tablets of ANDROCUR50 are bioequivalent

with Westlake's interval-test, which is equivalent to the planned Schuirmann's two one-sided t-tests procedure. The level of significance was 5% in all cases and, according to the study protocol, the real interval [ln0.8, ln1.25] = [-0.2231, 0.2231] was used as equivalence interval.

2.6 Storage, labelling, etc. of biological material

Collected samples were labelled with trial number, volunteer number, treatment and test point. Samples that were not immediately analyzed were stored at -18°C until processing.

2.7 Strains and risks

2.7.1 Strain/Risks due to the trial structure

Vein puncture during blood sampling may be accompanied by slight bleeding and in rare cases by a temporary inflammation of the wall of the vein. After initial irritation, the presence of the plastic cannula is generally painless and practically unnoticed.

2.7.2 Strain/Risks due to the trial preparation

The bioequivalence trial of two ANDROCUR formulations presented here was necessary for the following reasons: the daily dose in the treatment of prostate carcinoma can be as high as 300 mg, i.e. 6 tablets of ANDROCUR. Because this illness usually effects older patients, who often must take several medications, a reduction in the number of tablets which must be taken each day can be a relief to the patients. In addition, experience has shown that the reliability of taking medications drops with the number of tablets. Success in the treatment of prostate carcinoma can therefore be jeopardized by missed or irregular drug taking.

In this trial, the volunteers received two single doses of ANDROCUR (100 mg each) three weeks apart.

Cyproterone acetate has effects on the regulatory cycle of pituitary glands. As a highly effective progestagen, the substance has an antigonadatropic effect, which is, however, weakened in males. A temporary effect on pituitary gland function, for example a reduction of peripheral sexual steroids - is possible with a single administration, however this is only serologically determinable and without clinical relevance.

Tests show that the concentration of testosterone sinks with ANDROCUR, but that it rises again with extended continuous administration.

Only after extended use of ANDROCUR can changes in body weight and libido, tension in the chest, tiredness, a reduced ability to concentrate as well as depressive moods temporarily occur. These concomitant events were, however, not to be expected after a single administration of ANDROCUR.

As an antiandrogen, cyproterone acetate inhibits spermatogenesis.

Doses of 50 - 200 (-300) mg ANDROCUR/day as they are used therapeutically, have led over the course of several weeks to a reduction of the male sperm count as well as the percentual share of sperm in normal mobility and character.

Normal spermiogram results were found about 3-6 months after the discontinuation of treatment - partially carried out over a period of years - with these dosages.

Even low dosages down to 5 mg cyproterone acetate/day, which were administered to volunteers for several months, caused biochemical spermiogram changes which are characteristic for sub- and infertility. These, too, were fully reversible after discontinuation.

An effect on spermatogenesis was not expected after a single administration of ANDROCUR. A spermiogram was, however, performed before the beginning and after the end of the trial.

The administration of ANDROCUR did not comprise a specific risk to volunteers, because all findings correlating with cyprotene acetate's temporary pharmacological influence on the

androgen regulatory cycle were not demonstrable after a single administration and were always fully reversible after multiple administrations.

After the evaluation of benefit and risks, trial performance was considered to be ethically sound. The trial protocol was submitted to the appropriate Ethics Committee for approval.

2.7.3 Evaluating adverse events/effects

Adverse events or effects were either reported by the volunteer or observed/noted by one of the trial staff. This was documented accordingly.

Adverse events or effects were evaluated according to intensity as indicated below:

1 = "mild"	The event did not interfere with normal volunteer functions, but was perceived by the volunteer as bothersome.
2 = "moderate"	The event impaired volunteer function to some extent (uncomfortable or embarrassing), but did not threaten his health.
3 = "severe"	The event represented a clear danger to the volunteer's health; unmistakable damage to volunteer functions or capabilities.

Evaluating the degree of likelihood of a correlation between an adverse event or effect and the test preparation was graded as follows:

1 = "none"	No causal and/or time correlation between event and trial preparation.
2 = "possible"	The event correlated temporally with the administration of the trial preparation, but other causes for this effect were conceivable.
3 = "definite"	The event correlated temporally with the administration of the trial preparation, and there was no other plausible explanation for its occurrence.

2.7.4 Trial discontinuation

2.7.4.1 Criteria for the discontinuation of the entire trial

- Unexpected (according to the present level of knowledge) events, contingent on the trial substance cyproterone acetate, which occurred regularly with many participating volunteers. The following evaluation criterion applied:

  Evaluation of unexpected events: "severe"

2.7.4.2 Criteria for the discontinuation of individual volunteers

- Unexpected events which occurred repeatedly:

  Evaluation of unexpected events: "severe",
- Circulatory collapse during cannula insertion or blood sampling,
- Proof of drugs or disallowed medications during the trial,
- Failure to uphold trial conditions,
- Withdrawal of informed consent.

3. Results

3.1 Dropouts

36 volunteers met the criteria for inclusion and agreed to participate. Volunteer no. 5 was dropped from the trial 7 hours after the second administration, because of a positive drug screening test (barbiturate: 0.89 µg/ml). No substitute was used for this drop-out.

3.2 Pharmacodynamics

The substance was tolerated well.

The main adverse event reported by the volunteers was headache. Headache was reported by 4 volunteers in treatment A (ANDROCUR 100) and 2 volunteers in treatment B (ANDROCUR 50).The intensity of the event was mild to moderate, the onset and duration varied, a relation to the ANDROCUR treatment is possible.

The other adverse events were vomiting and diarrhea in volunteer no. 10 (treatment B), abdominal discomfort in volunteer no. 18 (treatment B) and conjunctivitis, earache and cough in volunteer no. 28 (treatment B). One volunteer (no. 14) collapsed during blood sampling. One volunteer (no. 6) underwent dental therapy because of toothache. One volunteer reported an infection of the upper respiratory tract. Both volunteers did not give any details about the time of onset, duration and intensity of the events. These events are not considered to be substance-related.

Table 7: Adverse events following administration of treatment A (SH T 548 A) and B (SH 8.0714-50 MG), (n=36)

TG	Vol. No.	Reported event	Codeterm[13]	Therapy	Onset p.a. Day/h:m	Duration Day/h:m	Intensity 14	Drug relation[15]
A SH T 548 A	4	Headache	Headache	none	0/11:54	0/2 h	2	2
	4	Headache	Headache	Aspirin®	2/0:54	0/2:0	2	1
	5	Slight congestion in the head	Headache	none	0/9:12	0/1:55	1	2
		Headache	Headache	none	19/12:12	0/0:55	2	1
	9	Headache	Headache	none	0/2:44	0/9:0	1	2
	13	Headache	Headache	none	2/1:53	0/8:0	2	1
	14	Collapsed during blood sampling	Syncope	symptomatic	0/0:31	0/0:2	3	1
B SH 8.0714-50 MG	2	Headache	Headache	none	0/4:58	0/1:45	1	2
	6	Toothache	Tooth dis	none	3/0:0	n.a.*	n.a.*	n.a.*
	8	Headache	Headache	none	0/0:0	0/15:0	1	2
	10	Vomiting, diarrhea	Gastro enteritis	none	1/20:0	1/6:0	2	1
	18	Unpleasant feeling in the stomach	Pain abdo	none	0/0:28	0/0:2	1	1
	28	Reddening of the eyes, earache, coughing	Infect upper resp	Wick Medinait® Doxyhexal®	0/12:43	2/0:15	2	1
	36	Infect of the upper resp. tract	Infect upper resp	Thomapyrin® Hexoral®	n.a.*	n.a.*	n.a.*	n.a*.

* not available

No clinically relevant changes or trends were observed following administration of the substance as SH T 548 A and SH 8.0714-50 MG in the post-trial examinations (hematology, clinical chemistry and spermiogram.

3.3 Pharmacokinetics

The individual serum concentration data obtained after oral administration of two tablets of ANDROCUR 50 and one tablet of ANDROCUR 100, respectively, are presented in Tables 1 and 2 (appendix I). The mean serum concentrations of CPA are shown in Figures 1 and 2,

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[13] HARTS code

[14] 1 = mild; 2 = moderate; 3 = severe

[15] 1 = none; 2 = possible; 3 = sure

respectively. The pharmacokinetic parameters of CPA are summarized in Tables 3 and 4, respectively (appendix I).

After the ingestion of two tablets of ANDROCUR 50, mean maximum serum levels of 285.6 ± 105.2 ng/ml were found at 2.6 ± 1.1 h. A second maximum was observed in the majority of subjects at about 8 to 12 h after drug intake and is probably due to enterohepatic recirculation of the drug. Thereafter, CPA levels in the serum declined during a time interval of typically 24 to 120 h with a mean terminal half-life of 43.9 ± 12.8 h. The AUC(0-120h) accounted for 5840.1 ± 1553.2 ng · ml^{-1} · h and the corresponding AUC was 6861.7 ± 2078.8 ng · ml^{-1} · h. Assuming complete bioavailability, total serum clearance of CPA was found to be 3.5 ± 1.5 ml · min^{-1} · kg^{-1} and the mean volume of distribution (V_Z) was calculated to be 978.7 ± 354.0 l (Table 3, appendix I).

Following the oral administration of one tablet of ANDROCUR 100, mean maximum concentrations of 239.2 ± 114.2 ng/ml were found in the serum at 2.8 ± 1.1 h. As already observed with the reference preparation, a second maximum was observed in the majority of subjects at about 8 to 12 h after drug intake which was attributed to an enterohepatic recirculation of the drug. Thereafter, the drug levels in the serum declined during a time interval of typically 24 to 120 h, with a mean terminal half-life of 42.8 ± 9.7 h. The AUC(0-120h) accounted for 5630.3 ± 1660.8 ng · ml^{-1} · h and the corresponding AUC was 6535.7 ± 2140.3 ng · ml^{-1} · h. Total serum clearance of CPA was found to be 3.8 ± 2.2 ml · min^{-1} · kg^{-1} and the mean volume of distribution (V_Z) was calculated to be 1070.3 ± 749.1 l (Table 4, appendix I).

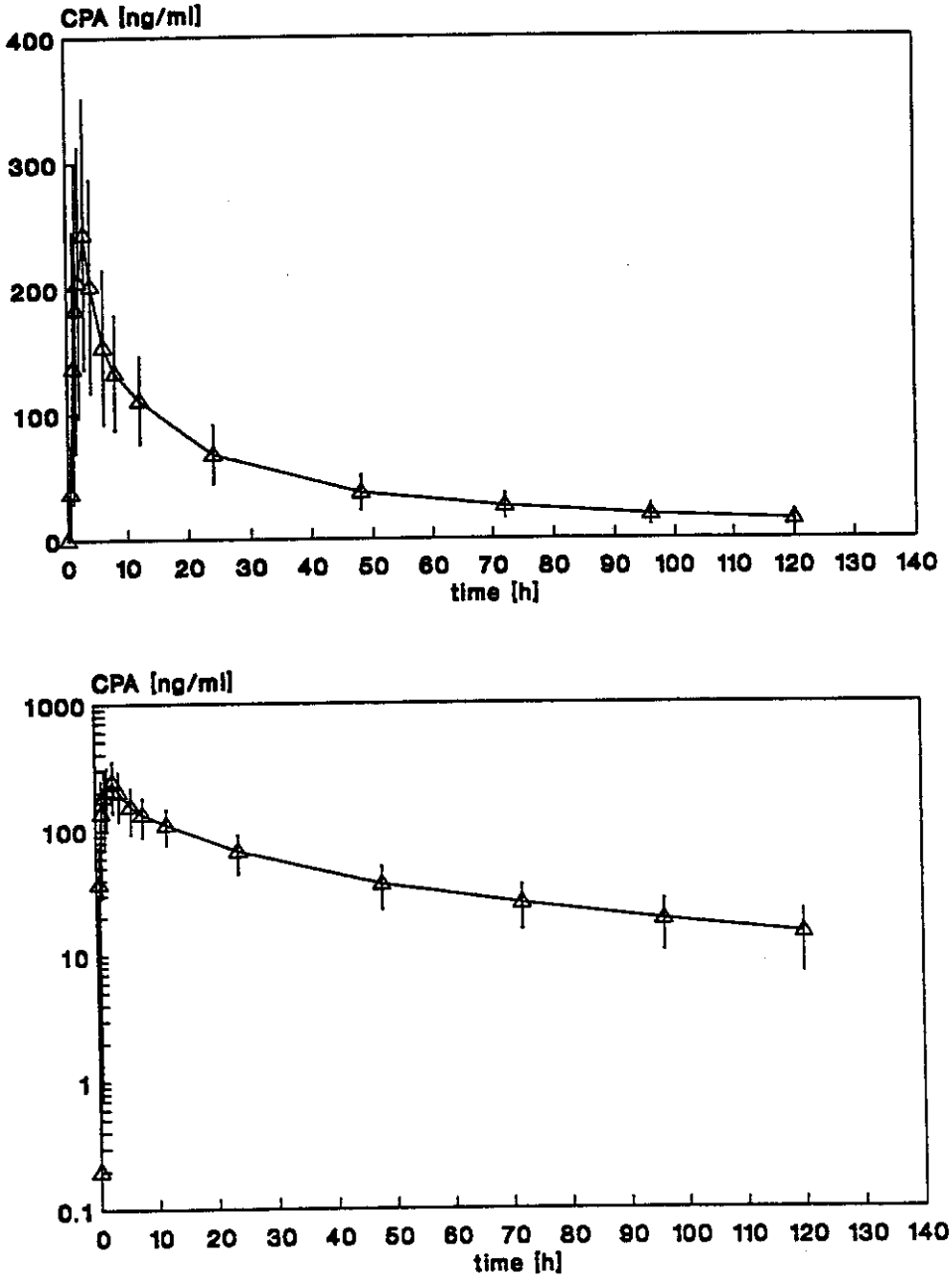

Figure 1: Concentration of CPA (mean ± S.D.) in the serum of 35 men following the oral administration of two tablets of ANDROCUR 50. Linear presentation (top) and semilogarithmic presentation (bottom).

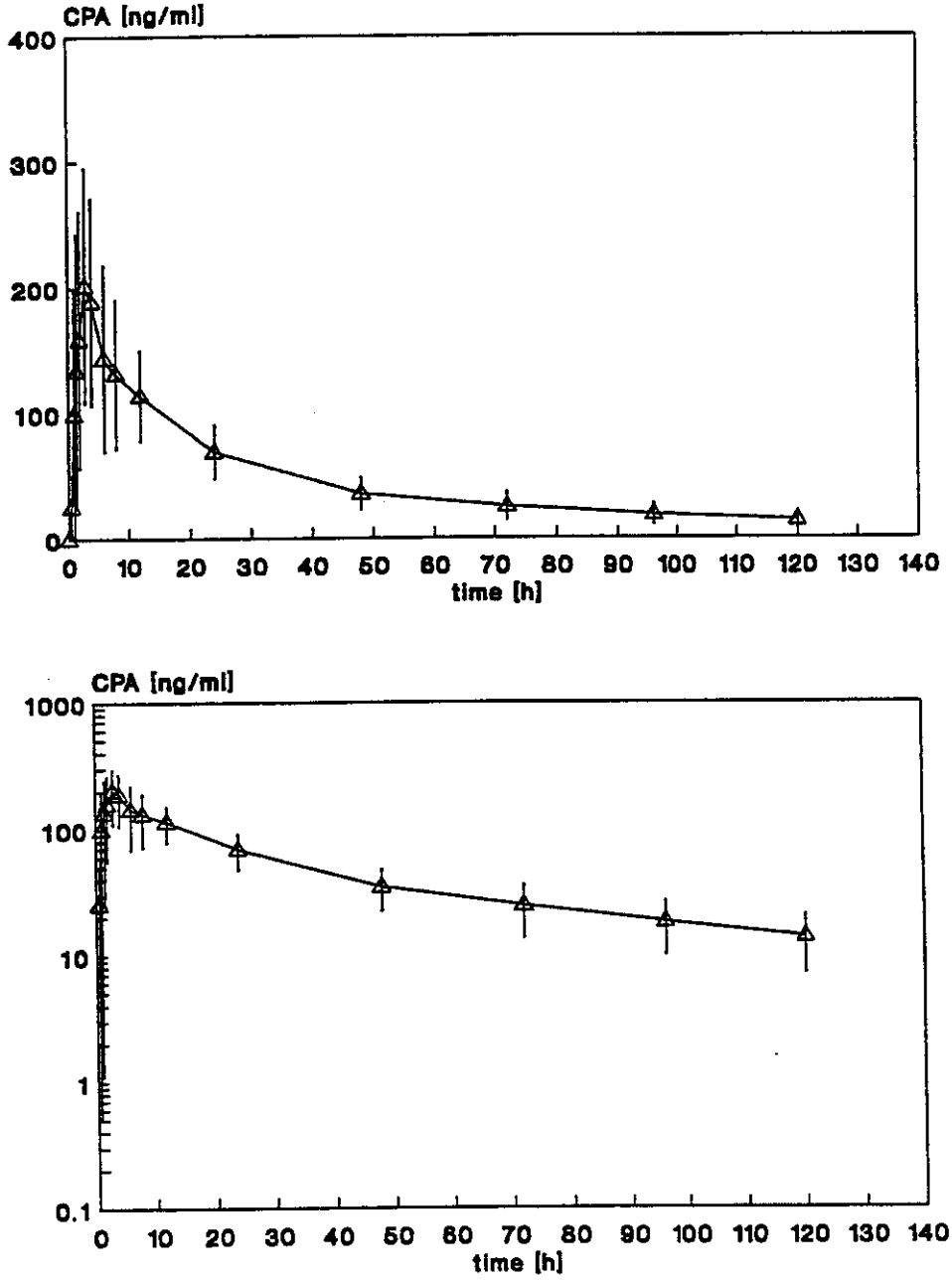

Figure 2: Concentration of CPA (mean ± S.D.) in the serum of 36 men following the oral administration of one tablet of ANDROCUR 100. Linear presentation (top) and semilogarithmic presentation (bottom).

3.4 Statistical analysis

None of the four sequence effects differs significantly from zero. The following table shows the results with respect to the treatments.

Table 8: Biometric results

Response variable	Treatment effect (standard error)	90%-confidence interval for treatment effect	Bioequivalence
Cmax	-0.207 (0.094)	[-0.367, -0.047]	no
t_{max}	0.059 (0.108)	[-0.124, 0.241]	no
AUC120	-0.046 (0.0285)	[-0.095, 0.002]	yes
AUC	-0.054 (0.029)	[-0.102, -0.005]	yes_1

4. Discussion

The aim of the present study was to investigate whether one tablet of the newly developed preparation ANDROCUR 100 was bioequivalent to two tablets of ANDROCUR 50. In a previously performed study, the in vitro dissolution had been examined and the results demonstrated equivalence of both preparations. In addition to the in vitro study, the present pharmacokinetic - clinical study was performed with 36 healthy male volunteers.

The pharmacokinetics of CPA had already been extensively investigated in previous studies using a radioimmunoassay for drug level analysis. This assay system has the advantage of high sensitivity but the specificity is impaired by the presence of a cross-reacting metabolite (15ß-hydroxy-CPA). Although a more specific HPLC method has also been available, the lower limit of detection of this method (50 ng/ml) was not sufficient for the present study. Therefore, a sensitive and specific GC/MS method was used for the analysis of CPA in the serum samples which were collected during the present study.

The pharmacokinetic parameters of CPA which were evaluated in this study are in agreement with the results obtained in previously performed studies. The time course of the drug levels in the serum showed two peaks in most volunteers, one between 1 and 6 h, and a second peak between 8 and 12 post administration. Although the first peak represented the maximum in the majority of cases, sometimes the second peak was of a similar height as the first one. This phenomenon occurred irrespective of the preparation administered. The first peak was attributed to the initial absorption of the preparation after administration, mean maximum serum levels being reached at about 3 h post dose. The second peak was probably due to the enterohepatic recirculation of the drug. Obviously, after oral administration CPA was not rapidly absorbed from the two preparations. Because of the relatively large range of 1 to 6 h

during which the major part of the drug was absorbed from the gastrointestinal tract, there is a concomitant large variation of the maximum concentrations in the serum as well. This explains why in this case, the criteria of bioequivalence cannot easily be met with respect to t_{max} and C_{max}. The main target variable, however, is the area under the serum level - time curve, and with respect to both AUC(0-120h) and AUC the two preparations were found to be bioequivalent.

Small differences in the maximum concentrations of CPA and the time when these values are reached following drug administration are of no clinical relevance. In the therapeutic indications of prostate cancer or severe androgenization in women, CPA has to be administered daily over an extended period of time. Due to the average terminal half-life of about 40 h, steady-state drug levels will hardly be affected by minor variations in the time interval required for drug absorption.

Furthermore it should be noted that ANDROCUR 50 has been on the market for many years and its clinical efficacy has been demonstrated in a large number of studies. Since in the present study, the absorption characteristics of both preparations were found to be almost the same, and the AUCs being identical, the clinical efficacy of ANDROCUR 100 can be granted to be equivalent to that of ANDROCUR 50.