



Article

**Efficacy of 7-day treatment with
metronidazole + miconazole (Neo-Penotran[®]) — a
triple-active pessary for the treatment of single and
mixed vaginal infections**

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Abstract

Objective: To evaluate the efficacy of Neo-Penotran[®] pessaries (metronidazole 500 mg + miconazole nitrate 100 mg) in candidal, bacterial and trichomonal vaginitis and in mixed vaginal infections. *Method:* Ninety-seven patients with clinical diagnosis of vaginitis entered this open, non-comparative study. Each patient inserted one pessary twice daily for 7 days. Gynecological and microbiological assessments were carried out before, and 8–10/21–23 days after the start of treatment. *Results:* Vaginitis symptoms were resolved in 91% of the 74 patients evaluated, and improved in a further 7%. Microbiological cure rates were 97.3% for trichomonal, 86.6% for bacterial and 81% for candidal vaginitis. Recurrence rates were 2.7, 3.8 and 16.1%, respectively. Overall microbiological cure rate for mixed infections was 86%, with 93% for trichomonal + bacterial, and 73% for bacterial + candidal vaginitis. In two out of three cases with trichomonal + bacterial + candidal infection, the microorganisms were eradicated completely. *Conclusion:* Neo-Penotran[®] provides immediate and effective treatment for vaginitis, irrespective of single or multiple infection, even when the diagnosis may be uncertain. © 2001 International Federation of Gynecology and Obstetrics. All rights reserved.

Keywords: Bacterial vaginosis; Vulvovaginal candidiasis; Trichomonal vaginitis; Mixed vaginal infections; Metronidazole; Miconazole

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1. Introduction

Infection of the vulva and vagina are among the most common medical problems seen in general practice. There are three common types of vaginitis: vulvovaginal candidiasis, bacterial vaginosis and trichomonal vaginitis [1,2]. Vaginitis due to simultaneous infection with at least two pathogens (mixed infection, e.g. bacterial vaginosis in a patient with vulvovaginal candidiasis) is also highly prevalent and makes up approximately 30% of all cases [3–6].

Effective management of vaginitis depends on accurate diagnosis, selection and administration of effective specific therapy and good compliance of the patient.

Since classic signs and symptoms of common types of vaginitis are often equivocal, the diagnosis cannot always be established on the basis of clinical manifestations alone [2,6]. Laboratory support is necessary for a differential diagnosis or to confirm the clinical diagnosis. However, accurate identification of the causative microorganism is technically difficult, often affected by a wide variety of factors such as availability of a quality microscope, insufficient training of the observer, poor reproducibility and simultaneous infection with at least two pathogens [2,3]. Clinical diagnosis of the cause of vaginitis is often incorrect.

A survey in the US in which office and laboratory diagnoses were compared, showed that office diagnosis found candidiasis in only 39.6% of the cases of candidal infection that were diagnosed in the laboratory. For trichomoniasis and bacterial vaginosis the figures were 75 and 76.5%, respectively [7].

‘When only women with multiple vaginal infections were considered, the percentages of correct clinician diagnoses for vulvovaginal candidiasis, vaginal trichomoniasis, and bacterial vaginosis were 49.3, 83.6 and 59.7%, respectively [7].

Moreover, laboratory tests take some time to obtain or may not be available at all in some clinical settings. Therefore, therapy is generally started before microbiological test results are available [2,6].

In such cases, where the cause of vaginitis is

unconfirmed and may be of mixed origin, a single form of medication capable of treating candidal, bacterial and trichomonal vaginitis and mixed infections effectively should be of particular value.

Neo-Penotran[®] pessaries (Embil Pharmaceutical Co. Ltd., Turkey), containing a combination of two effective and standard medications for the treatment of vaginitis [metronidazole (500 mg) and miconazole nitrate (100 mg)], is indicated for the treatment of vulvovaginal candidiasis, bacterial vaginosis and trichomonal vaginitis [8]. NeoPenotran[®] proved its efficacy and safety in several clinical trials, which have been previously reported [8–11]. The approved dosage and administration for Neo-Penotran[®] is one pessary at night and one pessary in the morning for 7 days, or one pessary inserted high into the vagina at night for 14 days. In recurrent cases, or when the vaginitis has been resistant to other treatments, one pessary should be inserted at night and in the morning for 14 days.

A tolerance, acceptability, and absorbance study with Neo-Penotran[®] in healthy volunteers has shown that the pessaries are well tolerated when administered twice daily for 14 days. Systemic absorption of metronidazole gave steady state plasma levels in a range approximately comparable with the standard 200-mg oral dose. Miconazole nitrate was not significantly absorbed [8].

Clinical studies carried out with Neo-Penotran[®] pessaries (Table 1) have shown that with both dosage regimens, twice daily for 14 days and twice daily for 7 days, high clinical and microbiological cure rates are achieved with an excellent safety profile [8–11]. Although in practice, most physicians prescribe Neo-Penotran[®] for both single and mixed vaginal infections, none of the above mentioned clinical trials evaluated its efficacy in vaginitis caused by mixed infections.

The objective of this study was to evaluate the efficacy of NeoPenotran[®] in the treatment of bacterial, trichomonal or candidal vaginitis, as well as in mixed vaginal infections.

2. Materials and methods

Ninety-seven women (age 18–50 years) with a

Table 1
Clinical studies carried out with Neo-Penotranl^{®a}

Clinical study [Ref.]	Trial design and dosing schedule	Patient no. enrolled/ evaluated	Clinical cure rate (%)	Microbiological cure rate (%)	
				Mycol.	Bacteriol.
15 Different general practices, UK [8]	Open, multicenter, non-comparative. Twice daily, 14 days	80/60 C = 90 B = 26	Overall clinical cure: 73 (resolved) 21 (improved)	97.6 (V2) 83.3 (V3)	95.2 (V2) 92.3 (V3)
Dr Z.T. Burak Women's Hospital, Turkey [9]	Open, non-comparative Twice daily, 14 days	100/80 C = 30 B = 45 T = 5	Overall clinical cure: 75 (resolved) 18 (improved).	93.3 (V2) T = 80 (V2)	93.3 (V2)
Cukurova Gynecology Group, Turkey [10]	Open, multicenter, non-comparative. Twice daily, 7 days.	245/179 C = 81 B = 76 T = 22	87.6 (rec.: 3.8) 93.3 (rec.: 2.7) 86.4 (rec.: 4.6)	86.4 (rec.: 7.4) T = 81.8 (rec.: 4.5)	89.5 (rec.: 2.6)
SSK İzmir Training Hospitals, Turkey [11]	Open, multicenter, Non-comparative Twice daily, 7 days	144/88 C = 28 B = 24 T = 36	85.7 (res.), 10.7 (imp.) 79.2 (res.), 12.5 (imp.) 83.3 (res.), 8.3 (imp.)	– –	

^aV2, end of treatment; 15th day; V3, follow-up; 22nd day; C, candidal; B, bacterial; T, trichomonal; rec, recurrence rate (%).

clinical diagnosis of vaginitis were included in this open, non-comparative study, which was carried out at the Department of Obstetrics and Gynecology, Central Clinical Research Hospital, Ashgabad, Turkmenistan. The study protocol was approved by an ethics committee and patients were enrolled into the study after their informed oral consent had been obtained.

Patients were excluded from the trial if they had known sensitivity to metronidazole or miconazole, were pregnant or lactating or had any gynecological condition that contraindicated the use of pessaries. Those who had had treatment with any systemic/local antibacterial, antiprotozoal or antifungal agent in the 2 weeks preceding the study or during the study period, as well as patients with any sexually transmitted disease except vaginitis and women using oral contraceptives, were also excluded.

Patients were treated twice daily (each morning and evening) for 7 days and assessed clinically and microbiologically at the beginning of the study, and 8–10/21–23 days after the start of the study.

2.1. Procedures / assessments

At visit 1 (entry, day 1) a detailed medical and gynecological history was taken and a physical examination was performed. A gynecological examination was carried out and the apparent condition of the external genitalia and of the vagina and cervix was recorded. Duration of vaginitis and details of key symptoms (i.e. discharge, irritation, itching, odor, coital pain) as well as signs (i.e. inflammation, discharge or non-menstrual bleeding) of vaginitis were recorded. Microbiological sampling was performed by taking vaginal swabs from the posterior fornix at the time of the gynecological examination. Since transport time to the laboratory did not exceed 2 h, the swabs were placed in tubes containing 0.3 ml of normal saline to maintain viability of the microorganisms.

Patients were given a package of 14 Neo-Penotran[®] pessaries, each containing 500 mg of metronidazole and 100 mg of miconazole nitrate, and they were instructed to insert one pessary each night and morning for 7 days.

The patients were advised to abstain from sexual intercourse and alcohol as well as to have good hygiene conditions (e.g. daily change of panty hose, at least weekly change of the sheets, not to use someone else's towels, not to use tight-fitting clothing, etc.) and not to use any agents which could alter vaginal pH (e.g. vaginal douche) during the 1 week of treatment. Concomitant medication (except any systemic/local antifungal/antibacterial/antiprotozoal medication) was allowed for the duration of the trial, if considered necessary for the patient's welfare.

For subjective assessment of side effects and/or adverse reactions, patients were given a diary chart in which they had to record any side effects or adverse events experienced throughout the 3-week study period.

At visit 2 (end of 7 days treatment, days 8–10), gynecological examination and recording of symptoms of vaginitis were performed as at visit 1. Microbiological samples were taken, and any side effects or adverse events experienced were recorded by the physician by asking the patient 'Have you felt different in any way since your last visit?' The patients were asked to return for a follow-up evaluation 2 weeks after the end of treatment.

At visit 3 (follow-up, days 21–23), gynecological examination and microbiological sampling were repeated as at previous visits. Diary charts for the subjective assessment of side effects were collected.

2.2. Clinical evaluation

Vaginitis and symptomatic improvement were assessed by recording detailed symptoms of vaginitis and by gynecological examination, especially the description of external genitalia and results of visualization of the vagina and cervix. Patients with two or more key symptoms (i.e. discharge, irritation, itching, odor, coital pain), and one or more signs of vaginitis (i.e. inflammation, discharge or non-menstrual bleeding) at visit 1 were clinically diagnosed as having vaginitis, and received the medication package without awaiting for the microbiological test results.

The severity of symptoms of vaginitis were

recorded using a graded scoring system (0 = none/absent; 1 = mild; i.e. noticeable but not causing discomfort; 2 = moderate, i.e. causing discomfort; 3 = severe, i.e. discomfort sufficient to interfere with normal activities).

Patients with missing microbiological sampling at visit 1, and those with missing gynecological/microbiological post-treatment assessments were excluded from the clinical evaluation.

2.3. Microbiological evaluation

The laboratory diagnosis of vaginitis was based on the following tests [2] carried out on vaginal swab samples:

- Bacterial vaginosis: release of fishy amine odor from the vaginal fluid when mixed with 10% KOH solution (positive odor test) and presence of 'clue cells' on wet mount or Gram stain vaginal specimens.
- Vulvovaginal candidiasis: identification of the pseudohyphae on potassium wet mount (10% potassium hydroxide solution).
- Trichomonal vaginitis: detection of the typical motile protozoa in a wet mount preparation using physiologic saline. *T. vaginalis* culture was performed, unless the motility of *T. vaginalis* was observed (Trichomonas-specific culture, GBL-0725, Istanbul, Turkey).

3. Results

Of the 97 patients initially recruited, a total of 74 patients (76%) fulfilled the criteria for efficacy and safety evaluation. Exclusion from the study was due to concomitant systemic/local antibacterial, antiprotozoal or antifungal medication (two patients), missed microbiological testing (six patients), non-compliance to the study protocol (nine patients) or other reasons (six patients). The mean age of the study population was 31 years (range 18–45 years).

Microbiological test results of 74 women with clinically documented vaginitis are given in Table 2. In 42 (56.8%) of the 74 patients, at least two

Table 2
Microbiological test results in 74 patients

Diagnosis	Patient no.	%
Trichomonal vaginitis	36	49
Vulvovaginal candidiasis	31	42
Bacterial vaginosis	52	70

pathogens responsible for the most common types of vaginitis (i.e. *Candida* species, *Trichomonas vaginalis* and anaerobes, including *Gardnerella vaginalis*) were simultaneously present in vaginal specimens (Table 3).

According to the subjective and objective clinical evaluation criteria mentioned in Section 2, vaginitis was resolved in 91% of the patients and improved in a further 7%. The medication was ineffective in 1.3% of the study population and the overall clinical recurrence rate was 1.3% (at visit 3).

Total symptom score for vaginitis declined from 5.45 (visit 1) to 1.67 (visit 2) and 0.37 (visit 3) (Fig. 1). Vaginitis symptoms and corresponding scores are detailed in Fig. 2.

The microbiological cure rates (Fig. 3) were 97.3% for the treatment of trichomonal vaginitis,

Table 3
Mixed vaginal infections

Diagnosis	Patient no.	%
Bacterial + candidal vaginitis	11	14.9
Bacterial + trichomonal vaginitis	28	37.8
Bacterial + candidal + trichomonal vaginitis	3	4.1
Total	42	56.8

86.6% for bacterial vaginosis and 81% for vulvovaginal candidiasis. The overall microbiological cure rate for mixed infections was 86%. Microbiological eradication was achieved in 93% (26 out of 28) of patients with trichomonal + bacterial infection and in 73% (8 out of 11) with bacterial + candidal infection. In two out of three cases with bacterial + candidal + trichomonal infection, all three microorganisms were eradicated completely.

Microbiological recurrence rates were 2.7% for trichomonal vaginitis, 3.8% for bacterial vaginosis, and 16.1% for vulvovaginal candidiasis.

In the clinical and microbiological evaluation, the responses were statistically significant both at the end of treatment and at follow-up: a reduc-

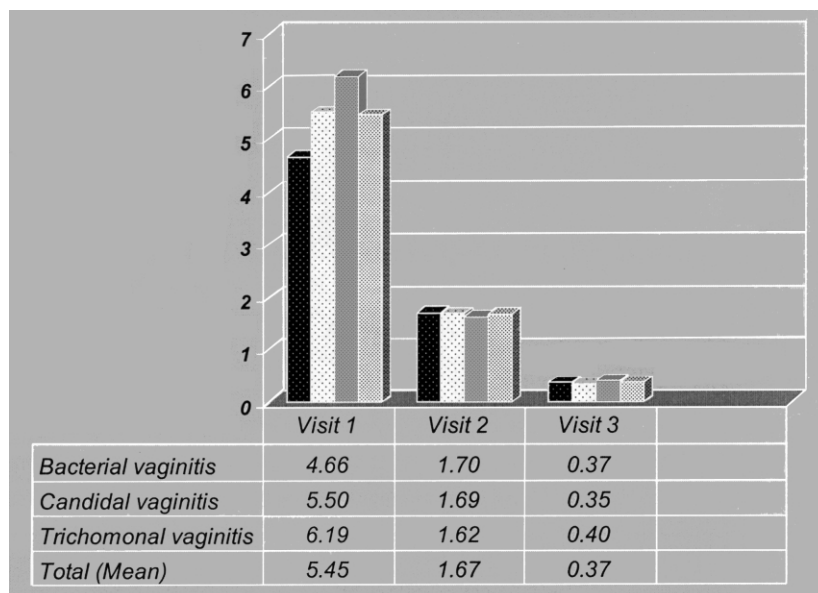


Fig. 1. Total symptom scores at visits 1–3.

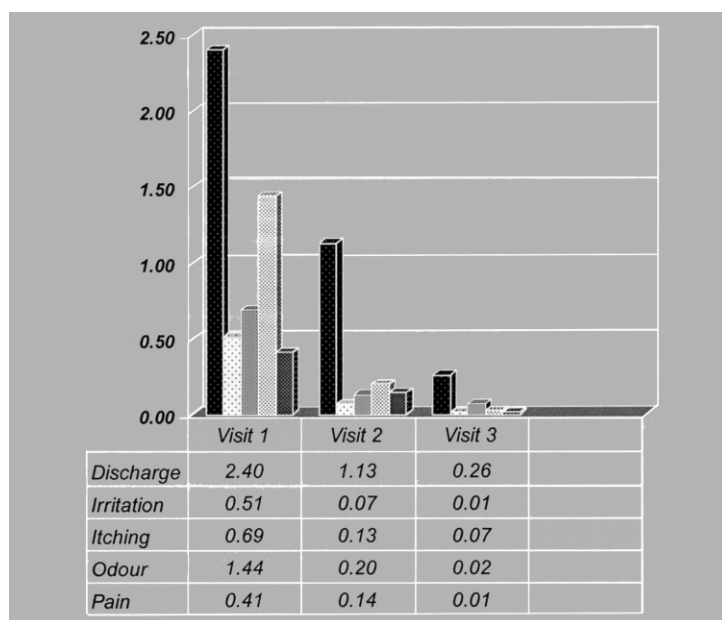


Fig. 2. Symptom scores at visits 1–3.

tion of anaerobes, *Trichomonas* and *Candida* in vaginal swabs between visit 1 and visits 2 and 3 ($P < 0.01$, Friedman's chi-square test), and a re-

duction in the symptoms of vaginitis (discharge, irritation, itching, odor and pain) between visit 1, and visits 2 and 3 ($P < 0.001$). There were signifi-

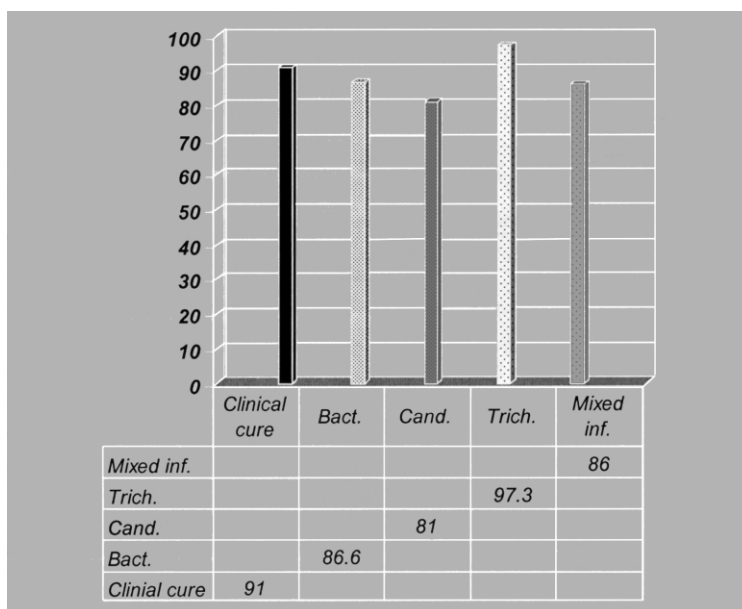


Fig. 3. Microbiological cure rates (%) in candidal, bacterial and trichomonal vaginitis, in mixed infections and the overall clinical cure rate.

cant improvements in vaginal inflammation and vaginal discharge after treatment, as assessed by gynecological examination ($P < 0.001$).

Only minor local reactions in two patients (vaginal burning) occurring in the first 2 days of the treatment were recorded. These complaints cleared spontaneously and it was not necessary to provide any treatment for these events.

4. Discussion

Vulvovaginal candidiasis, trichomonal vaginitis, and bacterial vaginosis are the most prevalent forms of vaginitis. Infection of the vagina with multiple pathogens is also very common; depending on the area in which the patient lives and hygiene conditions, mixed forms of vaginitis may be observed at a rate of between 10 and 30% [3–6]. Mixed infections are among the most important factors complicating the diagnosis and treatment of vaginitis [3]. Inaccurate diagnosis of vaginitis or not recognizing mixed infections may lead to inappropriate therapy, recurrence and re-infection [2].

Traditionally, the diagnosis of vaginitis is based on clinical findings observed during vaginal examination and laboratory analysis of vaginal specimens. Laboratory tests such as microscopic saline or KOH wet mount examination, odor test or measuring vaginal pH seem simple to perform, but are subject to many variables such as patient factors, clinician and laboratory technician skill, appropriate sampling, processing and interpretation. Other more complex tests are available for use [7], such as culture, Pap smear, tests for proline aminopeptidase, sialidases and various amine and acid byproducts. Although vaginal cultures provide a more sensitive and specific method for the diagnosis of vaginitis, they may require a minimum period of 5 days (*Trichomonas vaginalis*) or are not recommended routinely (bacterial vaginosis). In addition, some of the diagnostic tests mentioned above either lack sensitivity or may not be available to most clinicians; they are being expensive, time consuming, and labor intensive, and, thus, impractical for general clinical use [7]. Therefore, in practice, vaginitis is still diagnosed

on the basis of clinical findings, and treatment is generally started before the results of laboratory tests are available.

Since effective management of vaginitis depends on accurate diagnosis, the selection and administration of effective specific therapy, and good compliance of the patient, a single form of medication capable of treating candidal, bacterial and trichomonal vaginitis should provide a valuable form of therapy, especially in cases where the cause of vaginitis is unconfirmed and may be of mixed origin.

The Neo-Penotran[®] pessary is a logical combination of metronidazole (500 mg) and miconazole nitrate (100 mg), both standard medications at these doses. Earlier clinical studies with Neo-Penotran[®] [8–11] showed that with this combination, very high clinical and microbiological cure rates are achieved in patients with candidal, bacterial, and trichomonal vaginitis (Table 1). This study, for the first time, shows that Neo-Penotran[®] also provides effective and safe treatment in mixed vaginal infections.

The medication was well tolerated, and there was a drastic reduction in signs and symptoms of vaginitis at the end of 7 days treatment (visit 2) with follow-up examination carried out 2 weeks later (visit 3). The overall clinical cure rate was 91% with a further improvement in 7% of the patients (Fig. 3). Microbiological cure rates were 81, 87 and 97% for candidal, bacterial and trichomonal vaginitis, respectively, and 86% for mixed vaginal infections. The results for the microbiological evaluation (Fig. 3) are compared below with those from other trials carried out with Neo-Penotran[®], employing two different dosage schemes, as well as with those from other published trials in which the microbiological evaluation were similarly, but separately defined for metronidazole and miconazole.

In eight published studies in the treatment of bacterial vaginosis, three with vaginal metronidazole and five with oral metronidazole, the bacteriological cure rate ranged from 64 to 88%, the clinical cure rate ranged from 67 to 91% and the percentage showing improvement ranged from 80 to 92.3% [12–19].

Lugo-Miro et al. [20] published a meta-analysis of results of the treatment of bacterial vaginosis with metronidazole. Altogether 10 papers and 23 treatment regimens were analyzed. The combined cure rates, corresponding to the results at the end of treatment with Neo-Penotran[®], ranged according to the treatment regimen from 85 to 87%. In previous clinical studies with Neo-Penotran[®] the microbiological cure rates were 95.2 [8], 93.3 [9] and 89.5% [10]. In the present study, the microbiological cure rate (eradication of all microbes) was 87% at the end of 7 days treatment. This was highly comparable to the results of the meta analysis, as well as the cure rates obtained in previous studies carried out with two different dosage regimens of Neo-Penotran[®] (i.e. twice daily for 14 days or twice daily for 7 days). Microbiological recurrence rate in bacterial vaginosis was 3.8% in the present study, which is very similar to the results with previous NeoPenotran[®] studies and to other published studies with metronidazole.

In eight published trials with miconazole in the treatment of candidal vaginitis, the mycological cure rate at the end of treatment ranged from 62.5 to 91% [21–28]. Corresponding mycological cure rates obtained in earlier studies with Neo-Penotran were 97.6 [8], 93.3 [9] and 86.4% [10]. The equivalent cure rate in the present trial was 81%. Re-appearance of vulvovaginal candidal growth was found to be 16%, which is within the range of results previously published in the literature. Two out of five patients who had microbiological growth of candida at visit 3 were symptom-free (symptom score = 0); the remaining three had mild symptoms of vaginitis (symptom score = 1).

Published success rates for metronidazole in the treatment of trichomonal vaginitis vary between 50 and 97%, depending on the dosage regimen and the route of administration employed [2]. Clinical cure rates for trichomonal vaginitis obtained in previous trials with the 7-day regimen of Neo-Penotran[®] were 86.4 [10] and 83.3% [11]. Microbiological cure rates were 80 [9] and 82% [10], the dosage regimen being twice daily for 14 and 7 days, respectively. The microbiological cure rate obtained with 7 days treatment with Neo-Penotran[®] in the present study was

97.3%, similar to results obtained by other authors [2]. The microbiological recurrence rate (at visit 3) was 2.7% in this study, highly comparable to previous trials with Neo-Penotran[®] and to those found in the literature.

Forty-two out of 74 women with vaginitis presented multiple causative pathogens for vaginitis in their vaginal swabs. With 56.8%, the prevalence of mixed vaginal infections in this study population was very high when compared to previously published reports (up to 30%) [3–6]. Regional characteristics, poor hygiene conditions and multiple partners may be among a wide variety of factors affecting the high prevalence. After 7 days treatment with Neo-Penotran[®], microbiological eradication was achieved in 93% of patients with trichomonal + bacterial infection, and in 73% with bacterial and candidal infection. In 28 cases with trichomonal + bacterial infection, the recurrence rates (visit 3) were 3.6% (1/28) for trichomonal, and 7.1% (2/28) for bacterial infection. In 11 cases with bacterial + candidal infection, the recurrence rates were 0% for bacterial and 36.4% for candidal infection. In two out of three cases with bacterial + candidal + trichomonal infection, all three microorganisms were eradicated completely. Recurrence occurred in two out of three patients for candidal infection only. The overall microbiological cure rate for mixed infections was 86%. Although several published studies investigating the efficacy of various preparations in vaginitis included mixed vaginal infections, to our knowledge no corresponding data on metronidazole and/or miconazole nitrate are available in the literature.

Neo-Penotran[®] pessaries are well tolerated and relatively few, minor side effects have been recorded. Based on subjective and objective assessments, only minor local reactions in two patients (vaginal burning) occurring in the first 2 days of the treatment were recorded. These complaints cleared spontaneously and it was not necessary to treat them.

In conclusion, the Neo-Penotran[®] pessary represents a highly effective and safe medication for the treatment of common types of vaginitis, namely candidal, bacterial and trichomonal vaginitis and mixed vaginal infections. There appears to be no significant difference regarding

efficacy and safety between the 7-day and 14-day dosage regimens recommended for Neo-Penotran®.

Neo-Penotran® is of special value for the immediate treatment of vaginitis, irrespective of single or multiple infection, while the results of microbiological tests are awaited or where they are not available at all. Appropriate therapy is fundamental to successful treatment of vaginitis and diagnostic errors leading to inappropriate therapy have to be considered in the evaluation of treatment failures in patients with persisting, as well as recurrent symptoms. The results of this study, together with those published earlier, clearly show the value of NeoPenotran® in the treatment of vaginitis due to any or all of the three common causative agents even when the diagnosis may be uncertain.

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