Accordingly, the present disclosure relates to a vaginal use of furazidin for the treatment of bacterial vaginal infection.

In one aspect, the present disclosure refers to use of furazidin in the manufacture of a medicament for the treatment of a vaginal bacterial infection, wherein the medicament is to be administered to the vagina.

The term "vaginal use of furazidin for the treatment of bacterial vaginal infection" means that furazidin is to be applied inside the vagina. The term "vaginal use" is to be understand as "intravaginal use".

In one example, bacterial vaginal infection is caused by *Gardnerella vaginalis*, and in another example, bacterial vaginal infection is caused by *Atopobium vaginae*. In further example, bacterial vaginal infection is caused by *Gardnerella vaginalis* or by *Atopobium vaginae*.

In a further example, bacterial vaginal infection is of a mixed type. Preferably, in one example, the mixed type bacterial vaginal infection is caused by both *Gardnerella vaginalis*, and *Atopobium vaginae*. It should be emphasized that *Gardnerella vaginalis* and *Atopobium vaginae* are the most common cause of bacterial vaginal infections.

In one preferable example, the vaginal bacterial infection is a recurrent vaginal bacterial infection.

Bradshaw, C. S. *et al*. in The Journal of Infectious Diseases, Vol. 194, Issue 6, 15 September 2006, p. 828-836 reported that *G. vaginalis* was detected in 100% and *A. vaginae* in 75% of women with recurrent bacterial vaginitis. Accordingly, use of furazidin in such cases of recurrent bacterial infections is especially advantageous.

Therefore, in one example the recurrent bacterial vaginal infection is caused by *G. vaginalis*. In another example the recurrent bacterial vaginal infection is caused by *A. vaginae*. In further another example, the recurrent bacterial vaginal infection is caused by *G. vaginalis* and *A. vaginae*. Preferably, the recurrent bacterial vaginal infection is caused by *G. vaginalis*, more preferably by *G. vaginalis* and *A. vaginae*.

The term 'recurrent infection' means that the infection occurs again or repeatedly after previous treatment such as for example with metronidazol (such as orally) or clindamycin (such as orally or vaginally).

In yet another example, the vaginal bacterial infection is accompanied by a fungal infection. This bacterial/fungal mixed type is a very common type of vaginal infection, since a change in a composition of the bacteria of the vagina caused by abnormal growth of *Lactobacillus spp.* strain results also in an uncontrolled and pathologic growth of endogenous

*Candida albicans* and/or *Candida glabrata*. Thus, in one example the fungal infection is caused by *Candida albicans*, in another example, the fungal infection is caused by *Candida glabrata*, and in yet another example, the fungal infection is caused by *Candida albicans* and *Candida glabrata*.

Furazidin can be administered in any of the known pharmaceutical compositions used vaginally. Such a pharmaceutical composition will contain, of course, in addition to the active compound, furazidin, vaginally acceptable vehicle.

The pharmaceutical compositions suitable to treat infections caused by the bacteria mentioned above can be in solid, semi-solid or liquid forms, and can take a form of tablets, capsules, ovules, suppositories, or cream, ointment, gel, lotion, foam, solution, suspension, thin film or liposomal composition, to be applied or to put deeply into the vagina, with a content in furazidin from 1 to 1000 mg per single dose, more preferably from 10 to 500 mg per single dose, most preferably from 40 to 300 mg per single dose. The person skilled in the art will be able to select the right dosage depending on the selected preparation. Such preparations may be administered in infected patients according to conventional techniques; according to a preferred example, they are administered on a regular basis, preferably daily.

Pharmaceutical compositions may be prepared according to conventional techniques, and contains pharmaceutically and vaginally acceptable vehicle that can be formed using pharmaceutically and vaginally excipients, adjuvants and/or carriers, and may also contain, in combination, one or more active principles with complementary or, in any case, useful activity. Vaginally acceptable vehicles are vehicles, which can be used for vaginal forms and which are not toxic, not irritating and are readily usable. Guidance on the preparation of such pharmaceutical compositions and their forms can be found in *Farmacja Stosowana. Podręcznik dla studentów farmacji*. Ed. S. Janicki, A. Fiebiga, M. Sznitowska; Ed. IV, Wydawnictwo Lekarskie PZWL, 2008 Warszawa.

The active agents which may be used in combination with furazidin of the present disclosure include, as mentioned above, but are not limited to, antifungal agents, antibacterial agents, antiseptic agents, pH modifiers, probiotics; such active ingredients may be administered together with furazidin (i.e. they may be for instance contained in the same composition as furazidin) or they may be administered separately from or in temporal proximity with furazidin.

Examples of antifungal agents include 1-hydroxy-2-pyridone compounds and their salts, e.g. ciclopirox, rilopirox, piroctone, ciclopirox olamine; imidazole derivatives and their salts, e.g. clotrimazole, econazole, isoconazole, ketoconazole, miconazole, tioconazole, bifonazole, fenticonazole and oxiconazole; polyene derivatives and their salts, e.g. nystatin, natamycin and amphotericin; allylamine derivatives and their salts, e.g. naphtifine and terbinafine; triazole derivatives and their salts, e.g. fluconazole, itraconazole, terconazole and voriconazole; morpholine derivatives and their salts, e.g. amorolfine and morpholines disclosed in US-A-5,120.530, herein incorporated by reference; griseofulvin and related compounds, e.g. griseofulvin; undecylenic acid and its salts, in particular, the zinc and calcium salts of undecylenic acid; tolnaphtate and its salts; and flucytosine and its salts.

Examples of antibacterial agents include metronidazole, clindamycin, macrolide antibiotics such as erythromycin, oleandomycin, flurithromycin, azithromycin and claritromycin and salts thereof, beta-lactam antibiotics such as penicillin, ampicillin, amoxicillin and salts thereof, fluoroquinolones such as ofloxacine, norfloxacine, ciprofloxacine and salts thereof, aminoglycosides such as gentamycin, amikacin, kanamycin, neomycin and salts thereof.

Examples of the antiseptic agents include benzalkonium chloride, triclosan, salicylic acid, benzoic acid and their salts, p-hydroxybenzoic acid and its esters.

Examples of pH modifiers include ascorbic acid, acetic acid, lactic acid, and salts thereof.

Examples of probiotics include species of the genus *Lactobacillus*.

As mentioned above, furazidin can be used to treatment of mixed type bacterial vaginal infection.

Thus, in this case, in one example, the pharmaceutical composition comprises preferably an antifungal agent. The studies on antimicrobial activity of furazidin have surprisingly shown a synergy between furazidin and the antifungal agent.

Preferably, the antifungal agent is selected from nystatin, clotrimazole, econazole, miconazole, terconazole, natamycin, and ciclopirox olamine. Those antifungal agent are especially recommended by some guidelines (see *Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America Clinical Infectious Diseases* **2016**; 62(4):e1–50), and are active at relatively low doses. In a

particularly preferred example, the antifungal agent is nystatin. The applicant has found that combination of furazidin with nystatin exhibits synergistic effect against all tested bacteria. This will allow to reduce the total dose of furazidin in a pharmaceutical composition in comparison to a pharmaceutical composition comprising furazidin alone to achieve the same efficacy in the treatment of mixed type infections, especially of bacterial and fungal origin, but also mixed bacterial origin (*Gardnerella vaginalis* + *Atopobium vaginae*). The applicant has also found that furazidin exhibits synergistic effect with nystatin against *Candida glabrata*. It should be emphasized that none of other nitrofurans acts synergistically against *Candida glabrata*. Therefore, again, this creates possibility to reduce the total dose of antifungal agent in the pharmaceutical composition maintaining the same efficacy in the treatment of mixed type infections with *Candida glabrata*.

In another example, the pharmaceutical composition comprises preferably an antibacterial agent. The studies on antimicrobial activity of furazidin have surprisingly shown a synergy between furazidin and the antibacterial agent.

Preferably, the antibacterial agent is selected from metronidazole, clindamycin, macrolide antibiotics such as erythromycin, oleandomycin, flurithromycin, azithromycin and claritromycin and salts thereof, beta-lactam antibiotics such as penicillin, ampicillin, amoxicillin and salts thereof, fluoroquinolones such as ofloxacine, norfloxacine, ciprofloxacine and salts thereof, aminoglycosides such as gentamycin, amikacin, kanamycin, neomycin, and salts thereof. More preferably, the antibacterial agent is selected from metronidazole and clindamycin. In a particularly preferred example, the antibacterial agent is metronidazole. The applicant has found that combination of furazidin with metronidazole exhibits synergy against all bacterial strains as well as all yeast-like fungi tested.

The uses and the pharmaceutical compositions of the present disclosure will now be more fully described by the following examples.

## EXAMPLES

### 1. Analysis of the antimicrobial activity

Analysis of the antimicrobial activity of furazidin, nitrofurantoin, nifuratel, clindamycin metronidazole, and nystatin was performed to determine the minimum concentration which inhibits the growth of microorganisms – minimal inhibitory

## Claims

**1.** Use of furazidin in the manufacture of a medicament for the treatment of a vaginal bacterial infection, wherein the medicament is to be administered to the vagina.

**2.** The use according to claim 1, wherein the vaginal bacterial infection is caused by *Gardnerella vaginalis*.

**3.** The use according to claim 1, wherein the vaginal bacterial infection is caused by *Atopobium vaginae*.

**4.** The use according to claim 1, wherein the vaginal bacterial infection is a mixed type.

**5.** The use according to claim 4, wherein the mixed type vaginal bacterial infection is caused by *Gardnerella vaginalis*, and *Atopobium vaginae*.

**6.** The use according to claim 1 to 5, wherein the vaginal bacterial infection is a recurrent vaginal bacterial infection.

**7.** The use according to any of claim 1 to 6, wherein the vaginal bacterial infection is accompanied by a fungal infection.

**8.** The use according to claim 7, wherein the fungal infection is caused by *Candida albicans*, and/or *Candida glabrata*.

**9.** The use according to any of claim 1 to 8, wherein the medicament is to be administered as a pharmaceutical composition comprising furazidin and a vaginally acceptable vehicle.

**10.** The use according to claim 9, wherein the pharmaceutical composition comprises further an antifungal agent.

**11.** The use according claim 10, wherein the antifungal agent is selected from nystatin, clotrimazole, econazole, miconazole, terconazole, natamycin, and ciclopirox olamine.

**12.** The use according to claim 11, wherein the antifungal agent is nystatin.

**13.** The use according to claim 9, wherein the pharmaceutical composition comprises further an antibacterial agent.

**14.** The use according to claim 13, wherein the antibacterial agent is selected from metronidazole, clindamycin, erythromycin, oleandomycin, flurithromycin, azithromycin, clarithromycin, penicillin, ampicillin, amoxicillin, ofloxacine, norfloxacine, ciprofloxacine, gentamycin, amikacin, kanamycin, neomycin, and salts thereof.

**15.** The use according to claim 14, wherein the antibacterial agent is metronidazole.

**16.** The use according to claim 9 to 15, wherein the pharmaceutical composition is in the form of tablets, capsules, cream, gel, lotion, foam, pessary, or globules.