FINAL BIOMETRY REPORT

SHORT VERSION

MONOCENTRIC, OPEN CLINICAL STUDY

ON THE EFFICACY AND TOLERANCE OF **T P H** 56 16

IN SHORT-TERM ANTISPETIC TREATMENT OF THE MUCOSA AND THE ADJOINING SKIN IN THE VAGINAL AREA PRIOR TO DIAGNOSTIC OR SURGICAL INTERVENTIONS IN CHILDREN

FM-CODE: 1 - 071

STUDY SPONSOR: SCHÜLKE & MAYR GMBH, NORDERSTEDT

EVALUATING INSTITUTE : FRINO COMP ARZNEIMITTEL GMBH,GERETSRIED

NOVEMBER 1993

I. Summary

In a monocentric, open clinical study the efficacy and tolerance of Octenisept (TPH 5616) as an antiseptic to be applied prophylactically in the treatment of the external genital area and/or the vagina was tested in 54 girls aged 6 to 14 years.

The bacterial cell counts used to assess the efficacy after application of the product revealed on average a reduction of the bacterial cell counts by 96 percent relative to the initial values.

The tolerance, which was evaluated by both the physician and the female patients, could be regarded to be very good. The study included evaluations of local and general tolerance.

Apart from a slight rash on the vulva in two catheterized female patients, the cause of which remaining unclear, no undesirable secondary effects or side effects that were demonstrably associated with treatment occurred.

According to the statements made by the physicians, Octenisept (TPH 5616) proved to be applicable without causing any complications.

II. Introduction and Object of the Study

Octenisept (TPH 5616) is a dermal and mucosal antiseptic agent approved, among others, by the German Federal Health Agency and the Hungarian Health Agency. It has hitherto stood the test of time in the short-term antiseptic treatment of the mucosa and its adjoining skin in the vaginal area and on the glans penis, for example, prior to diagnostic surgical interventions in adults. Results on the application of Octenisept (TPH 5616) to children who constitute a considerable percentage of the entire clientele of potential female patients are as good as unavailable.

Since the experiences made with the vaginal application Octenisept (TPH 5616) in women are very positive, an application under controlled conditions to young girls appears to be justified, since pharmacological / toxicological and clinical studies with adults have already demonstrated the good tolerance of topically applied Octenisept (TPH 5616). The benefit resulting from treating young girls with Octenisept (TPH 5616) lies possibly in the good tolerance combined with sufficient efficacy after single administration and/or short-term treatment. It appears to be of significance that Octenisept (TPH 5616) would also be available for children as an alternative to PVP iodine which from the pharmacological / toxicological perspective should only be applied upon taking into consideration the thyroid gland status of the individual. The systemic burden with an antiseptic agent, often a problem of therapy, might thus be minimize.

The following issues were object of this study:

- Assessment of tolerance based on symptoms such as “burning sensation”, “itching”, numbness” etc.
- Registration of objectifiable, local alterations, e.g. reddening, swelling, etc.
- Registration of potential systemic effects
- Determination of the efficacy, here expressed in terms of reduced microbial growth in a before-after comparison
- Registration of undesirable secondary effects and interactions of the test product with secondary therapies.

III. Evaluation Scheme

The tolerance after application of Octenisept (TPH 5616)served as the main endpoint criterion, defined as the evaluation of the preset objective parameters “reddening”, “swelling”, and/or “other”, with score values and the subjective parameters “burning”, “itching”, “numbness”, and/or “other” with score values as an expression of acceptance and/or non-acceptance in the area of vaginal skin and mucosa.

In the scope of this evaluation, only one single statement was made by a female patient which was ascribable to the category “other” – namely a “tingling sensation” – , wherefore other parameters need not be discussed in detail here.

An evaluation of the differential blood cell count and the determination of liver and kidney values in the serum were taken to assess potential systemic effects.

As a further criterion, we undertook to evaluate the efficacy of Octenisept (TPH 5616), defined as the reduction of the microbiologically determined bacterial cell count upon comparison of the before and after situations (bacterial reduction factors).

In addition, an assessment of local and general tolerance was stated by the physician and the female patient upon termination of treatment. In this context, the practicability of the application was evaluated.

Finally, we were interested in answering the question whether the tolerance and the efficacy of Octenisept (TPH 5616) in young girls would be similarly given as had been the case in adults.

All the data compiled in this study were described descriptively, i.e. using classic (mean value, standard deviation, etc.) robust (median, maximum, minimum values, etc.), and locally descriptive (95 percent lower boundary, upper boundary, etc.) statistical parameters. The alpha error was set to a total alpha of 0.05 in order to attain an explorative statistical description of potential differences; two-sided tests were performed.

Line charts and column diagrams were primarily chosen as means of graphic representation.

The data of all female patients were separately documented in the shape of case-wise listings in the Original Report.

IV. Case Material

1 Overview

A total of 54 female children were included in the monocentric open study.

The following allocations resulted with regard to the treatment of the female patients with the antiseptic:

Table I: Allocation of Groups

GROUP	NUMBER OF FEMALE PATIENTS	PATIENT NO.
All female patients	54 (100%)	1 to 54
Group A: Patients with applications to the external genital region	8 (14.8 %)	1 to 8
Group B: Patients with applications to the vaginal region	22 (40.7 %)	9 to 30
Group C: Patients with applications to both regions	24 (44.4 %)	31 to 54
Patients with single application	34 (63.0 %)	1 to 31, 51, 53,54
Patients with multiple applications	20 (37.0 %)	32 to 50, 52
Patients with catheter applications	34 (63.0 %)	10,12 to 16, 18 to 20 22 to 30,33,34,39 to 43 45 to 50, 52 to 54
Patients with swab applications	20 (37.0 %)	1 to 9,11,17,21,31,32 35 to 38, 44, 51

The first female patients were included in the study on February 17, 1992, the last on May 17, 1993. All data were compiled under the supervision of Prof. Dr. Zsolnai in Budapest and the study physicians Dr. Siklos and Dr. Verebely. The initial doctoral visit took place on the day of intervention for 53 female patients, only in case of Patient No. 3 did intervention proceed three days after commencement of study.

The assessment of tolerance proceeded after application. Systemic tolerance tests were performed 24 hours after application. In addition, a final

assessments were conducted. The final assessments were conducted on average 12 (± 11) days after commencement of study, whereby the data vary between 0 and a maximum of 56 days.

In the 20 female patients with multiple applications, the additional doctoral visit took place on average 15 (± 14) days after commencement of study. Here as well, the time intervals varied between 1 and a maximum of 56 days. The subsequent final assessments mostly occurred on the same day but also as late as after 26 days.

2. Demographical Data

The demographical data of the 54 girls who all belonged to the Caucasian race revealed the following values:

Table II: Demographical Data

	ALL PATIENTS.	GROUP A	GROUP B	PATIENTS WITH SINGLE APPLICATION	PATIENTS WITH SINGLE APPLICATIONS
AGE(YEARS):					
MEAN	9.8	10.0	9.4	9.7	9.9
STD DEV	2.2	3.0	2.1	2.3	2.1
MIN	6	6	6	6	7
MEDIAN	10	11	9.5	10	7
MAX	14	14	14	14	13
WEIGHT (KG)):					
MEAN	35.0	34.1	35.6	35.5	34.2
STD DEV	10.0	9.7	11.8	10.8	8.7
MIN	18	22	20	20	18
MEDIAN	34	34	32	34	34
MAX	60	47	60	60	52
HEIGHT(CM):					
MEAN	143.2	144.2	141.2	142.4	144.5
STD DEV	13.7	11.1	14.9	13.5	14.2
MIN	114	130	122	122	114
MEDIAN	143	144	138.5	141.5	143
MAX	176	158	176	176	165
VALID N	54	8	22	34	20

The female patients were between 6 and 14 years of age (on average approx. 10 years (± 2)), weighing on average 35 kg (± 10). They were 143.2 cm (± 13.7) tall.

Looking at the demographical data of the single groups, differences were hardly noticeable. In this regard, comparability of the groups could be anticipated.

Study Inclusion and Medical Case History

At the time of study inclusion, surgical intervention was indicated in 13 percent of the female patients (7 out of 54), whereas 87 percent of the female patients (47 von 54) awaited diagnostic intervention.

Table III: Study Inclusion and Medical Case History

NUMBER	ALL PATIENTS (N = 54)	GROUP A (N = 8)	GROUP B (N = 22)	PATIENTS WITH SINGLE APPLICATION (N = 34)	PATIENTS WITH MULTIPLE APPLICATIONS (N = 20)
INCLUSION IN THE STUDY: PATIENTS AWAITING SURGICAL INTERVENTION	7(13%)	3 (37.5 %)	1 (4.5 %)	5 (14.7 %)	2(10%)
PATIENTS AWAITING DIAGNOSTIC INTERVENTION	47 (87 %)	5 (62.5 %)	21 (95.5 %)	29 (85.3 %)	18(90%)
CLINICAL SYMPTOMS:					
CONSPICUOUS (DISCHARGES)	49 (90.7 %)	5 (62.5 %)	22(100 %)	31 (91.2%)	18(90%)
INCONSPICUOUS (NO DISCHARGES)	5 (9.3 %)	3 (37.5 %)	0 (0 %)	3 (8.8 %)	2(10%)

Absence of discharges was recorded only in 9.3 percent of the female patients (5 out of 54). These female patients were also without clinical symptoms. Merely 3 of these 5 patients were found to belong to the small Group A (female patients with application to the external genital region), whereas none belonged to the female patients of Group B, with application to the internal vaginal region.

4. Secondary Diseases and Therapy

Out of a total of seven female patients with secondary diseases, four (7.4 %, n = 54) underwent therapy for this reason (Patient Nos. 6, 7, 8 and 51), whereas three of them did not (Patient Nos. 2, 17 and 20). Table IV shows these cases in detail:

Table IV: Secondary Diseases and Therapy of 7 Patients Affected

PATIENT NO.	SECONDARY DISEASES	CURRENT TREATMENT OF THE SECONDARY DISEASE	SECONDARY THERAPY IN THE COURSE OF STUDY PROGRESS (DAILY DOSE)
2	Retinoblastoma (enucleation)	no	
6	Kidney failure, kidney transplantation 91	no	Furosemide (2x40 mg), Prednisolone (5 mg), Sandimmum (0.75 ml), Nilacid (2x1 Tablet)
7	Appendicitis, subacute	no	
8	Pharyngitis, abdominal pain	no	
17	Coughing	no	
20	Coughing	no	
51*)	Hydronephrosis, rectal atresia	yes	Nevigramon/Nalidixin acid (1500 mg)

*) On the day of intervention (3 days after study commencement) secondary therapy changed to Cefobis/Cefoperazonum (3g per day).

5. General Medical Examination

Table V shows the information given by the physicians concerning their general medical examinations. In 40 of the 54 female patients (74,1 %) at least “vaginal discharge” was mentioned; “vulvitis” was diagnosed in 15 female patients (27,8 %, n = 54)

Table V: General Medical Examination: Information given by the Physicians and relating to all Patients prior to Onset of Treatment

PATIENT NO.	FINDINGS OF GENERAL MEDICAL EXAMINATION (n = 54)
1	Mild vulvitis
2	Vulvitis pruritus
3	Vulvitis
4	Abdominal pain, vulvitis, amenorrhea
5	Vulvitis pruritus
6	Tenckhoff catheter, Vulvitis
7-8	Vulvitis, recurrent abdominal pain
9-14	Vaginal discharge
15	Minimal vaginal discharge, pyuria
16-30	Vaginal discharge
31	Vaginal discharge, mild vulvitis
32	Vulvovaginitis
33	Vaginal discharge, Vulvitis
34	Vaginal discharge, pruritus vulvae
35	Vulvitis
36	Pruritus vulvae, vulvitis
37-43	Vaginal discharge
44	Vaginal discharge, vulvitis
45-46	Vaginal discharge
47	Vaginal discharge, vulvitis
48-50	Vaginal discharge
51	Sigmoidostomy, hematometra
52	Vaginal discharge
53	Vaginal discharge, pruritus vulvae
54	Vaginal discharge, vulvitis

6. Further Treatment

Further treatment and hence a documented doctoral visit took place in a total of 20 female patients (37 %, n = 54). At this point in time, the patients were at least on two and at maximum on five days, or 2.5 days on average (median: 2 days), whereby one application per day was not exceeded. Overall, 2.5 applications (median: 2 applications) were administered on average (Cf. Table VI).

Table VI: Further Treatment and Treatment Days and /or Frequency of Application

			APPLICATION	
PAT.-NR.	FURTHER TREATMENT	DAYS OF TREATMENT	PER DAY	TOTAL
1-31	no	-	-	-
32	yes	2	1	2
33	yes	3	1	3
34	yes	4	1	4
35-38	yes	2	1	2
39	yes	4	1	4
40-41	yes	2	1	2
42	yes	3	1	3
43	yes	2	1	2
44	yes	3	1	3
45-48	yes	2	1	2
49	yes	5	1	5
50	yes	2	1	2
51	no	-	-	-
52	yes	2	1	2
53-54	no	-	-	-
mean		2.5	1.0	2.5
std dev		0.89	0.00	0.89
min		2.0	1.0	2.0
median		2.0	1.0	2.0
max		5.0	1.0	5.0
valid n		20	20	20

V. Results

1. Microbiological Efficacy

In order to determine the microbiological cell counts, a baseline value was first obtained. To this end, a swab was moistened with brain-heart infusion (BHI) + inactivation agent and then rolled on the region foreseen for antiseptic treatment for 15 seconds and swabbed. The swab was then transferred immediately into a tube containing 5ml BHI + inactivation agent and vibrated on a vibrating shaker for 20 seconds. Subsequent evaluation proceeded in the laboratory.

The antiseptic procedure was then conducted on the external genitalia and/or posterior vaginal region with a ball swab previously soaked with Octenisept (TPH 5616), or with a catheter if the girls' anatomical condition would not allow using a swab.

The first post-treatment value was determined immediately after the exposure time of the antiseptic, the second post-treatment value was taken one half hour after disinfection, during or at the end of the operation, and in accordance with the abovementioned procedure.

Table VII and Figures 1 and 2 show the microbial cell counts in the before-after comparison, distinguishing between external and internal genital tests.

The results revealed that the microbial cell count reductions on the external and internal genitalia are comparable, as could be expected after treatment with Octenisept (TPH 5616). A statistical comparison among the groups confirmed this impression (Cf. Table VIIa).

It needs to be mentioned that the post-treatment values of Patient No. 53 could not be considered in the calculation of the parameter values on account of the absent baseline value.

Microbial cell counts derived from the external genitalia of all female patients (n = 18) revealed a mean logarithmic reduction of 1.79 and 1.50 relative to post-treatment values I and II, respectively. The values pertaining to the internal vagina (n = 42) were at 1.68 (post-treatment value I) und 1.66 (post-treatment value II).

Table VII: Bacterial Cell Counts (CFU/ml) and Logarithmic Reduction Factors (log RF) in Before-After Comparisons – All female patients. Mean Values.

		EXTERNAL GENITALIA (n = 18)	VAGINA (n = 42)
BASELINE VALUE:	mean	09.51 x 10^5	05.66 x 10^5
	std dev	16.19 x 10^5	10.83 x 10^5
	min	00.67x 105	00.01 x 10^5
	median	03.45 x 10^5	01.50x 10^5
	max	67.60 x 10^5	51.20x 10^5
LG RF 1:	mean	1.79	1.68
	std dev	1.24	1.19
	min	0.28	-0.30
	median	1.45	1.66
	max	4.48	4.91
LG RF 2:	mean	1.50	1.66
	std dev	1.08	1.08
	min	0.21	-0.31
	median	1.29	1.67
	max	4.06	3.49

Table VII a: P Values of Group Comparisons between Patients Receiving External and Internal Applications

	P VALUES	
INTER-GROUP COMPARISONS	LOGARITHMIC REDUCTION FACTOR I	LOGARITHMIC REDUCTION FACTOR II
All female patients with bacterial cell counts on external genitalia (n=18) versus all female patients with vaginal bacterial cell counts (n=42):		
t-Test	0.7337	0.5908
Wilcoxon-Mann-Whitney-U-Test	0.851	0.3761

2. Tolerance

2.1. Systemic Effects (Laboratory Values)

Systemic tolerance was assessed on the basis of comparing the differential blood cell count, kidney and liver values at the time of study inclusion with the values obtained approximately 24 hours after application of the antiseptic.

in summary, it can be stated that the laboratory values did not reveal any indication of undesirable effects.

2.1.1 Differential Cell Count

a) Hemoglobin

At the time of their study inclusion, hemoglobin was at 137.1 g/l in all female patients, and at 136.7 g/l approximately 24 hours after intervention; the median values of both time points were at 140 g/l. Only one female patient (Patient No. 54) had an initial value below normal range, and one female patient (Patient No. 48) displayed a post-treatment value which was likewise below normal range.

b) Hematocrit

The mean hematocrit values were at 41 percent at both time points. There were 6 female patients who were within normal range at commencement of the study but fell outside normal range after intervention. However, these female patients mostly already had displayed initial values which were near the margins of the reported normal range, so that a maximum increase or decrease of 3 percent explained the abovementioned result.

Conversely, 7 female patients showed quite the opposite development, displaying values within normal range after intervention, which they failed to do before (e.g. by means of a maximum absolute decrease of the hematocrit value by 6 percent).

c) Leukocytes

The leukocytes were inconspicuous, revealing average values of approximately 7,000/µl.

47 female patients remained within normal range of this parameter while therapy was in progress, 2 even displayed an improvement.

d) Erythrocytes

The erythrocytes ranged on average at about 4.5 million/µl, whereby

four female patients who had values within normal range at the time of inclusion in the study displayed increases or decreases in erythrocyte numbers of 0.8 or 0.1 and 0.3 million/µl, respectively, after the intervention and thus revealed values outside normal ranges.

Conversely, erythrocyte counts were outside normal range in seven female patients at the beginning but then dropped by 0.8 million/µl at maximum, or increased by this figure, so that they no longer appeared to be conspicuous.

e) Platelets

The individual values of the platelet count indicate that a total of four female patients had values above normal range at both time points. As was the case with these female patients, the values remained constant in most of the other female patients. One patient exhibited a decline of 150 thousand/µl to 130 thousand/µl, the latter value lying below normal range. This patient (Patient No. 51) had already attracted our attention on account of her secondary diseases consisting in hydronephrosis and rectal atresia.

The mean values of the platelet counts were at 256.1 thousand/µl and 254.7 thousand/µl, the median value was at 260 thousand/µl and 250 thousand/pl on the two days of examination.

2.1.2. Liver Values

a) GPT

GPT activity also revealed inconspicuous overall findings. The values of 51 female patients (of a total of 53 valid data) were within normal range.

The mean value of all female patients was at 9.8 U/l and 9,5 U/l; the median was at 9.0 U/l.

In two female patients, however, marked increases and decreases were observed; Patient No. 9 exhibited a GPT activity of 13 U/l lying within normal range at commencement of the study, which afterwards increased to 27 U/l above normal range. Conversely, Patient No. 19 displayed a marked decline from 37 U/l (outside normal range !) to an inconspicuous value of 9 U/l.

In the sign test referring to alterations, however, a significant P value could not be determined.

b) GOT

GOT activity assumed mean values at about 14 U/l. Here, three female patients were noticed who had values lying outside normal range at commencement of the study but returned to normal ranges in the course of the study, for example, by a maximum decrease of 20 U/l or a maximum increase of 6 U/l. However, one patient shifted out of normal range, owing to a GOT activity increase from 19 U/l to 23 U/l.

In this case, the sign test referring to alterations in GOT activity from inclusion in the study to 24 hours after invention revealed a P value of 0.0533.

c) Gamma-GT

As far as gamma-GT activity measurements are concerned, two female patients with alterations relative to normal activity ranges must be mentioned. One of them displayed a value within normal range after a decrease of 14 U/l obvious after invention, whereas the other female patient had a value outside normal range owing to an increase of 3 U/l.

Otherwise, the gamma-GT activity in 51 female patients varied within these limits only.

A mean gamma-GT activity of approx. 13.5 U/l and a median amounting to 12 U/l was determined.

d) Bilirubin

Bilirubin displayed a similar overall picture, whereby slight alterations in the values (from -2 to up to +1,7) were noticeable between the two time points.

The mean values were at 10 µmoles/l.

e) Alkaline Phosphatase (AP)

Since alkaline phosphates activity values are usually higher in children than in adults and also depend on age, it is hardly possible to define any normal ranges.

Obvious were the high values of Patient No. 9, however, which exceeded 1000 U/l (compare also the GPT values under 2.1.2.a).

Mean alkaline phosphates activity values of 356 U/l and 351.2 U/l were determined. The median values were at 330.5 U/l und 310 U/l. At maximum, an increase of 87 U/l (Patient No. 9) and a decrease of 82 U/l (Patient No. 24) were determined.

2.1.3. Kidney Values

a) Creatinine

At commencement of the study the mean creatinine values were at 69.5 µmoles/l (median: 67 µmoles/l) and with 71.4 µmoles/l (median: 69 µmoles/l) somewhat higher after intervention

Two female patients (Patient Nos. 19 and 24) initially demonstrated values within normal range which then attained values above or below normal range boundaries due to maximum increases of 28 µmoles/l or decreases of 13 µmoles/l, respectively. A maximum decrease of 19 µmoles/l within normal range was noticed in Patient No. 30.

The sign test indicating alterations also failed to produce significant P values for creatinine.

b) Uric Acid

Also with regard to uric acid, two female patients (Patient Nos. 19 and 24) must be mentioned once again. A value of 16.1 mmoles/l lying outside normal range and measured in Patient No. 19 dropped to 6.1 mmoles/l. Conversely, a value of 4,9 mmoles/l in Patient No. 24 increased to a maximum value of 32.7 mmoles/l lying far outside the upper boundary of normal range.

These two female patients displayed the maximum uric acid alterations within the entire course of the study; alterations in other female patients did not exceed or fall below values of +4,0 mmoles/l or. −1,6 mmoles/l, respectively. This was also demonstrated by the slight increase of the overall mean value from 5.44 mmoles/l to 5.70 mmoles/l. Likewise, the sign test referring to the alterations failed to reveal significance.

c) Urea

Patient No. 24 revealed, once again, maximum alterations of +113 µmoles/l, however, still within normal range. Only one female patient fell below the indicated normal range, owing to a decrease of 10 µmoles/l after intervention. The increases and decreases, however, displayed by the entire clientele did not prove to be significant.

The mean urea values remained rather constant in the course of the study and amounted to approx. 211 µmoles/l; the median value demonstrated a slight increase from 207.5 µmoles/l to 215 µmoles/l.

2.2. Subjective and Objective Parameters

2.2.1. Subjective Parameters

None of the female patients had reported to the physician, either upon being questioned or spontaneously, of burning sensations, itching or numbness subsequent to the application of Octenisept (TPH 5616).

Eight of the 54 female patients (14,8 %; Patient Nos. 9, 11,13, 29, 31, 42, 45, 53) reported that they have noticed a tingling sensation of various severity on the day of intervention. Five female patients qualified this sensation as being slight, two as moderate, and one as intensive.

Five of these eight female patients have been treated with catheters, 3 with swabs.

None of the three female patients (Patient Nos. 42, 45, and 53), who underwent multiple applications and had reported of a tingling sensation after initial treatment, complained of such uncomfortable feeling when the application was repeated.

One female patient (Patient No. 39) only expressed having noticed a slight tingling sensation once after the second application.

In total, 9 of 54 female patients (16.7 %) reported of the sensation here described.

As a conclusion, a good tolerance may be anticipated on account of these subjective assessments.

2.2.2. Objectifiable Parameters

The physician’s assessment of the antiseptic measures (objective parameter) was also in favor of good tolerance.

Isolated occurrences of reddening were noticed in only two female patients (3.7 %, n = 54) on the day of invention; a swelling was never noticed.

The two female patients nos. 42 and 45 displaying reddening of the skin were both treated with catheters and belonged to the multiple application group.

interestingly, reddening was not observed when the Octenisept (TPH 5616) applications were repeated in these patients.

2.2.3. Other Observations

During the final assessments minor-degree vulvar rashes were noticed in two female patients (Patient Nos. 20 and 43). Both were treated with catheters, whereby Patient No. 20 a received a single application inside the vagina, whereas Patient No. 43 had multiple applications to the external and internal areas.

3. Final Assessment

A final assessment of each female patient was made at the end of the study, in which both the local and the general tolerance were classified by the study physician and the patient. The study physician also referred in his statement to the practicability of the application.

At this point it needs to be emphasized that all female patients completed the study properly and according to the rules.

3.1. Local Tolerance

Local tolerance as assessed by both the physician and the female patient undergoing treatment, whereby possible statements ranged from excellent, good and moderate to bad. These statements revealed the following distribution:

Table VIII: Assessment of Local Tolerance as made by the Physician and the Female Patient

	ALL PATIENTS (n = 54)	GROUP A (n = 8)	GROUP B (n = 22)	PATIENTS WITH SINGLE APPLICATIONS (n = 34)	PATIENTS WITH MULTIPLE APPLICATIONS (n = 20)
PHYSICIAN:					
EXCELLENT	40 (74.1 %)	4 (50 %)	18(81.8%)	25 (73.5 %)	15(75%)
GOOD	14 (25.9 %)	4 (50 %)	4(18.2%)	9 (26.5 %)	5 (25 %)
MODERATE	0	0	0	0	0
BAD	0	0	0	0	0
PATIENT:					
EXCELLENT	39 (72.2 %)	6 (75 %)	20 (90.9 %)	28 (82.4 %)	11 (55 %)
GOOD	14 (25.9 %)	2 (25 %)	2 (9.1 %)	6(17.7%)	8 (40 %)
MODERATE	1 (1.9 %)	0	0	0	1 (5 %)
BAD	0	0	0	0	0

Here, the physician assessed local tolerance mostly to be excellent as well as good. The patients responded similarly, whereby only one patient who had received multiple external and internal applications (Patient No. 49) classified local tolerance as moderate.

Figure 3 shows clearly that the opinions of the physician and the patient did not match well as far as the allocations to excellent/good in Group A with patients receiving external genital applications (n = 8) or with female patients receiving multiple applications (n = 20) were concerned. However, the low case numbers in these groups do not permit any interpretations.

The same problem showed when Groups A and B, and female patients receiving single and multiple applications were compared. It can only be stated that patients having received a single application reported local tolerance to be excellent more often than the patients having received multiple applications did. Instead, the latter rated the local tolerance to be good, and only once chose moderate. Similarly, the ratings in Group B were somewhat better than in Group A.

Considering the assessments made by both the physician and the female patient, the statistical tests performed despite the low and dissimilar case numbers may only be evaluated tentatively on account of the low case numbers. P values below 0.05 were only revealed upon comparing female patients who received single and multiple applications with regard to local tolerance (Wilcoxon-Mann-Whitney-U test: P two-sided = 0.0437, Mantel-Haenszel test: 2*P one-sided = 0,0452).

3.2. General Tolerance

The general tolerance was estimated by the physician and the female patient in accordance with the same scheme, producing a result similar to the one received with local tolerance (Cf. Fig. 4). Here as well, only Patient No. 49 classified general tolerance as moderate, otherwise only statements ranging from good to excellent were found, whereby the latter were encountered more often than has been the case in the assessment of the local tolerances.

Table IX: Assessment of General Tolerance as made by the Physician and the Female Patient

	ALL PATIENTS (n = 54)	GROUP A (n = 8)	GROUP B (n = 22)	PATIENTS WITH SINGLE APPLICATIONS (n = 34)	PATIENTS WITH MULTIPLE APPLICATIONS (n = 20)
PHYSICIAN					
EXCELLENT	44(81.5%)	5 (62.5 %)	20 (90.9 %)	29 (85.3 %)	15(75%)
GOOD	10(18.5%)	3 (37.5 %)	2(9.1 %)	5 (14.7 %)	5 (25 %)
MODERATE	0	0	0	0	0
BAD	0	0	0	0	0
PATIENT:					
EXCELLENT	43 (79.6 %)	7 (87.5 %)	20 (90.9 %)	31 (91.2%)	12(60%)
GOOD	10(18.5%)	1 (12.5%)	2 (9.1 %)	3 (8.8 %)	7 (35 %)
MODERATE	1 (1.9%)	0	0	0	1 (5 %)
BAD	0	0	0	0	0

3.3. Practicability of the Application

The study physician also assessed the practicability of the application at the end of the study (cosmetic acceptance, etc.). This feature was reported to be excellent by 43 of the 54 female patients (79.6 %). Ten female patients (18.5 %)reported that practicability was good, whereas Patient No. 49 (1.9 %) assessed it again as moderate.

Besides, it was recorded in all 54 cases that the study physician would use the same medication again in the future.

The results permit us to conclude that Octenisept (TPH 5616) shows very good tolerance and applicability.

VI. Discussion

The primary object of this study was to investigate the tolerance of Octenisept (TPH 5616) in young girls at an age of 6 to 14 years.

The factors considered to this end, such as the subjective and objective parameters as well as the assessments made by the physician and the female patient, indicated a good tolerance. Neither did the laboratory values give any indication of systemic intolerance.

The circumstance that all female patients completed the study properly according to study design, i.e. that no premature terminations occurred, also confirmed the given tolerance to the product. Side effects did not appear, with the exception of a slight vulvar rash in two girls. In this regard, it could not be distinguished whether this had been a consequence of treatment with Octenisept (TPH 5616) or an incidental secondary incidence.

In addition, the physicians judged the application of Octenisept (TPH 5616) as very practicable.

The efficacy which was assessed on the basis of the reduction of microbiological cell counts in a before-after comparison produced good results. Microbial cell counts before commencement of the study, immediately prior to intervention, as well as 30 minutes after intervention, were reduced by log 1.7 on average (equivalent to a microbial cell count reduction of 96 percent).

Since there were very diverse and low case numbers in the individual subgroups of the 54 girls recruited, many comparisons between groups could not be interpreted with statistical reliability. All results, for example, those indicating differences in the efficacy between external and internal applications, or in the tolerances between single and multiple application, may only be regarded with caution.

It did not seem to be reasonable to differentiate applications which proceeded by using catheters and those which proceeded by using swabs, since catheter application inevitably causes a product flow over parts of the external genitalia, wherefore alterations on the external body regions have to be expected.

Altogether, Octenisept (TPH 5616) convinced owing to its good efficacy and especially its tolerance.

Geretsried, on November 9, 1993

[signature] (Dr. M. Gierend)

[signature] (Dipl. Statician A. Weber)