

Clinical Effects of Nifuratel in Vulvovaginal Infections

A meta-analysis of metronidazole-controlled trials

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Summary

Nifuratel (CAS 4936-47-4) displays a strong antiprotozoarian and antibacterial activity and is provided with a certain fungicidal effect, but it is not active against the physiologic flora. Its therapeutic effectiveness has been evaluated in more than 12,000 patients. The wide clinical experience with nifuratel confirms that the drug is safe and effective for the treatment of trichomoniasis, bacterial vaginosis, candidosis, and, particularly, in patients suffering from mixed vaginal infections.

A meta-analysis of clinical trials comparing nifuratel and metronidazole (CAS 443-48-1) in vulvovaginal infections was performed. All parallel-group metronidazole-controlled trials carried out in patients with vulvovaginal infections have been included, complying with the following criteria: 1) cure assessed both as disappearance of symptoms and signs, and negative microbiological findings; 2) microbiological tests performed with valid methods still used in current practice.

Seven clinical trials have been selected, including overall 1767 patients, 832 out of whom were treated with nifuratel and 935 with metronidazole. The results of the meta-analysis confirmed the equivalence between nifuratel and metronidazole: overall proportion of cured patients in the two groups were 88.5 % and 90.0 %, respectively, in the presence of homogeneity among studies ($p = 0.342$).

In the fixed and random effect analyses, the confidence interval of Odds ratio included 1 and the p values for testing the hypothesis of no difference between treatments were 0.656–1.266, $p = 0.582$ (fixed effects) and 0.643–1.290, $p = 0.599$ (random effects), respectively, indicating equivalence.

Furthermore, some controlled studies and the wide clinical experience showed that the cure rate of nifuratel in patients with mixed infections due to *Trichomonas vaginalis* + *Candida* or *Trichomonas vaginalis* + bacteria or with bacterial vaginosis and mixed bacterial flora is higher than that of metronidazole, due to the wide spectrum of action of nifuratel.

Key words

- Bacterial vaginosis
- CAS 4936-47-4
- Inimur[®]
- Macmiror[®]
- Metronidazole
- Nifuratel, meta-analysis
- Trichomoniasis

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Zusammenfassung

Klinische Wirkungen von Nifuratel bei vulvovaginalen Infektionen / Eine Meta-Analyse von Metronidazol-kontrollierten Studien

Nifuratel (CAS 4936-47-4) zeigt eine starke antiprotozoische und antibakterielle Aktivität und besitzt eine gewisse fungizide Wirkung, wirkt jedoch nicht gegen die physiologische Flora. Seine therapeutische Wirksamkeit wurde an mehr als 12 000 Patientinnen getestet. Die breite klinische Erfahrung mit Nifuratel bestätigt, daß das Präparat in der Therapie von Trichomoniasis, bakterieller Vaginose, Candida-Mykosen und insbesondere vaginalen Mischinfektionen sicher und wirksam ist.

Eine Meta-Analyse von klinischen Studien, in denen Nifuratel und Metronidazol (CAS 443-48-1) bei vulvovaginalen Infektionen verglichen wurden, wurde durchgeführt. Alle Metronidazol-kontrollierten Parallelgruppen-Studien mit Patientinnen mit vulvovaginalen Infek-

tionen, die folgende Kriterien erfüllen, wurden berücksichtigt: 1) Die Infektion galt als geheilt, wenn die Symptome und Krankheitszeichen verschwunden und gleichzeitig die mikrobiologischen Ergebnisse negativ waren. 2) Die mikrobiologischen Tests wurden mit validierten Methoden durchgeführt, die noch heute in der Praxis angewandt werden.

Sieben klinische Studien wurden ausgewählt, an denen sich insgesamt 1767 Patientinnen beteiligten; 832 von ihnen wurden mit Nifuratel und 935 mit Metronidazol behandelt. Die Ergebnisse der Meta-Analyse bestätigten die Äquivalenz von Nifuratel und Metronidazol: Der Gesamtanteil der geheilten Patientinnen betrug in den beiden Gruppen 88,5 % bzw. 90,0 % bei Homogenität der Studien ($p = 0,342$). In den Analysen der festen und zufälligen Effekte lag das Vertrauensintervall des Verhältnisfaktors (odds ratio) im Bereich von 1, und die p-Werte für die Überprüfung der Hypothese der Äquivalenz beider Präparate betrugen

0,656–1,266, $p = 0,582$ (feste Effekte) bzw. 0,643–1,290, $p = 0,599$ (zufällige Effekte), was auf Äquivalenz hindeutet.

Darüber hinaus haben einige kontrollierte Studien und die breite klinische Erfahrung gezeigt, daß die Heilungsraten von Nifuratel bei Patientinnen mit Mischinfektionen durch *Trichomonas vaginalis* + *Candida* oder *Trichomonas vaginalis* + Bakterien sowie bei Patientinnen mit bakterieller Vaginose und gemischte Bakterienflora höher sind als diejenigen von Metronidazol, was auf das breite Wirkungsspektrum von Nifuratel zurückzuführen ist.

1. Background

Most cases of discharge in women of childbearing age are caused by bacteria; bacterial vaginosis represents a complex change in vaginal flora characterised by a reduction in the prevalence and concentration of hydrogen peroxide producing lactobacilli, and an increase in the prevalence and concentration of *Gardnerella vaginalis*, *Mycoplasma hominis*, anaerobic gram-negative bacteria belonging to the genera *Prevotella*, *Bacteroides*, and *Peptostreptococcus* species [1]. Bacterial vaginosis has been associated with several upper genital tract infections and obstetrical complications, such as pelvic inflammatory disease (PID), post-caesarean endometritis, post-hysterectomy pelvic infection, chorioamnionitis, premature rupture of membranes, and preterm labour and delivery [2–4]. *Candida* vaginitis is the second most common cause of vaginal infections and *Candida albicans* is responsible for 80 to 94 % of episodes of *Candida* vulvovaginitis, while several investigators have reported an increased percentage of non-*albicans* *Candida* species. Many factors increase susceptibility to vaginal *Candida* infections, such as pregnancy, taking old high-dose oral contraceptives, diabetes, systemic steroids, obesity and HIV infections. The third cause of infectious vaginitis is due to *Trichomonas vaginalis*; this organism has been found to coexist with a number of other infections, including gonococcal infection and bacterial vaginosis. *Tricho-*

monas infection is also associated with complications, including abnormal Pap test, PID, and premature rupture of membranes in pregnancy and neonatal respiratory tract infection as well as neonatal genital infections [5–6].

Although the history and gynaecologic examination are the source of important diagnostic clues, laboratory tests, such as vaginal pool wet mount exam, the amine whiff test, vaginal pH, and the Q-tip test, should routinely be performed in all patients presenting a vaginal discharge to obtain a differential diagnosis, while vaginal cultures are required only for confirmation, according to the individual cases [7].

Metronidazole (CAS 443-48-1) continues to be regarded as the agent of choice in the management of both bacterial vaginosis and trichomoniasis. Although metronidazole is highly active against anaerobic bacteria, it is less active against *Gardnerella vaginalis* and poor against *Mobiluncus* species. Despite this, a repeated 7-day course of metronidazole is often effective treatment for a recurrence. A small number of women shows multiple recurrences. Prolonged oral use of metronidazole is associated with a high incidence of side effects located to the gastrointestinal tract and a risk of peripheral neuropathies. Its use in pregnancy has been a matter of concern due to its theoretically supposed teratogenic effects [8].

Several topical antifungals, such as clotrimazole, miconazole, tioconazole, terconazole, nystatin, achieve high cure rates in excess of 80 % in case of uncompli-

cated vulvovaginal candidoses. The differences in formulations are not considered to be clinically relevant.

Oral azoles, such as ketoconazole, itraconazole and fluconazole, have also been shown to achieve high cure rates, but they are currently contraindicated in pregnancy [9].

The vulvo-vaginal infections have progressively changed during the last years, both quantitatively and qualitatively, with the onset of mixed forms (where protozoa and mycetes are often associated with bacteria).

Nifuratel¹⁾ (CAS 4936-47-4) displays a strong antiprotozoarian and antibacterial activity and it is provided also with some fungicidal effect [10–11]. Unlike doxycycline, nifuratel is not active against *Lactobacillus* spp. This fact is important in the vaginal infections where the complete eradication of *Lactobacillus* spp. may produce change of vaginal microbial flora and vaginal pH. Nifuratel has a very safe toxicological profile and it is devoid of teratogenic effects; furthermore, the comparison among past and recent clinical studies confirms that no resistance phenomena to the treatment with nifuratel are reported [11]. Its therapeutic effectiveness has been evaluated in more than 12,000 patients, and it is on the market since 1965 in many European and extra-European Countries. The wide clinical experience so far with nifuratel confirms that the drug is effective for the treatment of trichomoniasis, bacterial vaginosis, candidoses, and, particularly, in patients suffering from mixed vaginal infections.

Several trials comparing nifuratel with metronidazole and other agents currently used in the treatment of vulvovaginal infections have demonstrated the therapeutic equivalence of the treatments [12–21]. Most of the studies have been performed before GCPs (good clinical practice) came into force, and they reflect suitable methods for that period.

In order to assess the homogeneity of the results obtained in these trials and to confirm the equivalence between nifuratel and metronidazole in the treatment of vulvovaginal infections, we applied the meta-analytical procedure, a retrospective quantitative technique that pools data from multiple trials.

2. Methods

An extensive search of all controlled clinical trials with nifuratel in vulvovaginal infections was performed. We included in the meta-analysis all parallel-group, metronidazole-controlled trials carried out in patients with vulvovaginal infections, like trichomoniasis, bacterial vaginosis, candidoses and mixed vaginal infections, that comply with the following criteria: 1) cure

assessed both as disappearance of symptoms and signs, and negative microbiological findings; 2) microbiological tests conducted with valid methods still used in current practice.

Seven studies have been selected, four out of which were performed in patients affected by *Trichomonas vaginalis* (T.v.) and three in mixed forms (see Table 1). A brief description of these trials is reported as follows.

Forty-two patients with recurrent trichomoniasis subsequent to treatment with nifuratel and 37 patients with recurrence after metronidazole treatment were assigned to receive a second treatment with nifuratel (40 cases – 200 mg oral three times daily for 7 days and 250 mg/day vaginally for 10 days) or metronidazole (39 cases – 250 mg orally twice a day and 100 mg/day intravaginally for 6 days). The cure rate was 87.5 % after nifuratel and 87.1 % after metronidazole [15]. No cross resistance between metronidazole and nifuratel could be proved in these cases.

Patients with trichomonal vaginitis were assigned to receive metronidazole at the dosage of 200 mg orally three times a day for 7 days (120 women) or nifuratel at the dosage of 200 mg orally three times a day for 7–10 days (90 women). The cure rate was 73 % and 77 %, respectively [16].

An open, randomised, parallel group trial compared the activity of oral nifuratel and metronidazole in female patients suffering from vaginitis due to *Trichomonas vaginalis*. The treatments (nifuratel 1200 mg/day for 10 days or metronidazole 750 mg/day for 10 days) were randomly assigned to 184 patients (92 for each treatment group). The cure rate after the 1st cycle of therapy was 73.9 % and 78.3 %, respectively, while the overall cure rate after 2 cycles was 80.4 % and 82.6 % [17].

A study compared nifuratel vaginal and oral treatment with metronidazole, given at the following dosage: 500 mg/day vaginally for 7 days + 600 mg/day orally for 10 days in trichomonal vaginitis. A second cycle of the two treatments was foreseen in case of failure after the first one; concomitant oral treatment for sexual partners was performed. The cure rates after the 1st cycle (80 % nifuratel – 79 % metronidazole) and the 2nd one (95 % nifuratel and 89 % metronidazole) were very similar [18].

The efficacy of nifuratel (oral 600 mg/day and vaginal 250 mg/day for 10 days) and that of metronidazole (oral 750 mg/day and vaginal 500 mg/day for 10 days) were compared in 1050 cases. The cure rates were 79 % for nifuratel and 90 % for metronidazole in patients with infections due to T.v. alone; 58 % and 45 %, respectively, in T.v. and fungi infections, 75 % and 65 %, respectively, in T.v. and mixed bacterial flora infections. A second course in patients who were not cured after the first treatment showed a cure rate of 80 % and 96 %, respectively, in patients with T.v., of 90 % and 81 %, respectively, in patients with T.v. and fungi and of 100 % and 95 % in patients with T.v. and mixed bacterial flora [19].

One hundred and forty patients with vaginitis due to T.v., *Candida*, bacteria or mixed infections were randomly assigned to receive oral nifuratel 600 mg/day for 7 days + vaginal nifuratel 250 mg/day for 10 days (70 cases) or oral metronidazole 600 mg/day for 7 days + vaginal nystatin 200000 IU/day for 7 days (70 cases). Cure rates were 75 % and 69.2 %, respectively [20].

Thirty six patients with vaginitis due to T.v., *Candida albicans* or “mixed non specific bacterial infections” [21] were treated with nifuratel (200 mg orally three times daily for 7 days and 250 mg intravaginally for 10 days) or metronidazole (250 mg 3 times daily orally and nystatin 1 vaginal pessary for 7 days). The cure rate was 54.5 % and 50 %, respectively.

¹⁾ Available as Inimur® / Macmiror® (Taurus Pharma GmbH, Polichem S.A.) in form of sugar coated tablets (200 mg nifuratel), pessaries (250 mg nifuratel) and 10 % ointment, respectively.

Table 1: Characteristics of the studies included in the meta-analysis.

Study (reference)	No. of patients enrolled (nifuratel / metronidazole)	Diagnosis	Route of administration / treatment duration	Dosage/day
Schmidt, H. [15]	40 / 39	<i>Trichomonas vaginalis</i>	N: oral, 7 days + vaginal, 10 days M: oral, 6 days + vaginal, 6 days	N: 600 mg + 250 mg M: 500 mg + 100 mg
Gjønnaess, H. [16]	90 / 120	<i>Trichomonas vaginalis</i>	N: oral, 7–10 days M: oral, 7 days	N: 600 mg M: 600 mg
Baron, A. [17]	92 / 92	<i>Trichomonas vaginalis</i>	N: oral, 10 days M: oral, 10 days	N: 1200 mg M: 750 mg
Block, E. [18]	50 / 50	<i>Trichomonas vaginalis</i>	N: oral, 7 days + vaginal 10 days M: oral, 7 days + vaginal 10 days	N: 600 mg + 500 mg M: 600 mg + 500 mg
Goisis, M. [19]	482 / 568	Trichomoniasis (170/230) <i>Trichomonas vaginalis</i> + fungi (50/38) <i>Trichomonas vaginalis</i> + mixed bacteria (262/300)	N: oral, 10 days + vaginal, 10 days M: oral, 10 days + vaginal, 10 days	N: 600 mg + 250 mg M: 600 mg + 250 mg
Pathak U.N. [20]	56 / 52	<i>Trichomonas vaginalis</i> (13/14) Moniliasis (28/23) Mixed bacterial flora (15/15)	N: oral, 7 days + vaginal, 10 days M: oral, 7 days + vaginal, 7 days *	N: 600 mg + 250 mg M: 600 mg + Nys 200,000 IU
Struthers J.O. [21]	22 / 14	<i>Trichomonas vaginalis</i> (7/7) Candidiasis (5/2) Mixed bacterial flora (10/5)	N: oral, 7 days + vaginal, 10 days M: oral, 7 days + vaginal, 7 days *	N: 600 mg + 250 mg M: 750 mg + Nys 1 pessary

N: nifurated, M: metronidazole, Nys: nystatin.

* Oral metronidazole combined with vaginal nystatin.

2.1. Measures of efficacy

This meta-analysis focused on recovery from vulvovaginal infection (eradication of the pathogen) at the end of treatment as measure of efficacy. In all cases in which data were available, intent-to-treat analyses were performed; withdrawal was considered as treatment failure.

2.2. Statistical analyses

The significance ($p < 0.05$, two-sided) of the overall treatment effect was evaluated by a chi-squared statistic (association test). Relative Risk (RR) and Odds Ratio (OR) with their 95% confidence intervals (CI) were calculated for individual trials and for the summary results. For the analysis of dichotomous variables, a treatment effect model (fixed or random effects model) was selected by testing for heterogeneity of the effect across the trials with a chi-square statistic, assuming a more liberal level of significance ($p < 0.1$). If the test of heterogeneity was significant, a random-effects analysis was carried out; in addition, for each outcome measure, we also used the fixed-effects and random-effects models to estimate summary treatment effects for all studies combined [22–23].

2.3. Sensitivity analyses

To determine whether the results were unduly influenced by a single trial or a small number of trials, we repeated the meta-analysis, by using fixed and random effects models, including trials in chronological order to assess the robustness of treatment effects over a period of time and after successively withdrawing trials in decreasing order of their Odds ratio.

Table 2: Summary results.

Study (reference)	No. of patients (nifuratel / metronidazole)	Recovery (nifuratel / metronidazole)	Odds ratio (Confidence Interval)
Schmidt H. [15]	40/39	35 (88 %) / 34 (87 %)	1.029 (0.273–3.878)
Gjønnaess H. [16]	90/120	69 (77 %) / 88 (73 %)	1.195 (0.634–2.253)
Baron A. [17]	92/92	74 (80 %) / 76 (83 %)	0.866 (0.411–1.824)
Block E. [18]	50/50	42 (84 %) / 42 (84 %)	1.000 (0.343–2.913)
Goisis M. [19]	482/568	462 (96 %) / 559 (98 %)	0.372 (0.168–0.825)
Pathak U.N. [20]	56/52	42 (75 %) / 36 (69 %)	1.333 (0.573–3.102)
Struthers J.O. [21]	22/14	12 (55 %) / 7 (50 %)	1.200 (0.314–4.594)
Total	832/935	736 (88 %) / 842 (90 %)	

Further tests and analyses

Test of heterogeneity (Q,p)	6.780, 0.342
Fixed effects analysis (Odds ratio, 95% Confidence Interval, p)	0.912, (0.656–1.266), 0.582
Random effects analysis (Odds ratio, 95% Confidence Interval, p)	0.911, (0.643–1.290), 0.599

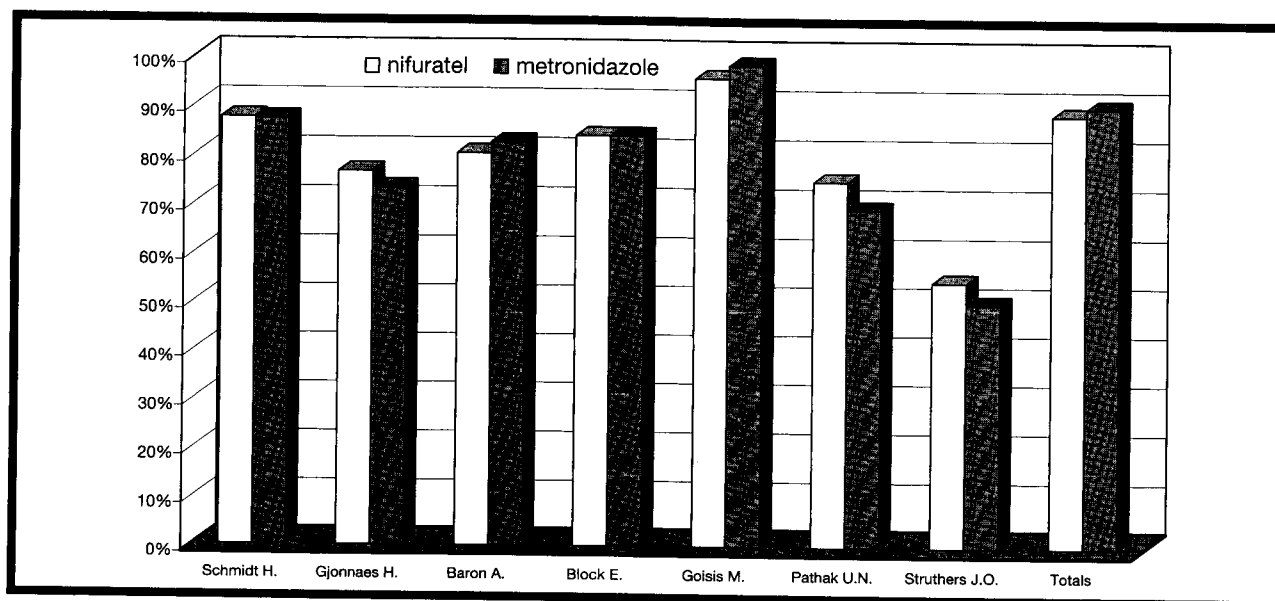


Fig. 1: Recovery rate (%) with nifuratel or metronidazole in vulvovaginal infections.

3. Results

Seven clinical trials with nifuratel in vulvovaginal infections met the inclusion criteria in the present analysis.

In these trials a total of 1767 patients has been enrolled, 832 out of whom were treated with nifuratel and 935 with metronidazole (Table 1). The results of the meta-analysis confirmed the equivalence between nifuratel and metronidazole (Table 2, Fig. 1): overall proportion of cured patients in the two groups were 88.5 % and 90.0 %, respectively, in the presence of heterogeneity among studies ($p = 0.001$). In the fixed and random effect analyses, the confidence interval of Odds ratio included 1 and the p values for testing the hypothesis of no difference between treatments were 0.656–1.266, $p = 0.582$ (fixed effects) and 0.643–1.290, $p = 0.599$ (random effects), respectively, indicating equivalence.

4. Discussion

Nifuratel is a drug endowed with a wide spectrum of activity against micro-organisms responsible for vulvovaginal infections, such as *Trichomonas vaginalis*, aerobic and anaerobic bacteria, *Gardnerella vaginalis* and *Candida* spp. In trichomoniasis, in order to reach the extravaginal localisations of the protozoa, it is essential to combine the topical therapies (pessaries, ointment) with the oral one (sugar coated tablets). The partner should undergo the oral therapy since he is often the symptomless carrier of the parasite. In case of evident local symptoms, also the local treatment of the male partner with the ointment is recommended. Oral treatment is also indicated in vaginitis of uncertain origin. In trichomonal vaginitis, when it is neither desirable nor practicable to carry out local therapy, good results will be obtained with oral therapy alone, using a higher dose.

Nifuratel is on the market since more than 30 years; clinical trials on the drug have been performed before Good Clinical Practice came into force and they reflect suitable methods for that period. However, a lot of experience has been gained in clinical practice up today and nifuratel has been confirmed to be effective in patients suffering from trichomoniasis, bacterial vaginosis, candidoses, and, particularly, in patients suffering from mixed vaginal infections.

The results of the present meta-analysis confirm that nifuratel is as effective as metronidazole, the gold standard therapy for trichomonal infections. The analysis was not adjusted for study quality and, therefore, potentially at risk for this bias. In fact, it has been shown that inclusion of studies of low methodological quality tend to show an increased estimate of benefits. However, the sensitivity analysis performed on the concerned data, did not detect any effect of exclusion of individual trials or a publication bias.

Furthermore, some controlled studies and the wide clinical experience showed that the cure rate of nifuratel in patients with mixed infections due to *Trichomonas vaginalis* + *Candida* or *Trichomonas vaginalis* + bacteria or with bacterial vaginosis and mixed bacterial flora is higher than that of metronidazole, due to the wide spectrum of action of nifuratel.

5. References

- [1] Hill, G. B., Microbiology of bacterial vaginosis. Am. J. Obstet. Gynaecol. 169, 450 (1993)
- [2] MacDermott, R. I. J., Bacterial vaginosis. Br. J. Obstet. Gynecol. 102, 92 (1995)
- [3] Oleen-Burkey, M. A., Hillier, S. L., Pregnancy complications associated with bacterial vaginosis and their estimated costs. Infect. Dis. Obstet. Gynecol. 3, 149 (1995)

- [4] Hillier, S. L., Martius, J., Krohn, M. et al., A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. *N. Engl. J. Med.* **319**, 971 (1988)
- [5] Carr, P. I., Felsenstein, D., Friedman, R. H., Evaluation and management of vaginitis. *J. Gen. Int. Med.* **13**, 335 (1998)
- [6] Sobel, J. D., Vulvovaginitis in healthy women. *Comp. Ther.* **25**, 335 (1999)
- [7] Quan, M., Vaginitis: meeting the Clinical Challenge. *Clin. Cornestone* **3**, 36 (2000)
- [8] SOGC (Society of Obstetricians and Gynaecologists of Canada), Clinical Practice Guidelines, Committee Opinion No. 14, March 1997
- [9] Reef, S., Levine, W. C., McNeil, M. M. et al., Treatment options for vulvovaginal candidiasis. Background paper for development of 1993 STD treatment recommendations. *Clin. Infect. Dis.* **20** (Suppl.), 580 (1995)
- [10] Dubini, F., Furneri, P., Attività antimicrobica del Nifuratel. *G. Ital. Chemioter.* **32**, 545 (1985)
- [11] Mendling, W., Mailland, F., Microbiological and pharmacotoxicological profile of nifuratel and its favourable risk/benefit ratio for the treatment of vulvo-vaginal infections. *Arzneim.-Forsch./Drug Res.* **52**, 8 (2002)
- [12] Evans, B. A., Catterall, R. D., Nifuratel compared with metronidazole in the treatment of trichomonal vaginitis. *Brit. Med. J.*, May 9, 1970, p. 335
- [13] Heiss, H., Klinische Auswertung aktiver Arzneimittel gegen Trichomoniasis vaginalis im Doppel-Blindversuch. *Wien. Med. Wochenschr.* **121**, 832 (1971)
- [14] Arnold, M., Vergleich von Nifuratel und Tinidazol bei Trichomonadenvaginitis. *Ther. Umschau* **31**, 202 (1974)
- [15] Schmidt, H., Soost, H. J., Treatment of vaginal trichomoniasis and mycosis with nifuratel, in: F. Gasparri, G. Gargani, P. Periti (eds.), *Diagnosis and chemotherapy of urogenital infections*, pp. 191–195. Edizioni Mediche P. Periti, Firenze (1972)
- [16] Gjønnaess, H., Aure, J. C., Treatment of vaginal infections due to *Trichomonas* or *candida*, in: F. Gasparri, G. Gargani, P. Periti (eds.), *Diagnosis and chemotherapy of urogenital infections*, pp. 153–155. Edizioni Mediche P. Periti, Firenze (1972)
- [17] Baron, A., Roznicz między leczeniem ogólnym i skojarzonym rzesistkowicy za pomoca metronidazolu i nifuratlu. *Wiad. Parazytol.* **19** (2), 511 (1973)
- [18] Block, E., Effekten av Nifuratel och metronidazol vid behandling av Trichomoniasis. *Läkartidningen* **69**, 5210 (1972)
- [19] Goisis, M., Oppo, G. T., Treatment of female trichomoniasis, in: F. Gasparri, G. Gargani, P. Periti (eds.), *Diagnosis and chemotherapy of urogenital infections*, pp. 197–202. Edizioni Mediche P. Periti, Firenze (1972)
- [20] Pathak, U. N., Sur, S. K., Farrand, R. J., Comparison of metronidazole/nystatin and nifuratel in the treatment of vaginitis. *Br. J. Clin. Pract.* **29**, 10 (1975)
- [21] Struthers, J. O., Treatment of patients with trichomonal, fungal and mixed bacterial vaginal infections at an out-patient gynaecological clinic, in: F. Gasparri, G. Gargani, P. Periti (eds.), *Diagnosis and Chemiotherapy of urogenital infections*, p. 157. Edizioni Mediche P. Periti, Firenze (1972)
- [22] Fleiss, J. L., The statistical basis of meta-analysis. *Stat. Methods Med. Res.* **2**, 121 (1993)
- [23] DerSimonian, R., Laird, N., Meta-analysis in clinical trials. *Control. Clin. Trials* **7**, 177 (1986)

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Microbiological and Pharmacotoxicological Profile of Nifuratel and its Favourable Risk/Benefit Ratio for the Treatment of Vulvo-vaginal Infections

A review

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Summary

Nifuratel (CAS 4936-47-4) is a furane-derivative provided with a strong trichomonocidal activity equivalent to that of metronidazole (CAS 443-48-1); it has a broad antibacterial spectrum of action, including both Gram-negative and Gram-positive organisms. It is active against *Chlamydia trachomatis* and *Mycoplasma spp.* and has also some degree of activity against *Candida spp.* and mycetes. Its broad spectrum of action, confirmed by in vitro and in vivo studies, covers virtually all the micro-organisms responsible for the infections of the genito-urinary tract.

Nifuratel has a very safe toxicological profile. It is practically non-toxic in acute tests in mice and rats and is also well tolerated after repeated oral and intravaginal administrations. Nifuratel is devoid of teratogenic effects.

The comparison among past and recent clinical studies confirms that, in contrast to metronidazole, no resistance phenomena to the treatment with nifuratel are reported. The drug can be used during pregnancy due to the absence of teratogenic effects. In conclusion, nifuratel shows a very favourable risk/benefit ratio for the treatment of patients with vulvo-vaginal infections.

Key words

- CAS 4936-47-4
- Inimur[®]
- Macmilur[®]
- Nifuratel, antimicrobial activity, pharmacotoxicological profile, resistance phenomena
- Vulvo-vaginal infections

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Zusammenfassung

Mikrobiologisches und pharmakotoxikologisches Profil von Nifuratel und sein günstiges Nutzen-Risiko-Verhältnis in der Therapie von vulvovaginalen Infektionen / Eine Übersicht

Nifuratel (CAS 4936-47-4) ist ein Furan-Derivat mit einer starken trichomo-

niziden Aktivität, die derjenigen von Metronidazol (CAS 443-48-1) entspricht; die Substanz besitzt ein breites antibakterielles Wirkungsspektrum, das sowohl die gramnegativen als auch die grampositiven Organismen einschließt. Sie wirkt gegen *Chlamydia trachomatis* sowie *Mycoplasma spp.* und zeigt auch eine gewisse

Aktivität gegen *Candida spp.* und Pilze. Das breite Wirkungsspektrum der Substanz, das durch In-vitro- und In-vivo-Studien bestätigt wurde, umfaßt praktisch alle Mikroorganismen, die für Infektionen des Urogenitaltrakts verantwortlich sind.

Nifuratel besitzt ein sehr sicheres toxi-kologisches Profil; in Akuttests mit Mäusen und Ratten zeigt es praktisch keine

Toxizität. Nach wiederholter oraler und intravaginaler Verabreichung ist es gut verträglich, und es ist frei von teratogenen Wirkungen.

Der Vergleich von früheren und neueren klinischen Studien bestätigt, daß im Gegensatz zu Metronidazol über keine Resistenz-Phänomene in der Therapie mit Nifuratel berichtet wird. Da die Substanz keine teratogenen Wirkungen aufweist,

kann es auch während der Schwangerschaft angewendet werden. Zusammenfassend kann festgestellt werden, daß Nifuratel eine sehr günstiges Nutzen-Risiko-Verhältnis in der Therapie bei Patientinnen mit vulvovaginalen Infektionen zeigt.

Diagnosis and treatment of vaginal infections

During the last ten years, a variation has occurred in the nature and incidence of vaginal infections due to changes in lifestyle resp. people's sexual behaviour [1], the wide-spread use of hormonal contraceptives or intra-uterine device [2, 3], an improper use of antimicrobial agents [4] and the employment of specific products for personal hygiene [5, 6].

Recent research has increased our understanding of the disease process and its potential sequelae resulting in improved diagnostic and treatment modalities [7]. Nevertheless, differential diagnosis in the office setting of all forms of vaginitis, which include different types of non-infectious and infectious vaginitis and among vaginal infections the mixed forms, is often problematic for practitioners. In fact, although the history and clinical examination are the source of important diagnostic clues, wet mount confirmation should routinely be performed in all patients presenting with a vaginal discharge, and laboratory investigations are necessary in many cases.

The saline wet mount examination remains the cornerstone of the diagnostic evaluation of the patient with a vaginal discharge by giving a „photograph“, in real time, of the vaginal flora and making it possible to estimate the presence of an abnormal amount of white blood cells, motile trichomonads, clues cells or budding yeast cells and pseudohyphae.

In addition, office laboratory tests that should be routinely performed include the amine Whiff test, and the determination of the vaginal pH [8].

When an infectious vaginitis has been confirmed, vaginal cultures can be used on a selective basis to identify the suspected pathogens, as there are yeasts, B-streptococci or chlamydia. It is not useful to prepare bacteriological cultures in all cases because facultative aerobes and anaerobes are present in the healthy and the ill vagina and differ only by count [9].

In order to get an idea of the incidence of the different infections, it seems useful to look at the epidemiological data reported in studies carried out throughout the Italian territory in 1993 [10] (Table 1). Vulvo-vaginitis actually represents the main reason for consulting a gynaecologist.

As a matter of fact, out of 3,069 women involved in the Italian study, 1,722 (i.e. 56.1 %) turned out to be affected by a vulvo-vaginal inflammatory disease. The history of the latest vulvo-vaginal episodes reveals a considerable increase in the number of infections caused by bacteria and mycetes, especially *Candida albicans*, whose frequency has nearly doubled [4] in England and the United States in the last few years. Moreover, the observation has pointed out that protozoa (*Trichomonas vaginalis*) are often associated with a bacterial infection, giving rise to a condition of mixed aetiology. These forms of vaginitis are extremely obstinate and tend to relapse after the treatment.

On the basis of such observations, it is not surprising that the therapy of vulvo-vaginitis is adjusting itself to the changing disease conditions. Accordingly, treatments are focussing on the possibility to cover these mixed vulvo-vaginal infections.

A remarkable progress in the „global“ struggle against the agents responsible for vulvo-vaginal infections has been achieved with the synthesis of metronidazole (CAS 443-48-1).

The clinical efficacy of metronidazole is very high (cure rate 74–99 %) towards anaerobic Gram-negative microorganisms [11, 12] but not so high towards *Gard-*

Table 1: History in 1722 patients with current vulvo-vaginitis [10].

Total patients with current vulvo-vaginitis (N)	1722
Total patients with first episode (N, %)	692 (40.2 %)
Total patients with previous episodes (N, %)	1030 (59.8 %)
Total episodes in the past (mean \pm SEM, range)	3.8 \pm 0.11 (1–30)
Episodes during the preceding 12 months (mean \pm SEM, range)	1.5 \pm 0.04 (1–8)
Etiology of the last episode (N, %):	
– mycetes	400 (38.8 %)
– <i>Trichomonas vaginalis</i>	119 (11.6 %)
– mixed	95 (9.2 %)
– enterobacter	65 (6.3 %)
– <i>Gardnerella vaginalis</i>	58 (5.6 %)
– viruses	14 (1.4 %)
– unknown	279 (27.1 %)

nerella vaginalis, on which metronidazole acts through the hydroxy metabolite produced in the liver [13].

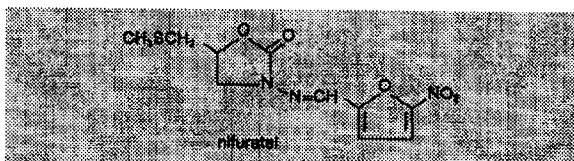
All the 22 *Mobiluncus mulieris* breeds are resistant to the drug [14]; 20 % of bacterial vaginosis either do not react to this antibiotic or develop resistance to it [15, 16]. Prolonged oral use of metronidazole is associated with a high incidence of side effects on the gastrointestinal tract and a risk of peripheral neuropathies; its use in pregnancy has been for years a matter of concern [17, 18].

Therefore it is quite obvious that in the treatment of mixed vulvo-vaginal infections there is a need for a drug provided with a broad spectrum of action, devoid of resistance phenomena, endowed with a good safety profile, and, finally, suitable for using during pregnancy.

Several drugs have been investigated during recent years, among these nifuratel¹⁾ (CAS 4936-47-4). This review aims at verifying, from a microbiological and pharmacotoxicological point of view, if nifuratel is a drug which can satisfy the medical needs mentioned above.

In vitro and in vivo antimicrobial activity of nifuratel

Nifuratel is a furane derivative, its chemical name is 5-[(methylthio)methyl]-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone, and it has a structural formula as shown below. It is provided with a broad spectrum of action against virtually all the microorganisms responsible for infections of the genito-urinary tract, such as *Trichomonas vaginalis*, *Gardnerella vaginalis*, aerobic and anaerobic bacteria, *Candida* spp., *Chlamydia trachomatis* and *Mycoplasma* spp.



In vitro studies showed that the activity of nifuratel against *Trichomonas vaginalis* is equivalent to that of metronidazole with a MIC₉₀ value (i.e. the minimum concentration of drug which inhibits 90 % of colony growth) for both compounds equal to 1 µg/ml. The inhibitory effect of nifuratel against *Gardnerella vaginalis* is higher than that of metronidazole (MIC₉₀: 1.9 µg/ml

¹⁾ Available as Inimur® / Macmiror® (Taurus Pharma GmbH, Polichem S.A.) in form of sugar coated tablets (200 mg nifuratel), pessaries (250 mg nifuratel) and 10 % ointment, respectively.

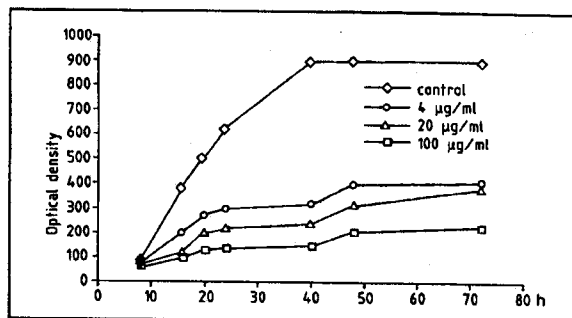


Fig. 1: In vitro antimicrobial activity of nifuratel: *Candida albicans* [20].

and 7.8 µg/ml, respectively). Against Gram-positive aerobic bacteria (β -haemolytic streptococci, *Staphylococcus aureus*, *Staphylococcus epidermidis*), nifuratel shows an inhibitory activity, while metronidazole is actually inactive. Metronidazole is also inactive against Gram-negative aerobic strains, while nifuratel shows a weak inhibitory effect in vitro against *E. coli* (but a good effect in vivo and in clinical trials) as well as against *Klebsiella pneumoniae*, *Enterobacter*, *Citrobacter* and *Shigella* [19] (see Fig. 1 and Table 2).

Towards *Chlamydia*, nifuratel showed an activity of the bacteriostatic type as cell inclusion appeared again in two subsequent subcultures treated without the drug. Even the effects on *Mycoplasma pneumoniae*, *Mycoplasma hominis* and *Ureaplasma urealyticum* remarkably increase the therapeutic interest of this drug.

Table 2: Comparative antibacterial activity of nifuratel (MIC: µg/ml; [19]).

	Metronidazole	Aminotriazole	Nifuratel
<i>Micrococcus pyogenes</i> var. aureus To4	> 200	50	5
<i>Micrococcus pyogenes</i> var. aureus To7	> 200	25	10
<i>Micrococcus pyogenes</i> var. aureus C 40	> 200	50	10
<i>Micrococcus pyogenes</i> var. aureus C 12	> 200	50	10
<i>Micrococcus pyogenes</i> var. aureus C 74	> 200	25	2.5
<i>Sarcina lutea</i> ATCC 9341	> 200	25	20
<i>Bacillus subtilis</i>	> 200	10	5
<i>Pseudomonas aeruginosa</i>	> 200	> 200	> 200
<i>Salmonella typhi</i> C 901	> 200	25	25
<i>Salmonella paratyphi</i> B	> 200	25	25
<i>Proteus vulgaris</i>	> 200	50	50
<i>Proteus mirabilis</i>	> 200	> 200	> 200
<i>Klebsiella pneumoniae</i>	> 200	100	100
<i>Shigella sonnei</i>	> 200	25	25
<i>Escherichia coli</i> To 110	> 200	25	5
<i>Escherichia coli</i> Coll. Ist. 1	> 200	25	10
<i>Escherichia coli</i> Coll. Ist. 2	> 200	50	5
<i>Escherichia coli</i> Coll. Ist. 3	> 200	50	5
<i>Gardnerella vaginalis</i>	7.8	—	1.9

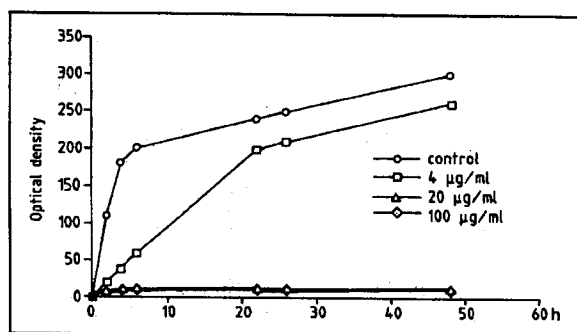


Fig. 2: In vitro antimicrobial activity of nifuratel: *Escherichia coli* [20].

Unlike metronidazole, which is inactive against fungi, nifuratel shows a certain degree of activity against *Candida* spp. (*C. albicans*, *C. krusei*, *C. pseudotropicalis*, and *C. guilliermondii*), the MIC ranging between 250 and 500 µg/ml (Fig. 2 and Table 3).

Furthermore, nifuratel is not active against *Lactobacillus* spp. This finding is important for vaginal infections where the complete eradication of *Lactobacillus* spp. may produce a change of vaginal microbial flora and vaginal pH.

In animals, nifuratel proved to be a particularly active agent against *Trichomonas vaginalis*, when administered with 50 mg/kg for four consecutive days, following an intraperitoneal injection of *T. vaginalis*, or after the concomitant intraperitoneal injection of *T. vaginalis* and 6.25 mg/kg of nifuratel. It showed a good in vivo activity like that of ciclopirox olamine against intravaginal infections with *Candida albicans* in female rats [20].

Mycotic superinfections after nifuratel

Contrarily to the mycotic superinfections developed after treatment with other antitrichomonal drugs [21], in a clinical study surveying 800 patients affected by

Table 3: Comparative antimycotic activity of nifuratel (MIC: µg/ml; [19]).

	Metronidazole	Amni-trazole	Nifuratel
<i>Candida albicans</i> Institute's Collection	> 500	> 500	> 500
<i>Candida albicans</i> vag. isolations	> 500	> 500	> 500
<i>Candida albicans</i> vag. isolations	> 500	> 500	500
<i>Candida guilliermondii</i> var <i>membranaefacens</i>	500	> 500	250
<i>Candida guilliermondii</i> B4 II	250	> 500	250
<i>Candida parapsilopsis</i> Dutch brood	250	> 500	250
<i>Debaryomyces neoformans</i>	> 500	> 500	125
<i>Turulopsis rosea</i>	> 500	> 500	500
<i>Trichophyton tonsurans</i>	> 500	> 500	31.25
<i>Cryptococcus neoformans</i>	> 500	> 500	62.5

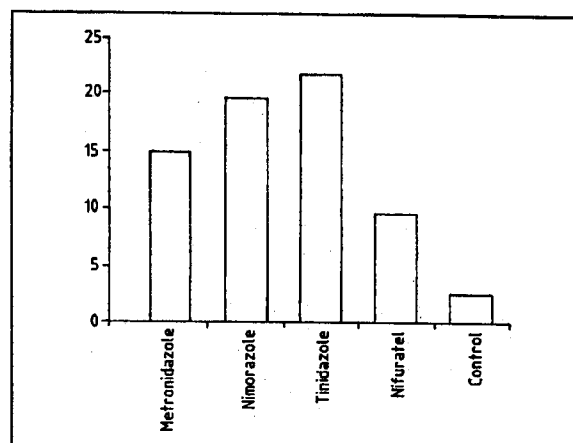


Fig. 3: Fungal superinfections after *Trichomonas*-killing therapy (% values) [22].

Trichomoniasis, treatment with nifuratel resulted in a lower urogenital incidence of fungi-induced superinfections in vivo if compared to metronidazole [22] (Fig. 3).

It has been assumed that the pro candida effect of antitrichomonal drugs takes place through a modification of the intestinal and vaginal bacterial flora.

Resistance phenomena

In order to define any possible appearance of resistance phenomena concerning nifuratel, the data reported in less recent papers have been compared to those reported in more recent ones. The papers dealing with vaginal treatment are those by Arias Huerta [23], Schmidt [24, 25], Baron [26], Heiss [27, 28], Turanova and Skuratovich [29], Block [30], and Rognoni and Sagone [31] (Table 4).

The development of resistance phenomena towards a chemoantibiotic drug is theoretically possible but not evidenced for nifuratel, as pointed out by Imperato [32], Scuri and Failla [33], Savoia and Leoncavallo [34], Barbier [35], Hamilton-Miller et al. [36], Dubini and Furneri [19] and Coppi [20] (Table 5) when comparing older

Table 4: Clinical experience with nifuratel during 10 years: nifuratel cure rate of trichomonal infections.

Author	Year	No. of patients	Trial design	Cure rate (%)
Arias Huerta [23]	1968	45	open	87
Schmidt et al. [24]	1969	137	open	84
Baron et al. [26]	1970	146	open	88
Heiss et al. [27]	1971	92	open	88
Heiss et al. [28]	1972	72	double blind	87
Schmidt et al. [25]	1972	40	open	88
Turanova et al. [29]	1972	48	open	85
Block et al. [30]	1975	44	double blind	80
Rognoni et al. [31]	1976	33	open	80

Table 5: Evidence of absence of resistance phenomena with nifuratel. Comparison of microbiological results during a period of 30 years.

Author	MIC values	
	<i>Trichomonas vaginalis</i> (µg/ml)	<i>Escherichia coli</i> (µg/ml)
Imperato 1963 [32]	0.2–0.5	10
Scuri and Failla 1964 [33]	0.02	10
Savoia and Leoncavallo 1970 [34]	0.50	5–10
Barbier 1974 [35]	0.25–1.0	2–3
Hamilton and Miller et al. 1978 [36]	–	6.10
Dubini and Furneri 1985 [19]	0.1–1.0	–
Coppi 1993 [20]	–	1.56–6.25

microbiological results with the newer data. During the last years, no occurrence of a significant resistance of pathogenic strains to the effects of nifuratel has been reported.

Safety profile of nifuratel

The preclinical safety evaluation [38, 39] has confirmed the good safety profile of nifuratel. Nifuratel proved to be practically non-toxic in acute tests in mice and rats. Indeed, it was impossible to determine the LD₅₀, since the single doses up to 5 g/kg orally and up to 2 g/kg intraperitoneally resulted in no mortality even after a 5-day oral administration to mice and rats [38] (Table 6). Nifuratel orally administered to Wistar rats over 47 days at 150 and 450 mg/kg/day (10 to 20 times the therapeutic dose) did not affect the weight gain nor did it cause any symptoms of toxicity or behavioural changes [39] (Table 7). No case of death was recorded with 150 mg, while with 450 mg, 5/20 animals died (2/20 in the untreated control group). In a 6-month toxicity study with dogs, a dose 10 times higher than the therapeutic one (i.e. 100 mg/kg/day administered orally) did not cause any toxic effect or any change in the behavioural experiments and blood tests.

Nifuratel is also well tolerated after repeated intravaginal administrations and it is devoid of teratogenic effects, as tested in mice, rats, and rabbits [37–39].

Table 6: Nifuratel acute toxicity [37].

Type of study	Species	Highest dose mg/kg/day without mortality	Multiple of human maintenance dose ^{a)}
p.o. (single dose)	mouse	5000	600X
	rat	5000	600X
i.p. (single dose)	mouse	2000	250X
	rat	2000	250X

^{a)} Human oral therapeutic dose = 8.57 mg/kg/day.

Table 7: Nifuratel repeated dose toxicity [37].

Species	Study	NOEL dose findings ^{a)}
Wistar rats	47 days	150 mg/kg/day
Dogs	6 months	100 mg/kg/day p.o.

^{a)} NOEL = no effect level, i.e. the maximum dose without any effect in toxicity studies.

Conclusions

On the basis of its microbiological and pharmacotoxicological profile, nifuratel is a good alternative agent to metronidazole in the treatment of vaginal trichomoniasis, and it can be considered a therapeutic agent of choice in mixed uro-genital infections due to its broad spectrum of antimicrobial activity. In fact, this spectrum of action includes *Trichomonas vaginalis*, aerobic and anaerobic bacteria, *Gardnerella vaginalis*, *Candida spp.*, *Chlamydia trachomatis*, and *Mycoplasma spp.* Its activity against *Trichomonas vaginalis* is quite equivalent to that of metronidazole. It does not alter the vaginal microflora due to its lack of activity against *Lactobacillus spp.*, it has a weak activity against *Candida spp.* It can be used also during pregnancy without risk of teratogenic effects. Finally, no resistance phenomena have been reported during more than 30 years of nifuratel use in clinical practice.

By considering all these data, nifuratel can be considered a drug with a favourable risk-to-benefit ratio for the treatment of vulvo-vaginal infections.

References

- [1] Spinillo, A., Zizzoli, G., Colonna, L. et al., Epidemiologic characteristics of women with idiopathic recurrent vulvovaginal candidiasis. *Obstet. Gynecol.* **81**, 1 (1993)
- [2] Oriel, J. D., Partridge, B. M., Danny, M. J. et al., Genital yeast infections. *Br. Med. J.* **4**, 761 (1972)
- [3] Guerreiro, D., Gigante, M. A., Teles, L. C., Sexually transmitted diseases and reproductive tract infections among contraceptive users. *Int. J. Gynaecol. Obstet.* **63** Suppl. 1; S167 (1998)
- [4] Sobel, J. D., Candidal vulvovaginitis. *Clin. Obstet. Gynecol.* **36**, 153 (1993)
- [5] Foxman, B., The epidemiology of vulvovaginal candidiasis: risk factor. *Am. J. Publ. Health* **80**, 329 (1990)
- [6] Rajamanoharan, S., Low, N., Jones, S. B., Poznaniak, A. L., Bacterial vaginosis, ethnicity, and use of genital cleaning agents: a case control study. *Sex. Transm. Dis.* **26**, 404 (1999)
- [7] Sobel, J. D., Vulvovaginitis in healthy women. *Comp. Ther.* **25**, 335 (1999)
- [8] Quan, M., Diagnosis and management of infectious vaginitis. *J. Am. Board. Fam. Pract.* **3**, 195 (1990)
- [9] Mendling, W., *Vaginose, Vaginitis und Zervizitis*. Springer-Verlag, Berlin-Heidelberg etc. (1995)
- [10] Conti, E., Petrone, M., Ferrari, A. et al., Indagine epidemiologica sulle vulvo vaginiti in Italia. *Giorn. It. Ost. Gin.* **2**, 118 (1995)

- [11] Bistoletti, P., Fredricsson, B., Hagstrom, B. et al., Comparison of oral and vaginal metronidazole therapy for non-specific bacterial vaginosis. *Gynecol. Obstet. Invest.* **21**, 144 (1986)
- [12] Pfeifer, T. A., Forsyth, P. S., Durfee, M. A. et al., Non specific vaginitis. Role of *Haemophilus vaginalis* and treatment with metronidazole. *N. Engl. J. Med.* **298**, 1429 (1978)
- [13] Greaves, W. L., Chungafung, J., Morris, B., Hailse, A., Townsed, J. L., Clindamycin versus metronidazole in the treatment of bacterial vaginosis. *Obstet. Gynecol.* **2**, 799 (1988)
- [14] Lossick, J. H., Treatment of sexually transmitted vaginosis/vaginitis. *Rev. Infect. Dis.* **12**, 665 (1990)
- [15] Biswas, M. K., Bacterial vaginosis. *Clin. Obstet. Gynecol.* **36**, 166 (1993)
- [16] Snipes, L. J., Gamard, P. M., Narcisi, E. M. et al., Molecular epidemiology of metronidazole resistance in a population of *Trichomonas vaginalis* clinical isolates. *J. Clin. Microbiol.* **38**, 3004 (2000)
- [17] Roe, F. Y. C., Toxicological evaluation of metronidazole with particular reference to carcinogenic, mutagenic and teratogenic potential. *Surgery* **93**, 158 (1983)
- [18] Carr, P. I., Felsenstein, D., Friedman, R. H., Evaluation and management of vaginitis. *J. Gen. Int. Med.* **13**, 335 (1998)
- [19] Dubini, F., Furneri, R., Attività antimicrobica del nifuratel. *G. Ital. Chemiot.* **32**, 545 (1985)
- [20] Coppi, G., Nifuratel (Inimur) in vitro and in vivo antimicrobial activity. Data on file Polichem, Lugano, Switzerland (1993)
- [21] Chachava, K. V., Zagareli, G. A., Kurzhalija, V. A. et al., The efficacy of Macmiror in the treatment of female genitourinary trichomoniasis. *Bull. Mem. Soc. Méd. Paris* **49** (1973)
- [22] Fari, A., Trevoux, R., Verges, J., Frequency, pathogenesis and prevention of fungal complications of trichomonacide therapy. *Rev. Franç. Gynéc. Obstét.* **72**, 406 (1977)
- [23] Arias Huerta, J., Vaginitis. Un nuevo tratamiento. *Actual. Obstet. Ginecol.* **8**, 400 (1968)
- [24] Schmidt, H., Soost, H. J., Treatment of vaginal Trichomonadosis with nifuratel. *Wiadomosci Parazitologiczne* **XV**, 373 (1969)
- [25] Schmidt, H., Soost, H. J., in: F. Gasparri, G. Gargani, P. Periti (eds), *Diagnosis and Chemiotherapy of urogenital infections*, pp. 191–195, Ed. Med. P. Periti, Firenze (1972)
- [26] Baron, A., Il Macmiror nella terapia della trichomoniasi vaginale. *Min. Ginecol.* **22**, 269 (1970)
- [27] Heiss, H., in: F. Gasparri, P. Periti, G. Gargani (eds.), *Diagnosis and Chemotherapy of Urogenital Infections*, pp. 145, Ed. Med. P. Periti, Firenze (1972)
- [28] Heiss, H., Klinische Auswertung aktiver Arzneimittel gegen Trichomoniasis vaginalis im Doppel-Blindversuch. *Wien. Med. Wschr.* **121**, 832 (1971)
- [29] Turanova, E. N., Skuratovich, A. A., Therapeutic efficacy of the Italian compound macmiror (nifuratel) in female patients with trichomoniasis. *Vestn. Dermatol. Venereol.* **46**, 78 (1972)
- [30] Block, E., Effekten av Nifuratel och metronidazol vid behandling av Trichomoniasis. *Läkartidningen* **69**, 5210 (1972)
- [31] Rognoni, V., Sagone, I., Nuovi orientamenti nella terapia della trichomoniasi femminile. *Riv. Ostet. Ginecol. Pat. Med. Perinat.* **56**, 544 (1976)
- [32] Imperato, S., Sull'attività tricomonica e battericida di Thiodinone. *Igiene Moderna* **56**, 635 (1963)
- [33] Scuri, R., Failla, L., Proprietà biologiche dell'N-(5-nitro-2-furfurilidene)-3-amino-5-metilmercaptometil-2-ossazolidone. *Il Farmaco [Sci.]* **19**, 301 (1964)
- [34] Savoia, D., Leoncavallo N. Investigaciones comparativas sobre algunos compuestos de actividad tricomonica. *Ginecol. Obstet. Mex.* **20**, 557 (1970)
- [35] Barbier, P., Ovules mystatine/nifuratel LE70. Etude de l'activité in vitro. Rapport de bacteriologie et Virologie, Faculté de Médecine Pitié-Salpêtrière, Université de Paris VI. Data on file Polichem, Lugano, Switzerland (1974)
- [36] Hamilton-Miller, J. M. T., Brumfitt, W., Williams, R. J., Comparative in vitro activity of five nitrofurans. *Chemotherapy* **24**, 161 (1978)
- [37] Scuri, R., Etude toxicologique de la méthylmercadone N-(nitro-5'-furfurylidène-2')amino-3-méthylmercaptométhyl-5 oxazolidone-2. *Bull. Chim. Théra.* **3**, 181 (1966)
- [38] Fraschini, F., Experts report on the pharmacological and toxicological documentation of Inimur of Taurus Pharma GmbH, Friedrichsdorf, Germany. Data on file Polichem, Lugano, Switzerland (1993)
- [39] Tynan, A. P., Macis, F. R., Ward-McQuaid J. N. Nifuratel in urinary infections. *Br. J. Urol.* **41**, 271 (1969)

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